RESEARCH PROTOCOL

Morphine for palliative treatment of refractory dyspnea in patients with advanced COPD: benefits and respiratory adverse effects
(MORDYC)

Amendments to the original study protocol are shown in **bold blue.**

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1. Summary

Rationale: Dyspnea is the most reported symptom of patients with advanced Chronic Obstructive Pulmonary Disease (COPD) and is undertreated. Morphine is an effective treatment for dyspnea and is recommended in clinical practice guidelines, but questions concerning benefits and concerns about respiratory adverse effects remain. For example, the effect on health-related quality of life and functional capacity is unknown. In one-third of the patients oral sustained release morphine (morphine SR) doesn't relieve dyspnea and it remains unknown whether severity and descriptors of breathlessness may predict a response to morphine. Finally, cost-effectiveness of morphine SR in this patient group is unknown. Therefore, prescription of morphine to patients with COPD is limited.
Objectives of this randomized controlled trial are 1.1) to study the effect of oral administration of morphine SR on health-related quality of life; and 1.2) to explore whether morphine SR leads to respiratory adverse effects in patients with advanced COPD. Secondary objectives are 2.1) to study the effect on functional capacity; 2.2) to explore whether description and severity of breathlessness are related with a clinically relevant response to morphine and 2.3) to analyse the cost-effectives of morphine SR in patients with advanced COPD.
Study design: double-blind randomized placebo controlled intervention study.
Study population: 124 clinically stable outpatients with COPD and severe dyspnea despite optimal treatment.
Intervention: patients will be randomized to an intervention group receiving morphine SR or a control group receiving placebo.
Main study parameters/endpoints: Health-related quality of life, respiratory parameters, functional capacity and changes in these outcomes will be compared between the intervention and the control group. The relationship between response to morphine and severity of dyspnea and descriptors of breathlessness will be explored. Finally, a trial-based economic evaluation from the societal and healthcare perspective **and a model-based economic evaluation will be performed**.
Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Participants will be asked to complete a baseline and outcome-assessment (two site visits between 2 and 3 hours); diary cards (four weeks); two home visits (1 hour each) and two phone calls (0.5 hour each) within four weeks. They will be asked to complete questionnaires and perform a Timed 'Up & Go' test. Two arterial blood gases will be drawn. Lung function will be measured. Also, overnight oximetry will be performed twice at their own homes. **Finally, questionnaires will be sent to the participants four, eight and twelve weeks after the completion of the intervention period.** Patients may experience adverse effects of morphine like nausea, constipation, and drowsiness. Adverse effects will be monitored closely and will be minimized because the maximum dosage of morphine will be 30mg per day. Patients will receive laxatives to prevent constipation and anti-emetics to prevent nausea.

2. Introduction and rationale

Nowadays, the need for palliative care for patients with Chronic Obstructive Pulmonary Disease (COPD) has been recognized.[1,2] Cornerstone of palliative care is optimal symptom management.[3] Dyspnea is the most frequently reported symptom of patients with advanced COPD with 94% reporting moderate to severe dyspnea and most patients reporting insufficient treatment.[4] Current national and international statements recommend the use of opioids to treat severe dyspnea in patients with COPD.[1,5-9] Previous authors[10] proposed a dyspnea ladder in COPD and stated that patients with severe dyspnea despite optimal pharmacological and non-pharmacological treatment (including pulmonary rehabilitation) should receive palliative pharmacological treatment with for example morphine. Two meta-analyses showed that opioids may relieve dyspnea in several populations of patients with life-limiting illness.[11,12] Furthermore, two studies were performed using sustained release morphine (morphine SR) and these studies confirmed that morphine can relieve severe dyspnea in patients with life-limiting diseases, including COPD.[13,14] Despite the recommendations in practice guidelines[1,5,6], only 2% of the Dutch clinically stable outpatients with advanced COPD is using opioids.[4] A recent survey of the Dutch Association for Chest physicians and Tuberculosis (NVALT) among Dutch chest physicians showed that physicians experience several barriers towards the prescription of opioids.[15] In addition, two international qualitative studies showed barriers among physicians towards the prescription of opioids in patients with COPD.[16,17] Most important barriers are uncertainty about positive effects, fear for respiratory adverse effects and lack of evidence-based guidelines. The current literature is insufficient to overcome these barriers. Therefore, scientific background for the current guidelines is limited.

While morphine can relieve dyspnea among patients with advanced COPD, the effect on health-related quality of life remains unknown. Abernethy et al.[13] found no effect on wellbeing, while Poole et al.[18] suggested that morphine SR may even impair health-related quality of life in COPD. A recent systematic review concerning opioid treatment for dyspnea concluded that a meta-analysis of HRQL could not be performed due to study heterogeneity and insufficient data.[12] The aim of interventions in palliative care is to improve quality of life.[3] Therefore, it is of major importance to explore whether and to what extent the use of morphine can influence health-related quality of life. Further, the effect of opioids on exercise capacity remains unknown. In fact, two meta-analyses[11,12] found no effect on exercise tolerance, mainly due to the administration of small and single doses[19], while a randomized, double-blind study[20] suggested a positive effect of fentanyl on exercise capacity in patients with COPD.

