BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-043156
Article Type:	Protocol
Date Submitted by the Author:	16-Aug-2020
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Keywords:	Interstitial lung disease < THORACIC MEDICINE, PALLIATIVE CARE, Clinical trials < THERAPEUTICS

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Study protocol for a randomised, placebo-controlled, single-blind phase II study of the efficacy of morphine for dyspnoea in patients with interstitial lung disease (JORTC-PAL 15)

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Word count: 2199

ABSTRACT

Introduction Dyspnoea is common in patients with interstitial lung disease (ILD) and often refractory to conventional treatment. Little is known about the efficacy of systemic morphine for dyspnoea in patients with ILD. The aim of this study is to estimate the efficacy of a single subcutaneous morphine injection for dyspnoea in patients with ILD.

Methods and analysis We will conduct a multicentre, prospective, randomised, placebo-controlled, single-blinded phase II study of a single subcutaneous morphine injection for dyspnoea in patients with ILD. Eligible subjects are ILD inpatients with dyspnoea at rest refractory to conventional treatment. The morphine dose will be 2 mg. The primary endpoint is to compare changes in dyspnoea intensity from baseline to 60 minutes after treatment, measured using an 11-point numerical rating scale, between the morphine and placebo groups.

Ethics and dissemination Ethical approval has been obtained. The results of this study will be submitted for publication in an international peer-reviewed journal and the findings will be presented at international scientific conferences.

Trial registration number jRCTs051190030; Pre-results.

Protocol version 1.21, 24 July 2019

Strengths and limitations of this study

- This is one of the few studies estimating the efficacy of systemic morphine for dyspnoea in patients with ILD.
- This study has a rigorous design including randomisation, a placebo control group, and blinding of participants.
- This is a single-blinded study.
- The observation period is short, i.e., the assessment of efficacy is within 60 minutes after treatment and assessment of adverse events is within 24 hours after treatment.

INTRODUCTION

Interstitial lung diseases (ILDs) are a heterogeneous group of lung diseases that affect the pulmonary interstitium. They include connective tissue disease-associated ILD, drug-induced ILD, occupational and environmental ILD, sarcoidosis, and idiopathic interstitial pneumonias.[1] A population-based registry study has shown that the prevalence of ILD was 80.9 per 100,000 in men and 67.2 per 100,000 in women.[2] ILD is often fatal or difficult to cure[3 4]; therefore, palliative care is essential for patients with ILD. However, palliative care available for patients with ILD is not sufficient compared to that for patients with cancer.[5 6]

Dyspnoea is the most frequent and burdensome symptom in patients with ILD,[7 8] and is associated with a decreased quality of life in ILD.[9-14] Multiple empirical studies and systematic reviews have confirmed that morphine is effective for refractory dyspnoea in patients with chronic breathlessness predominantly caused by cancer and chronic obstructive pulmonary disease.[15-18] On the other hand, studies on the efficacy and safety of morphine in patients with ILD are greatly limited. A case series of end-stage idiopathic pulmonary fibrosis patients has reported that diamorphine is an effective treatment for dyspnoea.[19] A few retrospective studies have also suggested that morphine is effective in treating dyspnoea in terminally ill patients with interstitial

pneumonia.[20 21] To the best of our knowledge, no published prospective study has examined the efficacy and safety of systemic morphine for dyspnoea in patients with ILD patients.[22-24] From the Phase I study we conducted to investigate the safety of systemic morphine and determine the recommended dose of morphine to be used in further clinical trials, we reported that the recommended dose of single subcutaneous morphine for dyspnoea in patients with ILD is 2 mg.[25] The aim of this study is to estimate the efficacy of a single subcutaneous morphine injection for dyspnoea in ILD patients.

METHODS AND ANALYSIS

Study design

This study is a multicentre, prospective, randomised, placebo-controlled, single-blinded phase II study and will be performed to estimate the efficacy of morphine. The study design is summarized in Figure 1.

Study settings and participants

Recruiting will be performed from nine hospitals across Japan.

The inclusion criteria are as follows: hospitalized patients who 1) are 20 years or

older; 2) are diagnosed with ILD by two respiratory physicians and one respiratory radiologist; 3) have dyspnoea at rest despite conventional treatment, with numerical rating scale (NRS) ≥ 3; 4) have an expected survival of 1 month or longer; 5) are capable of communication and do not have cognitive impairments; 6) have blood oxygen saturation levels (SpO_2) ≥ 90% (supplemental oxygen was allowed) and partial pressure of carbon dioxide ($PaCO_2$) ≤ 50 Torr; 7) have a normal liver and renal function (AST ≤ 100 IU/L, ALT ≤ 100 IU/L, T-Bil ≤ 2.0 mg/dL, and creatinine ≤ 2.0 mg/dL); and 8) have an ejection fraction ≥ 50% confirmed by echocardiography.

ILDs in this study include idiopathic pulmonary fibrosis, idiopathic non-specific interstitial pneumonia (NSIP), unclassifiable idiopathic interstitial pneumonia, collagen vascular disease-related interstitial pneumonia, chronic hypersensitive pneumonia, and pneumoconiosis. Idiopathic pulmonary fibrosis is diagnosed using the official American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Society statement.[26] NSIP and unclassifiable idiopathic interstitial pneumonia are diagnosed using the official American Thoracic Society/European Respiratory Society statement.[27]

The exclusion criteria are as follows: 1) patients with contraindications to morphine, 2) patients using opioids (if the patient is receiving any dose of codeine, that

was discontinued 12 hours prior to the study treatment), 3) patients with acute respiratory failure, pneumothorax, or asthma attack, 4) patients with dyspnoea mainly caused by an active infection or lung cancer, 5) patients using invasive or non-invasive positive pressure ventilation, 6) patients with a current or past history of drug abuse, or 7) patients who are pregnant.