Another reported barrier is fear for respiratory adverse effects.[10,16,17] Previous studies were not designed to assess safety.[13,14,21] The American College of Chest Physicians consensus statement on the management of dyspnea in patients with advanced lung or heart disease describes that there is no evidence for significant adverse respiratory effects.[6] A review of studies in cancer patients showed no relevant respiratory adverse effects.[22] Data concerning adverse respiratory effects in patients with COPD are limited and results are conflicting. Abernethy et al.[13] found similar respiratory rates for 18 patients (majority with COPD) receiving morphine and 20 patients receiving placebo. However, they did not assess carbon dioxide levels. A randomized study in 14 COPD patients showed that 2.5-7.5mg of diamorphine had no significant effect on dyspnea or blood gases.[23] Poole and colleagues found no change in oxygen saturation of 14 COPD patients during a six-week treatment with sustained-release morphine.[18] On the other hand, the use of higher dosages of oral morphine during exercise testing caused higher carbon dioxide levels and lower oxygen levels in a study including 13 normocapnic COPD patients.[24] A case report showed severe respiratory depression in a COPD patient using transdermal fentanyl.[25] A recent population-based prospective cohort study showed that lower dose opioids (≤30 mg oral morphine equivalents a day) were not associated with increased mortality, while a higher dose opioids was associated with increased mortality. Unfortunately, respiratory adverse effects were not investigated in this study.[26] Therefore, to date remains unknown whether and to what extent morphine leads to respiratory adverse effects in patients with COPD.

Finally, in about one-third of the patients oral morphine SR does not relieve dyspnea[14], and the current literature is conflicting concerning whether severity and description of dyspnea are related with response.[19,21,27] This knowledge is necessary to select the patients, which are likely to respond to morphine. The recent published 'American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea' described three sensory descriptors of dyspnea which may be linked by specific physiological processes: sensations of work or effort, tightness, and air hunger/unsatisfied inspiration.[28] We hypothesize that a response to opioids is related with these descriptions of breathlessness because of differences in the underlying physiological processes. In fact, a pooled analysis showed weak evidence for a relationship between response to opioids and the description 'cannot get enough air'.[27] Laboratory models in healthy persons showed that opioids reduced dyspnea in air hunger[29], but not in sensations of work or effort.[30]

To conclude, morphine is an effective treatment for dyspnea and is recommended in current guidelines, but questions concerning benefits and concerns about respiratory adverse effects remain. Indeed, the effect on health-related quality of life and functional capacity remains unknown. Moreover, in one-third of the patients oral sustained release morphine (morphine SR) does not relieve dyspnea and to date remains unknown whether severity of dyspnea and descriptors of breathlessness may predict a response to morphine. Finally, its cost-effectiveness is unknown.

3. Objectives

Primary objectives:

1.1) to study whether and to what extent oral administration of morphine SR improves health-related quality of life among patients with advanced COPD;
1.2) to explore whether and to what extent oral administration of morphine SR leads to adverse respiratory effects in patients with advanced COPD.

Secondary objectives:

2.1) to study whether and to what extent oral administration of morphine SR improves exercise capacity among patients with advanced COPD;
2.2) to study the relationship between severity and description of breathlessness and response to morphine SR among patients with advanced COPD;
2.3) to analyse the cost-effectives of oral administration of morphine SR in patients with advanced COPD.

We hypothesize a priori that:
1.1) morphine SR improves health-related quality of life among patients with advanced COPD;
1.2) morphine SR does not lead to adverse respiratory effects in patients with advanced COPD.
2.1) morphine SR improves exercise capacity among patients with advanced COPD;
2.2) descriptors of breathlessness (sensations of work or effort, tightness, and air hunger/unsatisfied inspiration) and severity of breathlessness are determinants of the response to morphine SR among patients with advanced COPD;
2.3) morphine SR for dyspnea in patients with COPD is cost-effective.

4. Study design

A double blind randomized placebo-controlled trial will be designed.

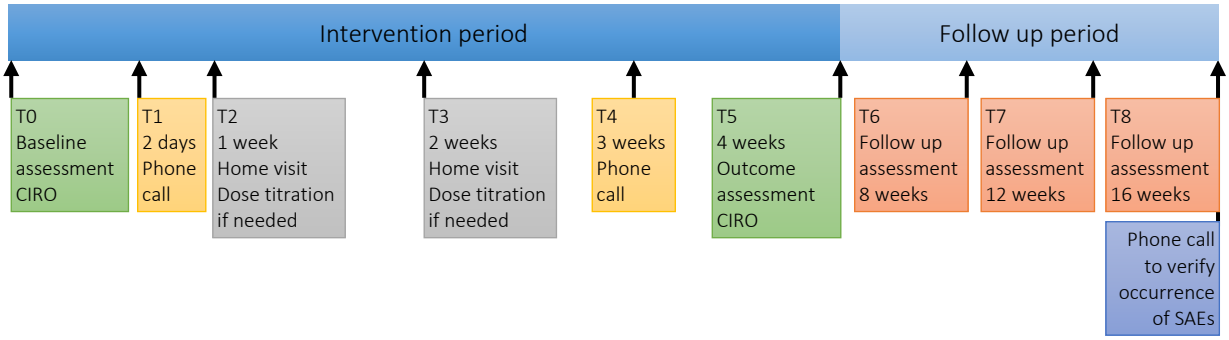
Participants will be outpatients with a confirmed diagnosis of COPD, who suffer from severe dyspnea despite optimal pharmacological and non-pharmacological treatment. Participants will be recruited at CIRO, a centre for pulmonary rehabilitation in Horn, the Netherlands after they completed a pulmonary rehabilitation program **within the last 2 years**. **Furthermore, participants will be recruited at the Zuyderland hospital in Heerlen, the Netherlands, and at VieCuri hospital in Venlo, the Netherlands, both after completion of a pulmonary rehabilitation program within the last 2 years.**

Intervention: After review of eligibility and consent, participants will be randomly allocated to a treatment group or control group. Allocation will be concealed. Patients in the intervention group will receive regular clinical care and morphine SR 10mg, administered twice daily (20mg/24h), which can be increased after one or two weeks to three times per day 10mg (30mg/24h) in non-responders. Patients will be defined as non-responders if the mean dyspnea numeric rating scale (NRS) score was not reduced by 1 point in comparison with baseline.[31] The control group will receive regular clinical care and placebo medication. Patients will receive morphine or placebo for four weeks. In addition, both groups will receive laxatives at the start of the intervention and will be instructed to adjust the dose as needed. Finally, patients will receive a prescription for metoclopramide and will be instructed to use these as needed.

A treatment period of four weeks will be sufficient to show results of treatment with morphine on dyspnea. Indeed, a previous study showed effect of morphine after four days.[13] However, another study showed that dose increase after one week may be needed and showed the benefits of a four week treatment period.[14,32] Moreover, we expect that a four week treatment period is needed to show a change in disease-specific health status.

Measurements consist of baseline and outcome-assessment **in CIRO**; diary cards; home visits; phone calls **and completion of questionnaires** (figure 1).

Figure 1. Study design



Collaboration: The current project is a collaboration of the Centre of Expertise for Palliative Care of the Maastricht UMC+ and CIRO, centre of expertise for patients with chronic organ failure. The project is embedded in research school CAPHRI of the Maastricht University.

5. Study population

5.1 Population (base)

Participants will be outpatients with a confirmed diagnosis of COPD, who suffer from severe dyspnea despite optimal pharmacological and non-pharmacological treatment. Participants will be recruited at CIRO, a centre for pulmonary rehabilitation in the Netherlands after they completed a pulmonary rehabilitation program **within the last 2 years**. **Furthermore, participants will be recruited at the pulmonary rehabilitation program of the Zuyderland hospital in Heerlen, the Netherlands, and the VieCuri hospital in Venlo, the Netherlands.**Yearly, about ~~600~~ **450** patients with COPD are seen at CIRO**, about 85 patients are seen in the Zuyderland hospital and about 35 patients are seen in the VieCuri hospital**. About ~~50~~ **83**% of these patients report a Modified Medical Research Council Dyspnea Scale (mMRC) score of **2,** 3 or 4 before pulmonary rehabilitation.[33] After completion of the pulmonary rehabilitation program about ~~22~~ **51**% of the patients report an mMRC score of **2,** 3 or 4 points. About ~~10~~ **25**% of these patients won't be eligible for this study because of a recent exacerbation, history of substance misuse, renal failure or because patients are not opioid-naïve. Based on ~~an on-going study among patients with advanced COPD~~ **the first 7 months of recruitment** we expect a response rate of about ~~50~~ **30**%. Therefore, it seems reasonable to recruit 124 patients within two years. Moreover, a recent study has shown that recruitment and sustained participation of patients with advanced COPD in this region is possible.[34]

5.2 Inclusion criteria

- Diagnosis of COPD according to the current Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (GOLD) [9];
- Optimal pharmacological treatment**, including treatment with a combination of a long-acting muscarinic antagonist and a long-acting β-agonist** [35];
- Grade **2,** 3 or 4 dyspnea on the mMRC [36];
- Optimal non-pharmacological treatment defined as completed a comprehensive pulmonary rehabilitation program [37,38].

5.3 Exclusion criteria

- History of substance misuse;
- Exacerbation of COPD within two weeks of study enrolment;
- Waiting list for lung transplantation;
- Pregnant or childbearing potential not using contraception;
- Renal failure (creatinine clearance <15mL/min);
- Age under 18;
- Not being able to read or fill in the questionnaires or diary;
- Allergy for morphine or its excipients;
- Concomitant use of irreversible MAO blockers;
- Use of opioids;
- History of convulsions;
- Head injury;
- Intestinal obstruction;
- Gastroparesis;
- Liver disease.

5.4 Sample size calculation

A sample size calculation with a level of significance of 5% and power of 90% has shown that 54 patients per treatment group are needed in order to detect a clinically relevant change in CAT score of 3.8 points (SD 6.1 points (CAT-score in patients with mMRC **2,** 3 or 4))[39,40]. In addition, a sample size calculation with a level of significance of 5% and power of 90% has shown that 10 patients per treatment group are needed in order to detect a change in $PtcCO_2$ level of 1.0kPa (SD 0.7[33]). We expect a drop-out rate of about 13%.[41] Therefore, 62 patients will be included per group.