Recruitment, randomisation, masking and follow-up

Recruitment

Potentially eligible patients will be screened by site investigators. If the patients comply with the inclusion criteria, they will be invited to participate in the study.

Randomisation

During enrolment and after providing a written informed consent, patients will be randomly allocated to the intervention (morphine) or control (placebo) groups in a web-based central randomisation system using minimisation methods and a computer-generated randomisation schedule with a 1:1 allocation ratio. In performing this allocation, we will minimise the following adjustment factors to avoid a large bias: (1) current dyspnoea intensity measured by the NRS ($\leq 6, \geq 7$), (2) the use of codeine (Yes,

No), and (3) the study site.

Masking

Patients will be blinded to the administration of morphine or placebo. The intervention will be unblinded 60 minutes after treatment, only if patients in the placebo group do not experience relief of dyspnoea and want to receive morphine. Clinicians and medical staff will be unblinded because the process of disposing opioid in Japan is very complex. However, clinicians or medical staff who will check the self-administered sheet for current dyspnoea intensity (primary endpoint) will be blinded.

Data management, central monitoring and audit

Evaluation will be performed at five timepoints: time of enrolment, baseline, and 30 minutes, 60 minutes, and 24 hours after treatment. The timing and details of the assessments are shown in Table 1. The investigators at each study site will keep the individual records of each patient as source data, which include signed informed consent forms, medical records, laboratory data and other records or notes. All data will be collected by the JORTC data centre. The JORTC data centre will oversee the intra-study data sharing process. The clinical data entry, data management and central

monitoring will be performed using the electric data capture VIEDOC 4 (PCG Solutions, Sweden). An interim analysis will not be performed. Auditing will not be done in this study.

Table 1 Study procedure and time point for evaluation

Time point	Inclusion	Baseline	30 minutes	60 minutes	24 hours
Consent, randomisation	✓				
Modified MRC scale	✓				
ECOG PS	✓				
Medicines History	✓				
Smoking History	✓				
Weight	✓				
AST, ALT, T-Bil, Cre	✓				
$PaCO_2$	✓				
Ejection fraction	✓				
NRS for current dyspnoea	✓	✓	✓	✓	
Vital signs		✓	✓	✓	
Oxygen		✓	✓	✓	
RASS		✓		✓	
Number of vomiting		←	—	→	
Adverse events		←	—	—	→

ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cre, creatinine; ECOG PS, European Cooperative Oncology Group Performance Status; MRC, Medical Research Council; NRS, Numerical Rating Scale; RASS, Richmond Agitation-Sedation Scale; T-Bil, total bilirubin.

Treatment

Interventions

Single subcutaneous injection of morphine 2 mg or placebo (normal saline 0.2 mL) will be conducted. Injection will be conducted by an unblinded physician. Patients in the placebo group who do not experience relief of dyspnoea and who want to receive morphine after assessment for 60 minutes after injection will be administered 2 mg of morphine. Following previous studies,[19 28] we decided to use subcutaneous injection, not oral preparations, for practical reasons, such as the feasibility of a placebo (normal saline) in future clinical trials, and simple logistics in the study institution.

Cotreatments

Generally, change in oxygen flow rate and oxygen delivery devices will not be allowed. In addition, hypotensive drugs, diuretics, hypnotics, anxiolytics, and anti-psychotics will not be administered one hour after treatment. Codeine will be permitted until 12 hours before treatment. The use of inhaled bronchodilators and pulmonary rehabilitation will be restricted 1 hour before and after treatment.

Data collection

Blood pressure, heart rate, respiratory rate, SpO_2, and oxygen requirement will be recorded at baseline, 30 minutes, and 60 minutes after morphine administration. Furthermore, sedation (assessed by the Richmond agitation sedation scale[29 30]), vomiting frequency (events/60 minutes), and the Common Terminology Criteria for Adverse Events (CTCAE) will be assessed at baseline and 60 minutes after drug administration. In addition, CTCAE will be recorded for 24 hours following drug

administration.

Measures

Demographics and clinical characteristics

Participants' sex, age, body weight, type of ILD, concomitant drug use (corticosteroids, immunosupressants, anti-fibrotic agents, bronchodilators, pulmonary vasodilators, anxiolytics, and codeine), the modified Medical Research Council Dyspnea scale,[31] the European Cooperative Oncology Group Performance Status, ejection fraction by echocardiography, $PaCO_2$, SpO_2, oxygen flow rate, oxygen delivery devices, AST, ALT, T-Bil, creatinine, and current dyspnoea intensity at rest in the NRS will be assessed before enrolment.

Numerical Rating Scale

Current dyspnoea intensity will be assessed by an 11-point Likert-type NRS from 0 (no dyspnoea) to 10 (worst possible dyspnoea).[32]

Richmond Agitation-Sedation Scale (RASS)

Agitation and sedation will be assessed by the RASS. The RASS is a validated 10- point scale that ranges from -5 (unarousable) to +4 (combative).[29 30]

Common Terminology Criteria for Adverse Events

The worst grade of an adverse event (AE) during the preceding period will be assessed using the CTCAE V.5.0, Japanese Clinical Oncology Group (JCOG) version. Three AEs including somnolence, nausea, and delirium will be investigated because they

occur at a relatively high frequency. Other AEs may also be assessed.

Study endpoints

Primary endpoint

The primary endpoint is a comparison of changes of dyspnoea intensity at rest from baseline to 60 minutes after treatment measured using NRS between the morphine and placebo groups.