6. Treatment of subjects

6.1 Investigational product/treatment

Patients in the intervention group will receive regular clinical care and morphine SR 10mg, administered twice daily (20mg/24h), which can be increased after one or two weeks to three times per day 10mg (30mg/24h) in non-responders. Patients will receive the study drug for four weeks. The control group will receive regular clinical care and placebo medication.

6.2 Use of co-intervention (if applicable)

Patients can use their usual medication and will be prescribed a laxative (Movicolon) to prevent constipation and metoclopramide as needed treat possible side-effects.

7. Investigational product

7.1 Name and description of investigational product(s)

Investigational product:
Patients will receive morphine SR 10mg (Centrafarm B.V) two to three times daily or placebo. Hard gelatine capsules of size AA in Swedish orange containing one morphine SR tablet 10 mg per capsule will be produced. Morphine SR has a marketing authorisation for pain and will be used according to current Dutch and international guidelines for treatment of dyspnea.[1,5-9]

Placebo:
Patients in the control group will receive placebo, consisting of microcrystalline cellulose (FMC BioPolymer). Hard gelatine capsules of size AA in Swedish orange containing microcrystalline cellulose will be produced.

7.2 Summary of findings from clinical studies

The Cochrane review exploring the effectiveness of opioid drugs given by any route in relieving the symptom of breathlessness in patients receiving palliative treatment included 18 studies.[42] They found a small but statistically significant positive effect of opioids on breathlessness in the analysis of studies using non-nebulised opioids. There was no statistically significant positive effect seen for exercise tolerance in either group of studies or for breathlessness in the studies using nebulised opioids. They concluded that there is evidence to support the use of oral or parenteral opioids to palliate breathlessness although numbers of patients involved in the studies were small. No evidence was found to support the use of nebulised opioids. Since the publication of the Cochrane review, another systematic review and meta-analysis has been performed [12], which confirmed that morphine can relieve severe dyspnea in patients with COPD. This review also explored the effect on health-related quality of life and concluded that a meta-analysis of HRQL could not be performed due to study heterogeneity and insufficient data.

7.3 Summary of known and potential risks and benefits

Known adverse effects from morphine are nausea, vomiting, constipation, dizziness and drowsiness. In the study from Currow et al.[14] 18% of the patients experienced important adverse effects.

A few studies explored adverse respiratory effects. (Please see attachment: literature respiratory side-effects) One previous study including 48 patients (42 patients with COPD) showed no change in respiratory rate after administration of 20 mg oral morphine.[13] Three studies (including 8 patients[43]; including 16 patients[18]; and including 12 patients[44]) did not show a change in spirometry following administration of opioids. The study from Poole et al. (n=16) showed no change in oxygen saturation.[18] One study, including 13 patients showed a change in blood gases.[24] However, in this study a very high morphine dosage was used (0.8mg/kg).

A recent population-based prospective cohort study showed that lower dose opioids (≤30 mg oral morphine equivalents a day) were not associated with increased mortality, while a higher dose opioids was associated with increased mortality.[26]

7.4 Description and justification of route of administration and dosage

Oral route of administration will be used, according to the Dutch guideline for palliative treatment of dyspnea.[7] Two previous reviews showed no effect of nebulized administration of morphine.[12,42] Previous studies showed the effectiveness of orally administered opioids[14,42], so parenteral administration is not needed.

7.5 Dosages, dosage modifications and method of administration

Patients in the intervention group will receive morphine 10mg SR, administered twice daily (20mg/24h). After one and two weeks the response will be evaluated. If the mean dyspnea NRS score won't be reduced by 1 point in comparison with baseline[31], the dosage will be increased until morphine 10mg SR three times daily (30mg/24h). A recent study showed that improvement may occur during the first week of treatment. Therefore, dosage increase should not occur within one week.[32] We have chosen a maximum dosage of 30mg/24h because a recent population-based prospective cohort study showed that lower dose opioids (≤30 mg oral morphine equivalents a day) were not associated with increased mortality, while a higher dose opioids was associated with increased mortality.[26]

7.6 Preparation and labelling of Investigational Medicinal Product

Preparation and labelling of the investigational medicinal products will be done according to the guideline Good Manufacturing Practice (2003/94/EG, via http://ec.europa.eu/health/files/eudralex/vol-4/2009_06_annex13.pdf)

For the label text we refer to section D3.

7.7 Drug accountability

The investigational products will be delivered by Basic Pharma Manufacturing and will be stored at the pharmacy of the Maastricht UMC+. The patient will receive the investigational product from the researcher. At the end-of-the study the investigational product that is not used will be returned to the pharmacy and will be destroyed.

8. Non-investigational product

8.1 Name and description of non-investigational product(s)

Movicolon:
Patients will receive a prescription for one sachet Movicolon (13.8g) a day at the start of the study. Movicolon is a powder for oral solution, containing macrogol. Movicolon has a marketing authorisation for constipation.

Metoclopramide:
Patients will receive a prescription for metoclopramide 10mg tablets as needed. Metoclopramide has a marketing authorisation for nausea.

8.2 Description and justification of route of administration and dosage

Oral route of administration will be used for Movicolon and metoclopramide.