Secondary endpoints

The secondary endpoints include the following: 1) a comparison of changes in dyspnoea intensity at rest from baseline to 30 minutes after treatment measured using NRS between the morphine and placebo groups; 2) a comparison of rates of patients with NRS $\geq$ 1 improvement of dyspnoea intensity at rest from baseline to 60 minutes after treatment between the morphine and placebo groups; 3) respiratory rate; 4) blood pressure; 5) SpO_2; 6) heart rate; 7) the number of vomiting; 8) RASS; 9) adverse events from baseline to 24 hours after treatment.

Safety

Investigators will record all AEs in electric data capture systems. All AEs are to be followed up throughout the course. All severe AEs will be reported to the Certified Review Board and investigators in all sites and discussed.

Statistical considerations

Statistical analysis

Comparison of the primary endpoint of the changes in the NRS score for dyspnoea from baseline to 60 minutes after treatment between the morphine and placebo groups will be conducted using two-sided Student's t-test at a significance level of 5% according to the intention-to-treat principle. Point estimates and 95% CIs for the difference between two group means will be calculated.

Comparison of the secondary endpoint of the changes of NRS score for dyspnoea from baseline to 30 minutes after treatment between the morphine and placebo groups will be evaluated similarly to the primary endpoint. Comparison of the rates in patients who experienced an improvement in the NRS of ≥ 1 from baseline to 30 minutes or 60 minutes after treatment will be evaluated using chi-square test or Fisher's exact test. Point estimates and 95% CIs for the difference between two means will be calculated. A full statistical analysis plan (including the handling of missing values) will be written prior to the data evaluation.

Sample size calculation

The aim of this study is to estimate the efficacy of morphine for dyspnoea in patients with ILDs and gain the data to calculate the sample size for future phase III study. Therefore, we set the sample size we will be able to enroll during three-year scheduled period.

Patient and public involvement

Patients and the public will not be involved in this study.

Ethics and dissemination

Ethics

All patients will be required to provide a written informed consent. The study will be conducted in accordance with the Declaration of Helsinki and the Clinical Trials Act. The protocol was approved by the Osaka City University Certified Review Board (CRB; approved number OCU0006). This trial has been registered at the Japan Registry of Clinical Trials (jRCT) as jRCTs051190030. This study protocol adheres to SPIRIT 2013. Modifications in the study protocol will be communicated to the CRB as well as the independent data monitoring committee of JORTC.

Dissemination

The results of this study will be submitted for publication in international peer-reviewed journals and the key findings will be presented at national and international conferences. Authorship will be ascribed in accordance with the International Committee of Medical Journal Editors guidance.

DISCUSSION

This study protocol describes multicentre, prospective, randomised, placebo-controlled, single-blinded phase II study of morphine against dyspnoea in patients with ILDs. In this phase II study, we expect to obtain data to estimate the efficacy of a single subcutaneous injection of morphine for dyspnoea in patients with ILD and be able to use the data to calculate the sample size for the phase Ⅲ study.

The strengths of this study are as follows: first, this is one of the few studies to assess the efficacy of morphine for dyspnoea in patients with ILDs; second, this study is randomised placebo controlled study, therefore we can compare the efficacy of

morphine with placebo even though this study is phase II study.

Several issues related to the content of the trial require discussion. First, this trial is single-blinded trial. Clinicians and medical staff, except those who check the self-administer sheet, will be unblinded. If clinicians and medical staff are blinded, other unblinded clinicians or medical staff need to dispose the treatment drug, i.e., morphine or normal saline. To minimize the burden of the clinicians and medical staff in each site, we decided that the clinicians and medical staff would be unblinded. However, the primary endpoint will be assessed using a self-administration sheet and checked by blinded clinicians or medical staff. Thus, the effect of un-blinded clinicians or staff will be minimised. Second, the observation period is short in our study, i.e., assessment of efficacy is within 60 minutes after treatment and assessment of AEs is within 24 hours after treatment. This is because we assume the patients with ILD in this study to be vulnerable, and longer study periods may result in decreased feasibility; treatments other than morphine could be changed, including providing supplemental oxygen. Finally, we do not exclude patients who use codeine because many patients with ILD use codeine for cough. However, codeine will be discontinued 12 hours prior to study treatment to minimize the effect of codeine to dyspnoea.

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Authors' Contributions

YM is lead author of the study protocol and principal investigator. YM, TM, SO, KA, TY and SI participated in the design of the study. SO and TY designed the statistical analysis plan. All authors contributed to writing and revising the manuscript critically, and all gave their final approve of the version to be published.

Funding statement

This work was supported by the following grants: 2018-2020 Grant-in-Aid for Scientific Research (Grant-in-Aid for Young Scientists B; grant number 17K15909) and Osaka Medical Research Foundation for Intractable Diseases (grant number 23-2-41). The funders had no role in the study design and will have no role in the data collection, analysis or dissemination of study results.

Competing interests None declared.

Trial status

The enrolment started in June 2019. At the time of manuscript submission (July 2020), 17 patients have participated. We expect to complete the recruitment by March 2022.

Confidentially

Data will be retained in accordance with the Clinical Trials Act. Participants will be allocated a unique identification (ID) number at entry. The master list linking participant personal information and ID number will be maintained in a paper file or password-protected hard drive in a locked room at each institution. Data will be

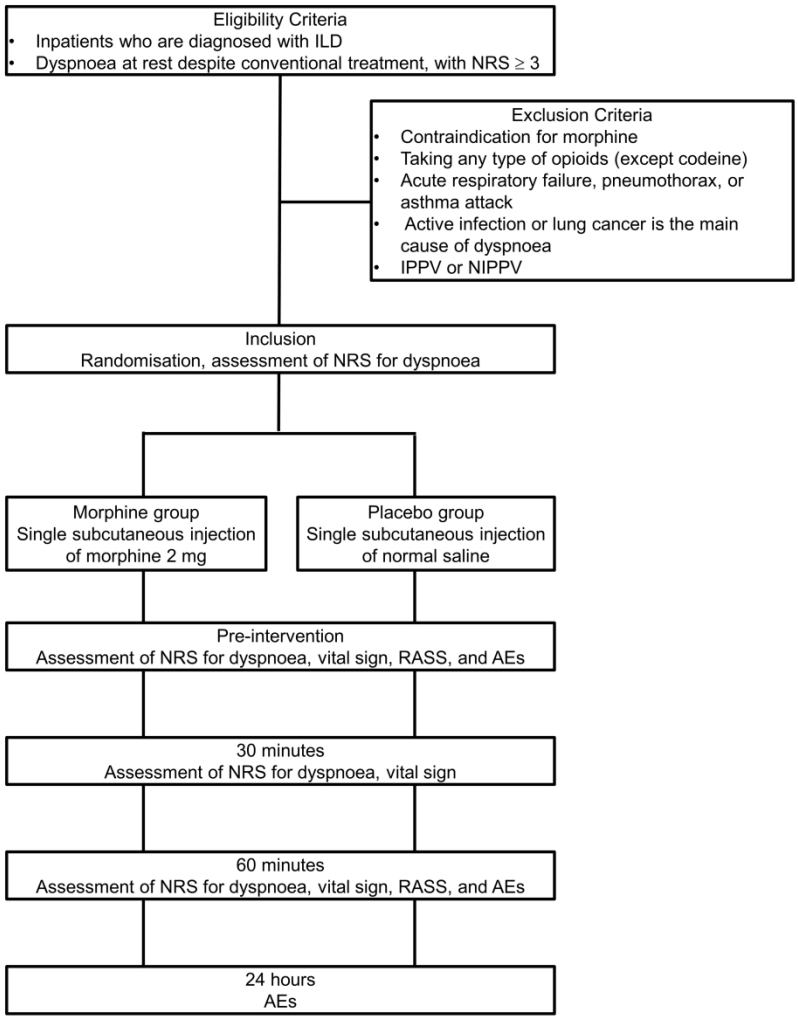
analysed by ID number only. Records will be retained for 5 years after study completion and then destroyed by the JORTC data centre.

Acknowledgements

This work was supported by the following grants: 2018-2020 Grant-in-Aid for Scientific Research (Grant-in-Aid for Young Scientists B; grant number 17K15909) and Osaka Medical Research Foundation for Intractable Diseases (grant number 23-2-41).

Figure Legend

Figure 1 Flow chart of the procedures in the study. Participants will be randomized (1:1 allocation ratio) into the morphine group or the placebo group. Assessment will be made at baseline, 30 minutes, 60 minutes, and 24 hours. AEs, Adverse Events; ILD, Interstitial Lung Disease; IPPV, Invasive Positive Pressure Ventilation; NPPV, Non-invasive Positive Pressure Ventilation; RASS, Richmond Agitation Sedation Scale.



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274x383mm (300 x 300 DPI)

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	p1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	p3
	2b	All items from the World Health Organization Trial Registration Data Set	Not applicable
Protocol version	3	Date and version identifier	p3
Funding	4	Sources and types of financial, material, and other support	p20
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	p1, 20
	5b	Name and contact information for the trial sponsor	Not applicable
	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	p20
	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)	p9

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	p5-6
	6b	Explanation for choice of comparators	p12
Objectives	7	Specific objectives or hypotheses	p6
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)	p6
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	p6-7
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)	p6-7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	p12
	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)	Not applicable
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Not applicable
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	p12
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	p13-14
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)	p12-13

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	p15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	p8
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	p8
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	p8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	p8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	p9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	p9
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	p12-13
	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	Not applicable

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	p8-9
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	p14-15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Not applicable
	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)	p15
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	p16
	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	Not applicable
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	p14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	p10
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	p15-16
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)	p16

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	p15
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not 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	p9-10, 20-21
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	p20
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	Not applicable
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	p12
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	p16
	31b	Authorship eligibility guidelines and any intended use of professional writers	p16
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not applicable
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Not applicable
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	Not applicable

*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.

BMJ Open

Study protocol for a randomised, placebo-controlled, single-blind phase II study of the efficacy of morphine for dyspnoea in patients with interstitial lung disease (JORTC-PAL 15)

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-043156.R1
Article Type:	Protocol
Date Submitted by the Author:	16-Feb-2021
Complete List of Authors:	Matsuda, Yoshinobu; National Hospital Organisation Kinki Chuo Chest Medical Center Department of Psychosomatic Internal Medicine Morita, Tatsuya; Seirei Mikatahara Hospital, Palliative and Supportive Care Oyamada, Shunsuke; Japanese Organisation for Research and Treatment of Cancer, Biostatictics Ariyoshi, Keisuke; Institute of Medical Science, The University of Tokyo, Palliative Medicine Yamaguchi, Takuhiro; Division of Biostatistics, Iwase, Satoru; Institute of Medical Science, The University of Tokyo,, Department of Palliative Medicine
Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	Palliative care, Respiratory medicine
Keywords:	Interstitial lung disease < THORACIC MEDICINE, PALLIATIVE CARE, Clinical trials < THERAPEUTICS

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Study protocol for a randomised, placebo-controlled, single-blind phase II study of the efficacy of morphine for dyspnoea in patients with interstitial lung disease (JORTC-PAL 15)

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Word count: 2480

ABSTRACT

Introduction Dyspnoea is common in patients with interstitial lung disease (ILD) and often refractory to conventional treatment. Little is known about the efficacy of systemic morphine for dyspnoea in patients with ILD. The aim of this study is to estimate the efficacy of a single subcutaneous morphine injection for dyspnoea in patients with ILD.