8.3 Dosages, dosage modifications and method of administration

Patients will start with one sachet Movicolon a day. The need for dosage adjustment will be assessed after 2 days, 1, 2 and 3 weeks by the researcher. Patients can always contact the researcher or physician on call at CIRO between these appointments with questions about management of side effects. If a patient has constipation or diarrhoea the researcher will contact one of the palliative care physicians in the project team. The palliative care physician will advise to reduce the dosage stepwise to once every two or three days in case of diarrhoea or to increase stepwise to two or a maximum of three sachets a day in case of constipation.

Patients will receive a prescription for metoclopramide and will be instructed to start with metoclopramide if they experience nausea in a dosage of 3 times a day 1 tablet of 10mg. The need for metoclopramide will be assessed after 2 days, 1, 2 and 3 weeks by the researcher. Patients can always contact the researcher or physician on call at CIRO between these appointments with questions about management of side effects.

8.4 Drug accountability

The patient will receive a prescription for Movicolon and Metoclopramide. The patient's own pharmacy will deliver the medication.

9. Methods

9.1 Study parameters/endpoints

9.1.1 Main study parameter/endpoint

- Change in disease-specific health-related quality of life (COPD Assessment Test (CAT)[39,45]);
- Change in respiratory parameters: arterial blood gas (partial pressure of carbon dioxide (pCO2); partial pressure of oxygen (pO2); respiratory rate; pulse oximetric saturation (SpO2); transcutaneous carbon dioxide (PtcCO2); Overnight oximetry; lung function.

9.1.2 Secondary study parameters/endpoints

- Change in exercise capacity (6 minute walking distance (6MWD)[46]);
- Change in functional capacity (care dependency (Care Dependency Scale, CDS[47]) and mobility (Timed 'Up & Go' (TUG) test[48]);
- Sensory and affective dimensions of dyspnea (Multidimensional Dyspnea Profile (MDP))[49];
- Impact of dyspnea (modified Pulmonary Functional Status and Dyspnea Questionnaire, PFSDQ-M))[50,51];
- Dyspnea (Numeric Rating Scale (NRS)[31]);
- Adverse effects (including nausea, vomiting, constipation, drowsiness (Epworth Sleep Questionnaire[52]), cognition (Montreal Cognitive Assessment, MoCA[53]));
- Compliance;
- Exacerbations (defined as an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication[9]);
- Costs and cost-effectiveness.

9.1.3 Other study parameters

- Demographic characteristics;
- Comorbidities;
- Smoking status;
- Use of long-term oxygen therapy (LTOT);
- Use of non-invasive positive pressure ventilation (NIV).

9.2 Randomisation, blinding and treatment allocation

After providing **verbal** informed consent **during a phone call**, patients will be randomized using ALEA randomization. Minimisation will be used to guarantee equal distribution between intervention and control group. No stratification will be done. Members of the research team who perform measurements will be blinded for treatment allocation.

To allow safety interim analyses, in case of an exacerbation resulting in hospital admission or death during the study period treatment allocation (group 1 or 2) will be checked. The researcher won't know which of the two groups is the intervention group.

9.3 Study procedures

Measurements at baseline will be performed at CIRO and include: demographics; medical history; medication; co-morbidities; LTOT; NIV; 6 minute walking distance (6MWD)[46]; lung function; inspiratory capacity–to-total lung capacity ratio (IC/TLC); creatinine clearance; arterial blood gas; respiratory rate; pulse oximetric saturation (SpO_2); transcutaneous carbon dioxide ($PtcCO_2$); generic health-related quality of life (EuroQol-5 Dimensions, EQ-5D-5L); disease-specific health-related quality of life (COPD Assessment Test (CAT)[39,45]); severity of dyspnea (NRS)[31]); sensory and affective dimensions of dyspnea (Multidimensional Dyspnea Profile (MDP))[49]; and impact of dyspnea (mMRC and modified Pulmonary Functional Status and Dyspnea Questionnaire, PFSDQ-M))[50,51]; cognition (MoCA)[53]; Epworth Sleepiness Questionnaire; care dependency (Care Dependency Scale, CDS[47]) and mobility (Timed 'Up & Go' (TUG) test[48]). Overnight oximetry will be performed in the home environment at baseline.
A member of the research team will visit patients after 1 and 2 weeks in their home environment to assess: CAT; TUG test; respiratory rate at rest; SpO_2; $PtcCO_2$; **and changes in use of medication**.

A member of the research team will call the patient after 2 days and 3 weeks to assess adverse effects (including but not limited to nausea, constipation, and drowsiness); compliance; and exacerbations (defined as an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication[9]).
After 4 weeks the following measurements will be performed at CIRO: **change in use of medication; use of LTOT and NIV**; lung function; IC/TLC ratio; arterial blood gas; respiratory rate; SpO_2; $PtcCO_2$; 6MWD; EQ-5D-5L; CAT; MDP; PFSDQ-M; CDS; TUG test; adverse effects (including MoCA and Epworth Sleepiness Questionnaire) and general well-being. Subsequently, overnight oximetry will be performed in the home environment.
Finally, the patients will be sent the CAT, EQ-5D-5L and NRS four and twelve weeks after the end of the intervention. One of their informal caregivers will be asked to fill out the cost diary and an overview of their medication use, including morphine, at that moment and in the preceding four weeks four. These will be sent four, eight and twelve weeks after the end of the intervention. After the final questionnaire has returned, the patient will be called to check the occurrence of SAEs.
All measurements are summarized in table 1.