Methods and analysis We will conduct a multicentre, prospective, randomised, placebo-controlled, single-blinded phase II study of a single subcutaneous morphine injection for dyspnoea in patients with ILD. Inpatients with ILD who have dyspnoea at rest refractory to conventional treatment will be eligible for participation in this study. The morphine dose will be 2 mg. The primary endpoint is changes in dyspnoea intensity from baseline to 60 minutes after treatment as measured using an 11-point numerical rating scale and compared between the morphine and placebo groups.

Ethics and dissemination Ethical approval has been obtained by the Osaka City University Certified Review Board. The results of this study will be submitted for publication in an international peer-reviewed journal and the findings will be presented at international scientific conferences.

Trial registration number jRCTs051190030; Pre-results.

Protocol version 1.21, 24 July 2019

Strengths and limitations of this study

- This is one of the few studies estimating the efficacy of systemic morphine for dyspnoea in patients with interstitial lung disease.
- This study has a rigorous design including randomisation, a placebo control group, and blinding of participants.
- This is a single-blinded study.
- The observation period is short, i.e., efficacy is assessed within 60 minutes after treatment and monitoring for adverse events is performed for 24 hours after treatment.

INTRODUCTION

Interstitial lung diseases (ILDs) are a heterogeneous group of lung diseases that affect the pulmonary interstitium. They include connective tissue disease-associated ILD, drug-induced ILD, occupational and environmental ILD, sarcoidosis, and idiopathic interstitial pneumonias.[1] A population-based registry study has shown that the prevalence of ILD was 80.9 per 100,000 in men and 67.2 per 100,000 in women.[2] ILD is often fatal or difficult to cure[3 4]; therefore, palliative care is essential for patients with ILD. However, palliative care available for patients with ILD is insufficient compared to that for patients with cancer.[5 6]

Dyspnoea is the most frequent and burdensome symptom in patients with ILD,[7 8] and it is associated with a decreased quality of life.[9-14] Multiple empirical studies and systematic reviews have confirmed that morphine is effective for refractory dyspnoea in patients with chronic breathlessness predominantly caused by cancer and chronic obstructive pulmonary disease.[15-18] On the other hand, studies on the efficacy and safety of morphine in patients with ILD are limited. A case series of patients with end-stage idiopathic pulmonary fibrosis has reported that diamorphine is an effective treatment for dyspnoea.[19] A few retrospective studies have also suggested that morphine is effective in treating dyspnoea in terminally ill patients with interstitial pneumonia.[20 21] A

randomised controlled trial found that oral morphine did not significantly reduce dyspnoea compared with placebo in patients with fibrotic ILD.[22] To the best of our knowledge, no published prospective study other than the one mentioned above has examined the efficacy and safety of systemic morphine for dyspnoea in patients with ILD.[23-25] From the Phase I study we conducted to investigate the safety of systemic morphine and determine the recommended dose of morphine to be used in further clinical trials, we reported that the recommended dose of single subcutaneous morphine for dyspnoea in patients with ILD is 2 mg.[26] The aim of this study is to estimate the efficacy of a single subcutaneous morphine injection for dyspnoea in patients with ILD.

METHODS AND ANALYSIS

Study design

This is a multicentre, prospective, randomised, placebo-controlled, single-blinded phase II study that will be performed to estimate the efficacy of morphine. The study design is summarized in Figure 1.

Study settings and participants

Participants will be recruited from nine hospitals across Japan.

The inclusion criteria are as follows: hospitalized patients who 1) are 20 years or older; 2) have been diagnosed with ILD by two respiratory physicians and one respiratory radiologist; 3) have dyspnoea at rest with numerical rating scale (NRS) ≥ 3 despite conventional treatment; 4) have an expected survival of 1 month or longer; 5) are capable of communication and do not have cognitive impairments; 6) have blood oxygen saturation levels (SpO_2) ≥ 90% (supplemental oxygen was allowed) and partial pressure of carbon dioxide ($PaCO_2$) ≤ 50 Torr; 7) have normal liver and renal function (aspartate aminotransferase [AST] ≤ 100 IU/L, alanine aminotransferase [ALT] ≤ 100 IU/L, total bilirubin [T-Bil] ≤ 2.0 mg/dL, and creatinine ≤ 2.0 mg/dL); and 8) have an ejection fraction ≥ 50% as confirmed on echocardiography.

ILDs in this study include idiopathic pulmonary fibrosis, idiopathic non-specific interstitial pneumonia (NSIP), unclassifiable idiopathic interstitial pneumonia, collagen vascular disease-related interstitial pneumonia, chronic hypersensitivity pneumonia, and pneumoconiosis. Idiopathic pulmonary fibrosis is diagnosed according to the criteria in the official American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Society statement.[27] NSIP and unclassifiable idiopathic interstitial pneumonia are diagnosed according to the criteria in the official American Thoracic Society/European Respiratory Society statement.[28]

The exclusion criteria are as follows: 1) patients with contraindications to morphine including allergy to morphine, 2) patients using opioids (if the patient is receiving any dose of codeine, that was discontinued 12 hours prior to the study treatment), 3) patients with acute respiratory failure, pneumothorax, or asthma attack, 4) patients with dyspnoea predominantly due to an active infection or lung cancer, 5) patients using invasive or non-invasive positive pressure ventilation, 6) patients with a current or past history of drug abuse, or 7) patients who are pregnant.

We do not exclude patients who use codeine because codeine is frequently used for cough in patients with ILD. We exclude other weak opioids such as tramadol.