All participants will receive a patient card, listing the research they are participating in along with contact details for investigator and the doctor on call at CIRO in order to alert them in the event of an emergency.

Table 1. Measurements

Measurement	T0	T1	T2	T3	T4	T5	T6	T7	T8
Demographics	X*								
Medical history	X*								
Smoking history	X*								
Medication	X*		X	X		X	X	X	X
Use of LTOT	X*					X			
Use of NIV	X*					X			
6MWD	X*					X			
Lung function (FEV1, FVC)	X*					X			
Measurement IC/TLC ratio	X					X			
Creatinine clearance	X*								
CAT	X*		X	X		X	X		X
CDS	X*					X			
Arterial blood gas	X					X			
Respiratory rate at rest	X		X	X		X			
SpO_2	X		X	X		X			
$PtcCO_2$	X		X	X		X			
EQ-5D-5L	X					X	X		X
mMRC	X*					X			
MDP	X					X			
PFSDQ-M	X					X			
TUG test	X		X	X		X			
Dyspnea (NRS)	X	X	X	X	X	X	X		X
Cognition (MoCA)	X					X			
Epworth Sleepiness Questionnaire	X					X			
Overnight oximetry (at home)	X					X			
Adverse effects	X	X	X	X	X	X	X		X
Compliance		X	X	X	X	X			
Exacerbations		X	X	X	X	X	X	X	X
Healthcare use		X	X	X	X	X	X	X	X
Costs diary		X	X	X	X	X	X	X	X
Morphine use							X	X	X

*** For patients that enter the study immediately after completion of the rehabilitation program, these outcomes will be used from the end evaluation of the rehabilitation program, where possible.**

9.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

9.4.1 Specific criteria for withdrawal

Hospital admission because of an exacerbation.
Unacceptable adverse effects.

9.5 Replacement of individual subjects after withdrawal

Individual subjects will not be replaced after withdrawal.

9.6 Follow-up of subjects withdrawn from treatment

After withdrawal and discontinuation of the study drug the general practitioner and the chest physician will be informed by letter. Patients will receive usual care after withdrawal.

9.7 Premature termination of the study

Criteria for termination of the study prematurely:

- Statistically significant higher proportion of deceased patients in the intervention group;
- Statistically significant higher proportion of hospitalized patients in the intervention group.

In the case of premature termination of the clinical trial, the investigator will inform the reviewing accredited METC and the sponsor. Reasons for termination will be stated in writing. All participants will be informed. Participants will receive usual care.

10. Safety reporting

10.1 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.

10.2 AEs, SAEs and SUSARs

10.2.1 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 investigational product. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

10.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events.

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

10.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are SUSARs if the following three conditions are met:

1. the event must be serious (see chapter 9.2.2);
2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in:
    a. Summary of Product Characteristics (SPC) for an authorised medicinal product;
    b. Investigator's Brochure for an unauthorised medicinal product.

The sponsor will report expedited the following SUSARs through the web portal *ToetsingOnline* to the METC:

- SUSARs that have arisen in the clinical trial that was assessed by the METC;
- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern.

The expedited reporting of SUSARs through the web portal Eudravigilance ToetsingOnline is sufficient as notification to the competent authority.

The sponsor will report expedited all SUSARs to the competent authorities in other Member States, according to the requirements of the Member States.

The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

10.3 Annual safety report

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, and competent authorities of the concerned Member States.
This safety report consists of:
a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

10.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.
SAEs need to be reported till end of study within the Netherlands, as defined in the protocol

11. Statistical analysis

11.1 Primary study parameter(s)

Baseline characteristics such as age, sex, FEV_1, respiratory parameters, comorbidities, smoking status, use of LTOT, use of NIV, mMRC score, NRS score, 6MWD, CDS, TUG test in seconds and MocA will be compared between the intervention and control group using descriptive statistics. Chi square tests will be used for categorical variables. Independent sample T-tests and Mann-Whitney U-tests will be used for continuous variables, according to the variable distribution.

Objective 1.1

Change in disease-specific health-related quality of life (CAT-score) between baseline and four weeks will be compared between patients in the intervention and the control group. First, mean change in CAT-score will be compared between the two groups using an independent sample T-test or Mann-Whitney U test, according to the variable distribution. Afterwards, multivariate analyses for longitudinal data will be performed. A linear mixed model will be developed including CAT-score at baseline, one, two and four weeks and exploring the effect of treatment according to trial arm. Analyses will be controlled for baseline level of dyspnea (NRS) and age, while previous studies have shown that these are predictors of opioids response*.[27] Analyses will be done using an intention-to-treat approach. Point measures and measures of variability will be provided.

Objective 1.2

Change in respiratory parameters (pCO_2; pO_2; respiratory rate; SpO_2; $PtcCO_2$; percentage of the time overnight with $PtcCO_2$† below 90%; FEV_1) between baseline and four weeks will be compared between patients in the intervention and the control group. First, mean change in these respiratory parameters will be compared between the two groups using an independent sample T-test or Mann-Whitney U test, according to the variable distribution. Afterwards, multivariate analyses for longitudinal data will be performed. If measures of disease severity differ between groups, these will be included as possible confounders. Analyses will be done using an intention-to-treat approach. Point measures and measures of variability will be provided.