Recruitment, randomisation, masking and follow-up

Recruitment

Potentially eligible patients will be screened by site investigators. Patients who fit the inclusion criteria will be invited to participate in the study.

Randomisation

During enrolment and after providing a written informed consent, patients will be randomly allocated to the intervention (morphine) or control (placebo) groups by a web-

based central randomisation system using minimisation methods and a computer-generated randomisation schedule with a 1:1 allocation ratio. In performing this allocation, we will minimise the following adjustment factors to avoid a large bias: (1) current dyspnoea intensity as measured using the NRS (≤ 6, ≥ 7), (2) codeine use (Yes, No), and (3) study site.

Masking

Patients will be blinded to the administration of morphine or placebo. The intervention will only be unblinded 60 minutes after treatment, if patients in the placebo group do not experience dyspnoea relief and wish to receive morphine. Clinicians and medical staff will be unblinded because the process of disposing opioids in Japan is very complex. However, the clinicians or medical staff who will check the self-administered questionnaire for current dyspnoea intensity (primary endpoint) will be blinded.

Data management, central monitoring and audit

Evaluation will be performed at five timepoints: enrolment; baseline; and 30 minutes, 60 minutes, and 24 hours after treatment. The timing and details of the assessments are shown in Table 1. The investigators at each study site will maintain records of each

patient as source data, which include signed informed consent forms, medical records, laboratory data and other records or notes. All data will be collected by the JORTC data centre. The JORTC data centre will oversee the intra-study data sharing process.

Clinical data entry, data management and central monitoring will be performed using the VIEDOC 4 (PCG Solutions, Sweden) electric data capture system. An interim analysis will not be performed. Auditing will not be done in this study.

Table 1 Study procedure and time point for evaluation

Time point	Inclusion	Baseline	30 minutes	60 minutes	24 hours
Consent, randomisation	✓				
Modified MRC scale	✓				
ECOG PS	✓				
Medicines History	✓				
Smoking History	✓				
Weight	✓				
AST, ALT, T-Bil, Cre	✓				
$PaCO_2$	✓				
Ejection fraction	✓				
NRS for current dyspnoea	✓	✓	✓	✓	
Vital signs		✓	✓	✓	
Oxygen		✓	✓	✓	
RASS		✓		✓	
Number of vomiting		←	—	→	
Adverse events		←	—	—	→

ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cre, creatinine; ECOG PS, European Cooperative Oncology Group Performance Status; MRC, Medical Research Council; NRS, Numerical Rating Scale; $PaCO_2$, arterial partial pressure of carbon dioxide; RASS, Richmond Agitation-Sedation Scale; T-Bil, total bilirubin.

Treatment

Interventions

Single subcutaneous injection of morphine 2 mg or placebo (normal saline 0.2 mL) will be performed. Injection will be performed by an unblinded physician. Patients in the placebo group who do not experience dyspnoea relief and who wish to receive morphine after the assessment performed 60 minutes after injection will be administered 2 mg of morphine. Following previous studies,[19 29] we decided to use subcutaneous injection, not oral preparations, for practical reasons, such as the feasibility of a placebo (normal saline) in future clinical trials, and simple logistics at the study site.

Cotreatments

Uniformity in oxygen flow rate and oxygen delivery device use will be maintained except in cases of unacceptable hypoxia. In addition, hypotensive drugs, diuretics, hypnotics, anxiolytics, and anti-psychotics will not be administered until one hour after treatment. Codeine use will be permitted until 12 hours before treatment. The use of inhaled bronchodilators and pulmonary rehabilitation will be restricted for 1 hour before and after treatment.

Data collection

Blood pressure, heart rate, respiratory rate, SpO_2, and oxygen requirement will be recorded at baseline and at 30 and 60 minutes after morphine administration. Furthermore, sedation (assessed using the Richmond Agitation Sedation Scale[30 31]), vomiting frequency (events/60 minutes), and the Common Terminology Criteria for Adverse Events (CTCAE) will be assessed at baseline and 60 minutes after drug

administration. In addition, the CTCAE of all patients will be recorded for 24 hours following drug administration.

Measures

Demographics and clinical characteristics

Participants' sex, age, body weight, type of ILD, concomitant drug use (corticosteroids, immunosupressants, anti-fibrotic agents, bronchodilators, pulmonary vasodilators, anxiolytics, and codeine), the modified Medical Research Council Dyspnea scale,[32] the European Cooperative Oncology Group Performance Status, ejection fraction on echocardiography, $PaCO_2$, SpO_2, oxygen flow rate, oxygen delivery devices, AST, ALT, T-Bil, creatinine, and current dyspnoea intensity at rest in the NRS will be assessed before enrolment.

Numerical Rating Scale

Current dyspnoea intensity will be assessed using an 11-point Likert-type NRS from 0 (no dyspnoea) to 10 (worst possible dyspnoea).[33]

Richmond Agitation-Sedation Scale (RASS)

Agitation and sedation will be assessed using the RASS. The RASS is a validated 10-point scale that ranges from -5 (unarousable) to +4 (combative).[30 31]

Common Terminology Criteria for Adverse Events

The worst grade of an adverse event (AE) during the preceding period will be assessed using the CTCAE V.5.0, Japanese Clinical Oncology Group version. Three AEs

including somnolence, nausea, and delirium will be investigated because they occur at a relatively high frequency. Other AEs may also be assessed.

Study endpoints

Primary endpoint

The primary endpoint is the changes in dyspnoea intensity at rest from baseline to 60 minutes after treatment as measured using the NRS and compared between the morphine and placebo groups.