A 13% drop out rate has been taken into account in the sample size calculation for the primary analysis to allow for missing data. Missing data will be reported and investigated to see whether it is missing at random. Sensitivity analyses will be performed as appropriate. If the data indicate that the level and type of missingness suggest that imputation is appropriate, we will use the recommended technique (e.g. multiple imputation) to deal with missing data.

11.2 Secondary study parameters

Objective 2.1

Change in 6MWD between baseline and four weeks will be compared between patients in the intervention and the control group. First, mean change in 6MWD will be compared between the two groups using an independent sample T-test or Mann-Whitney U test, according to the variable distribution. Afterwards, multivariate analyses for longitudinal data will be performed. If measures of disease severity differ between groups, these will be included as possible confounders. Analyses will be done using an intention-to-treat approach. Point measures and measures of variability will be provided.

Objective 2.2

The relationship between response to opioids and severity of dyspnea and descriptors of breathlessness will be explored using univariate analysis, followed by a binary logistic regression model. Response to opioids will be included as dependent variable (defined as a decrease in mean dyspnea NRS score by 1 point or more in comparison with baseline).[31] Descriptors of breathlessness (MDP) will be included as independent variables. Baseline dyspnea (NRS) and age will be included as possible confounders. Patients who discontinue morphine during the study because of lack of effect and/or intolerable adverse effects will be analysed as non-responders.

Objective 2.3

A trial-based economic evaluation will be performed, based on empirical data obtained in the RCT. The economic evaluation will be performed from the societal and healthcare perspective, the first including costs inside and outside the health care sector, and will follow published international guidelines.[54] The time horizon

* Controlling for baseline levels of dyspnea (NRS) and age were not performed, since within an RCT it can be assumed baseline characteristics are equal.

† Since an oximeter was used, overnight SO_2 was measured instead of overnight $PtcCO_2$.

of the trial-based economic evaluation will be four weeks. The intervention offered in this study is primarily expected to affect morbidity. So, health-related quality of life is considered as an important outcome in these patients. Therefore, a cost-utility analysis will be performed, with the number of quality adjusted life years (QALYs) as the primary outcome measure, based on the EQ-5D-5L.[55] Additionally, a cost-effectiveness analysis will be performed in which the primary outcome measure is used as measure of effectiveness. So, incremental cost-effectiveness ratios will be expressed as 1) the incremental costs per QALY (societal perspective) and the 2) additional patient with a clinically relevant improvement on the CAT (health care perspective). The cost analysis will be performed according to Dutch guidelines for cost calculations.[56] Study related costs will be excluded. Hospital resource use such as outpatient visits, diagnostic procedures, hospital admissions due to exacerbations etc. will be registered by means of Case Report Forms. For costs outside the hospital, such as costs of morphine and other medications, visits to the GP, physiotherapist, loss of daily activities, and out of pocket costs, patients will be asked to fill out a prospective cost diary for a period of 4 weeks. Costs will be calculated by multiplying resource use with standard unit prices. Standard sensitivity analyses and bootstrap analysis will be performed to investigate the uncertainty surrounding the cost-effectiveness ratios. Based on the bootstrap results, cost-effectiveness acceptability curves will be constructed, showing for a range of cost-effectiveness threshold values, the probability that morphine (in addition to usual care) are cost-effective to placebo (in addition to usual care).

~~A~~ **Since a** time horizon of 4 weeks (which is considered to be the maximum follow up for the placebo group from an ethical perspective) may be insufficient to obtain valid estimates of the cost-effectiveness of the use of morphine, **collection of data on costs, health-state and side effects will be prolonged for twelve weeks. Data on** long term cost and effects will additionally be estimated by means of a decision analytical model with a lifelong time horizon.[56] First a structure and working model will be created that will facilitate the necessary analyses to be performed throughout the project. Once the structure of the model is established and discussed with the project group, four essential types of data will be used as input: probabilities, costs, survival and health utilities (QALYs). Model input will be based on the trial results, literature review and expert opinion where necessary. The model will probably take the form of a Markov model; however this will be decided upon during the study. Estimates of the economic impact will first be made using fixed estimates of probabilities, costs, and health outcomes. Probabilistic sensitivity analysis will additionally be performed to address uncertainty.

11.3 Interim analysis

Monitoring will consist of one site initiation visit, eight interim monitoring visits and one close out visit. Every interim monitor visit the proportion of hospitalized patients and deceased patients will be compared between the intervention and control group by the principal investigator. So, these interim analyses will be performed eight times during the study period of three years. When a patient is hospitalized or a patient dies treatment allocation will be checked (group 1 or 2). The researcher won't know whether group 1 or 2 is the intervention or control group. Therefore, the proportion of hospitalized and the proportion of deceased patients can be compared between two groups. For both analyses, Fisher's Exact Test will be used. The code will be broken in case of a statistically significant higher number of hospital admissions or deaths in one group. To prevent inappropriate termination of the trial because of an unequal distribution in a small sample size, the level of statistical significance will be set at $p<0.01$. Moreover, in the final decision to terminate the trial, the probability that a hospital admission or death of a patient is an undesirable reaction to the medicinal product under investigation will be taken into account. This will be decided by the researcher and a chest physician in CIRO who is not a member of the project team.

12. Ethical considerations

12.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO).

12.2 Recruitment and consent

Patients who fulfil the inclusion criteria will be informed about the study by their clinician, during the end evaluation of their rehabilitation program or during a phone call. If patients show interest in the study the patient information letter will be handed or sent. If patients provide their permission, the researcher will call the patients after about 7 days to ask for **verbal informed** consent to participate in the study. An appointment will be made for the baseline assessment at CIRO. At the start of this assessment written informed consent will be obtained.

12.3 Benefits and risks assessment, group relatedness

Participants in both groups will be asked to perform two site visits lasting between 2 and 3 hours; complete diary cards for four weeks; two home visits of 1 hour each and two phone calls of 0.5 hour each within four weeks. During these visits they will be asked to complete questionnaires, measurement of lung function and a Timed 'Up & Go' test. Two arterial blood gases will be drawn, which may lead to a hematoma, which will heal within a few days. **Furthermore, they will be asked to fill out two times three questionnaires of 0.25 hour within twelve weeks after the intervention has ended. Finally, one of the informal caregivers will be asked to complete a cost diary three times, lasting about 0.25 hour each time.** We expect that the burden from the study will be acceptable.

The positive effect of morphine on dyspnea is well-supported in the current literature.[11,13,14] We expect that the majority of the patients in the intervention group experience a decrease in dyspnea. Patients may also experience adverse effects such as nausea, vomiting, constipation, or drowsiness. In the current study, adverse effects as well as the benefits of morphine will be closely monitored. If the adverse effects exceed the benefit of the study drug, patients will discontinue the study drug and will be analysed as non-responders. The risks of the current study are minimized because only a low dosage of morphine will be used. A previous study showed that 30 mg oral morphine a day is not associated with increased mortality.[26]

Patients in the control group will receive placebo, despite the fact they experience severe dyspnea and that current guidelines[1,5,6], recommend to prescribe opioids. However, in regular clinical care only 2% of the Dutch clinically stable outpatients with advanced COPD is using opioids.[4] Moreover, if patients in the control group or intervention group prefer, they will be prescribed morphine after completion of the study by a palliative care specialist in collaboration with their general practitioner.

12.4 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7, subsection 9 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of 23th June 2003). This insurance provides cover for damage to research subjects through injury or death caused by the study.

1. € 450.000,-- (i.e. four hundred and fifty thousand Euro) for death or injury for each subject who participates in the Research;
2. € 3.500.000,-- (i.e. three million five hundred thousand Euro) for death or injury for all subjects who participate in the Research;
3. € 5.000.000,-- (i.e. five million Euro) for the total damage incurred by the organisation for all damage disclosed by scientific research for the Sponsor as 'verrichter' in the meaning of said Act in each year of insurance coverage.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

12.5 Incentives

Patients will receive reimbursement for travel costs (0.19 ct. per kilometre or taxi costs).

13. Administrative aspects, monitoring and publication

13.1 Handling and storage of data and documents

Data will be handled confidentially and anonymously. Only authorized personnel will have access to these confidential files. A subject identification code list will be used to trace data to an individual subject. The code (001, 002 etc.) will not be based on the patient initials and birth-date. The key to the code will be safeguarded by the investigator. The handling of personal data will comply with the Dutch Personal Data Protection Act (in Dutch: De Wet Bescherming Persoonsgegevens, Wbp). Data will be saved for 15 years.

13.2 Monitoring and Quality Assurance

Monitoring will be performed by the Clinical Trial Center Maastricht. Monitoring will follow the international ICH-GCP guidelines. Monitoring will consist of: site initiation visit; interim monitoring visits; and close out visit.

13.3 Amendments

A 'substantial amendment' is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority.

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

13.4 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.

13.5 Temporary halt and (prematurely) end of study report

The sponsor will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary half of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC and the competent authority 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 and the Competent Authority.

13.6 Public disclosure and publication policy

The investigator will be responsible for the quality of the study performance, and he/she has the right to publish the results of this study in the appropriate well-accepted scientific journals. All publications will be confirming the basic principles of the CCMO publication policy (www.ccmo.nl). The study will be registered in the trial register (www.trialregister.nl)

14. Structured risk analysis

14.1 Synthesis

Paragraph 13.1 is omitted because morphine SR has a marketing authorisation and will be used according to current daily practice guidelines.[7] The risks of the current study are minimized because only a low dosage of morphine will be used. A previous study showed that 30 mg oral morphine a day is not associated with increased mortality.[26] Moreover, patients with an increased risk of adverse effects will be excluded from the current study (e.g. renal failure, use of irreversible MAO blockers). To date, there is uncertainty about respiratory adverse effects in patients with COPD. Nevertheless, available studies don't show evidence for respiratory adverse effects of low dosages morphine in COPD.[13,18,23] In the current study, respiratory adverse effects will be monitored closely. Patients may experience adverse effects such as nausea, vomiting, constipation, or drowsiness. Also these adverse effects as well as the benefits of morphine will be closely monitored. If the adverse effects exceed the benefit of the study drug, patients will discontinue the study drug and will be analysed as non-responders.

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