Secondary endpoints

The secondary endpoints include the following: 1) changes in dyspnoea intensity at rest from baseline to 30 minutes after treatment as measured using the NRS between the morphine and placebo groups; 2) percentage of patients with NRS $\geq$ 1 improvement in dyspnoea intensity at rest from baseline to 60 minutes after treatment and compared between the morphine and placebo groups; 3) respiratory rate; 4) blood pressure; 5) SpO_2; 6) heart rate; 7) the frequency of vomiting; 8) RASS; 9) adverse events from baseline to 24 hours after treatment.

Safety

Investigators will record all AEs in electronic data capture systems. All AEs will be followed up throughout the course. All severe AEs will be reported to the Certified Review Board and investigators at all sites and discussed.

Statistical considerations

Statistical analysis

Comparison of the primary endpoint of changes in NRS score for dyspnoea from baseline to 60 minutes after treatment between the morphine and placebo groups will be conducted using the two-sided Student's t-test or Wilcoxon rank-sum test, as appropriate, at a significance level of 5% according to the intention-to-treat principle. Point estimates and 95% confidence intervals (Cis) for the difference between two group means will be calculated.

Comparison of the secondary endpoint of changes in NRS score for dyspnoea from baseline to 30 minutes after treatment between the morphine and placebo groups will be evaluated similarly to the primary endpoint. Comparison of the rates of patients who experienced improvement in the NRS of ≥ 1 from baseline to 30 minutes or 60 minutes after treatment will be evaluated using the chi-square test or Fisher's exact test. Point estimates and 95% CIs for the difference between two means will be calculated. A full statistical analysis plan (including the handling of missing values) will be written prior to the data evaluation. We will report adverse events separately for patients who receive placebo alone and for those who receive placebo followed by morphine.

Sample size calculation

The aim of this study is to estimate the efficacy of morphine for dyspnoea in patients with ILDs and gain the data to calculate the sample size for future phase III study. Therefore, we set the sample size as all patients we will be able to enrol during the three-year scheduled period. We plan to recruit 50 patients (25 patients in each group).

Patient and public involvement

Patients and the public will not be involved in this study. However, the Certified Review Board included a representative of a patient group as a member to assess our protocol.

Ethics and dissemination

Ethics

All patients will be required to provide a written informed consent. The study will be conducted in accordance with the Declaration of Helsinki and the Clinical Trials Act. The protocol was approved by the Osaka City University Certified Review Board (CRB; approved number OCU0006). This trial has been registered at the Japan Registry of Clinical Trials (jRCT) as jRCTs051190030. This study protocol adheres to SPIRIT 2013. Modifications in the study protocol will be communicated to the CRB as well as the independent data monitoring committee of the JORTC.

Dissemination

The results of this study will be submitted for publication in international peer-reviewed journals and the key findings will be presented at national and international conferences. Authorship will be ascribed in accordance with the International Committee of Medical Journal Editors guidelines.

DISCUSSION

This study protocol describes multicentre, prospective, randomised, placebo-controlled, single-blinded phase II study of morphine against dyspnoea in patients with ILDs. In this phase II study, we expect to obtain data to estimate the efficacy of a single

subcutaneous injection of morphine for dyspnoea in patients with ILD and be able to use the data to calculate the sample size for the phase Ⅲ study.

Recently, Kronborg-White et al. found in a randomised controlled trial that oral morphine did not significantly reduce dyspnoea compared with placebo in patients with fibrotic ILD.[17] Despite similarities between their trial and our study, there are some differences. First, their trial included outpatients with Medical Research Council scores of ≥ 3, while our study included inpatients with dyspnoea at rest in NRS ≥ 3. Therefore the patients in our study would be at a more terminal stage of their illness than the patients in their study. Second, the primary endpoint of their study was dyspnoea during the past week, whereas we plan to assess current dyspnoea at rest. Furthermore, trial conducted by Kronborg-White et al. was small, and theirs was a single-centre study. Therefore the efficacy of morphine for dyspnoea in patients with ILD should be evaluated in other studies such as ours.

The strengths of this study are as follows: first, this is one of the few studies to assess the efficacy of morphine for dyspnoea in patients with ILD. Second, this study is a randomised placebo-controlled study; therefore, we can compare the efficacy of morphine with placebo even though this is phase II study.

Several issues related to the content of the trial require discussion. First, this is a single-blinded trial. Clinicians and medical staff, except those who check the self-administered sheet, will be unblinded. If clinicians and medical staff are blinded, other unblinded clinicians or medical staff will be needed to dispose of the treatment drug, i.e., morphine or normal saline. To minimize the burden on the clinicians and medical staff at each site, we decided that the clinicians and medical staff would be unblinded. However, the primary endpoint will be assessed using a self-administered sheet and

checked by blinded clinicians or medical staff. Thus, the effect of un-blinded clinicians or staff will be minimised. Second, the observation period in our study is short, i.e., efficacy is assessed within 60 minutes after treatment and monitoring for AEs is performed for 24 hours after treatment. This is because we assume the patients with ILD in this study to be vulnerable, and longer study periods may result in decreased feasibility; treatments other than morphine could be changed and supplemental oxygen could be provided. Finally, we will not exclude patients who use codeine because many patients with ILD use codeine for cough. However, codeine will be discontinued for 12 hours prior to the study intervention to minimize its effect on dyspnoea.

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Authors' Contributions

YM is lead author of the study protocol and principal investigator. YM, TM, SO, KA, TY, and SI participated in the design of the study. SO and TY designed the statistical analysis plan. All authors contributed to writing and revising the manuscript critically, and all gave their final approval of the version to be published.

Funding statement

This work was supported by the following grants: 2018–2020 Grant-in-Aid for Scientific Research (Grant-in-Aid for Young Scientists B; grant number 17K15909) and Osaka Medical Research Foundation for Intractable Diseases (grant number 23-2-41). The funders had no role in the study design and will have no role in the data collection, analysis, or dissemination of study results.

Competing interests None declared.

Trial status

The enrolment started in June 2019. At the time of manuscript submission (February 2021), 26 patients have participated. We expect to complete the recruitment by March 2022.

Confidentially

Data will be retained in accordance with the Clinical Trials Act. Participants will be allocated a unique identification (ID) number at enrolment. The master list linking participant personal information and ID number will be maintained in a paper file or

password-protected hard drive in a locked room at each institution. Data will be analysed by ID number only. Records will be retained for five years after study completion and then destroyed by the JORTC data centre.

Acknowledgements

This work was supported by the following grants: 2018–2020 Grant-in-Aid for Scientific Research (Grant-in-Aid for Young Scientists B; grant number 17K15909) and Osaka Medical Research Foundation for Intractable Diseases (grant number 23-2-41).

Figure Legend

Figure 1 Flow chart of the study procedures. Participants will be randomised (1:1 allocation ratio) into the morphine group or the placebo group. Assessment will be made at baseline and at 30 minutes, 60 minutes, and 24 hours after treamtment. AEs, Adverse Events; ILD, Interstitial Lung Disease; IPPV, Invasive Positive Pressure Ventilation; NPPV, Non-invasive Positive Pressure Ventilation; RASS, Richmond Agitation Sedation Scale.

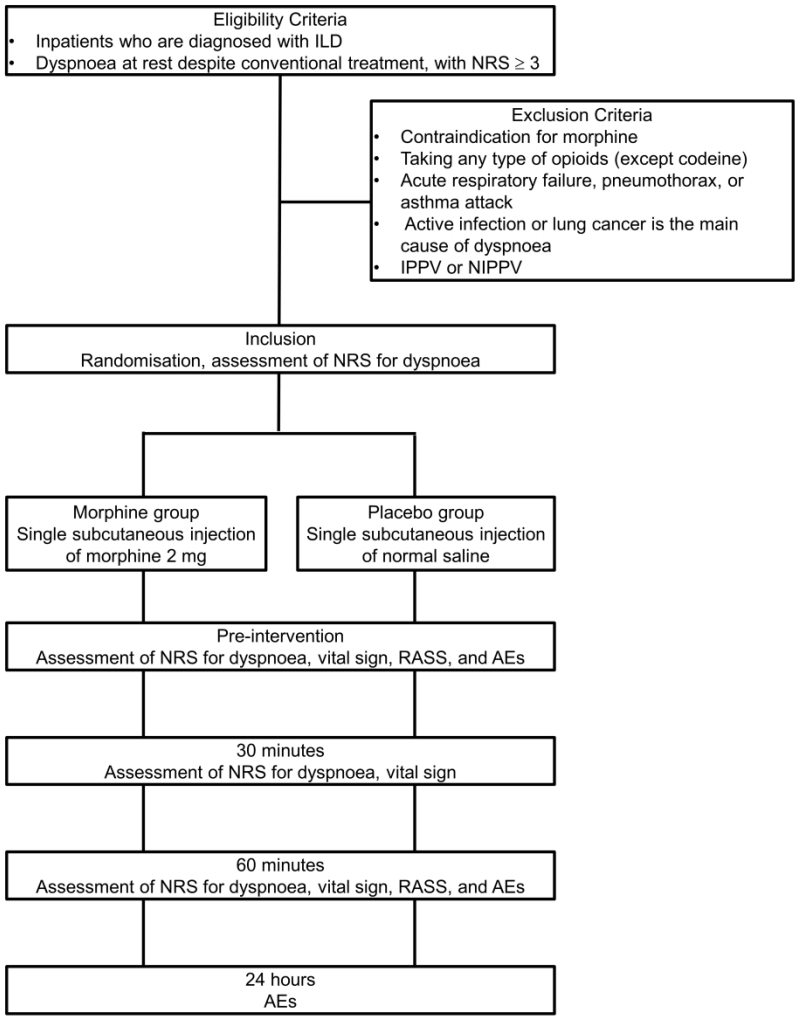

Figure 1 Flow chart of the procedures in the study. Participants will be randomized (1:1 allocation ratio) into the morphine group or the placebo group. Assessment will be made at baseline, 30 minutes, 60 minutes, and 24 hours. AEs, Adverse Events; ILD, Interstitial Lung Disease; IPPV, Invasive Positive Pressure Ventilation; NPPV, Non-invasive Positive Pressure Ventilation; RASS, Richmond Agitation Sedation Scale.

274x383mm (350 x 350 DPI)

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	p1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	p3
	2b	All items from the World Health Organization Trial Registration Data Set	Not applicable
Protocol version	3	Date and version identifier	p3
Funding	4	Sources and types of financial, material, and other support	p20
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	p1, 20
	5b	Name and contact information for the trial sponsor	Not applicable
	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	p20
	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)	p9

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	p5-6
	6b	Explanation for choice of comparators	p12
Objectives	7	Specific objectives or hypotheses	p6
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)	p6
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	p6-7
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)	p6-7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	p12
	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)	Not applicable
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Not applicable
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	p12
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	p13-14
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)	p12-13

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	p15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	p8
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	p8
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	p8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	p8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	p9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	p9
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	p12-13
	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	Not applicable

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	p8-9
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	p14-15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Not applicable
	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)	p15
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	p16
	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	Not applicable
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	p14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	p10
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	p15-16
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)	p16

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	p15
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not 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	p9-10, 20-21
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	p20
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	Not applicable
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	p12
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	p16
	31b	Authorship eligibility guidelines and any intended use of professional writers	p16
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not applicable
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Not applicable
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	Not applicable

*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.