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Morphine and BrEathLessness trial (MABEL)

Submission date
31/01/2019

Recruitment status
No longer recruiting

Registration date
25/02/2019

Overall study status
Completed

Last Edited
26/11/2026

Condition category
Respiratory

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Chronic breathlessness affects most people with advanced lung cancer, lung fibrosis, chronic obstructive pulmonary disease (COPD), emphysema, and heart failure. People are often disabled by this long-term breathlessness despite best treatments of the underlying condition(s). Chronic breathlessness is frightening for patients and their families. It reduces quality of life, limits how people manage at home with everyday functions (bathing, dressing, preparing food) and at work, increases the number of emergency hospital visits and admissions, and shortens life (although some people may live with chronic breathlessness for many years). Studies of a few days of regular, low doses of ”long-acting” morphine show that this can help reduce chronic breathlessness safely, particularly for people with COPD - but we don't know if it keeps working when used for longer periods, or if it does any harm in the longer term. At present, some doctors will prescribe morphine for breathlessness and others won’t.
We will test if regular, low dose morphine capsules regularly twice a day are better than placebo (dummy) ones for chronic breathlessness and whether morphine improves daily activity in 158 people. We will also see any effect on the need to go to accident and emergency, call an ambulance, phone a GP after hours, or go into hospital. We will cost this care and, if it works, find the best ways to provide long-acting morphine to people who need it and would safely benefit from it.

Who can participate?
Men and women with chronic (long-lasting) breathlessness due to heart or lung disease or cancer or following COVID-19 that continues despite best treatment of their underlying disease.

What does the study involve?
People with fully treated disease still causing chronic breathlessness participating in the study will be chosen at random to have either morphine or a placebo capsule twice a day for two months. After a week, the dose will be increased if breathlessness isn’t improving and they don’t want to stop because of side-effects. At the end, participants can try morphine as part of their usual care if they want, while being followed up by the study team. We will judge success on how participants’ worst daily breathlessness feels. We will also measure how much activity they actually do (daily step count using a small monitor worn on the wrist), quality of life, how well the person sleeps, possible side-effects, overall ability to function, use of healthcare services and - as the study includes people with serious illness - survival. Family members will also be able to help by completing questionnaires telling us about caring for someone with breathlessness.

Alongside the study, we will ask clinicians and study participants about issues which would help or hinder patients to have routine access to regular, low dose morphine for breathlessness if the study shows it is the better treatment.

Participant consent and study assessments will be conducted by the research team via telephone, video call, at a home visit or when attending routine clinic. Participants will complete the study questionnaires and measures when needed (the research nurse will help) and continue with any treatment the usual medical team advises. The activity monitor will be worn for 7 days before the study starts and again during the last 7 days of the first month.

What are the possible benefits and risks of participating?
Although this study may not directly benefit participants, it may improve future treatment of breathlessness. Morphine has been used in medical practice for many years. We therefore know what side-effects might occur. Most patients cope very well with the low doses of morphine that we intend to use. We will check regularly about the known side effects that people can get. These include nausea or feeling sick, constipation or sleepiness. In some people concentration may be affected until they get used to the steady dose after a few days. Therefore participants will be advised to observe the usual warnings about operating machinery or driving during the first week of taking the medicine. After this time they should carefully consider whether concentration is affected before driving - if in doubt, they should not drive. If side effects persist which may affect driving, participants would need to inform the DVLA if they wished to continue with study medication. As with any other change in medication, participants should inform their motor insurance company to ensure cover is valid. Although people may worry about becoming addicted to morphine, we rarely see this in people who take it for health reasons. However, if the body has become accustomed to morphine over time, then it may take a few days to readjust when morphine is stopped. This is not expected to be an issue with this study but all participants will receive a phone call in the few days after the end of the study to check all is well.

Where is the study run from?
The study is run by the Hull Health Trial Unit (HHTU) on behalf of the sponsor (Hull University Teaching Hospitals NHS Trust) and Chief Investigator (Prof. Miriam Johnson, University of Hull). About 14 centres in the United Kingdom will be involved with each centre recruiting about 1-2 participants per month.

When is the study starting and how long is it expected to run for?
March 2019 to January 2024

Who is funding the study?
National Institute for Health Research Health Technology Assessment (NIHR HTA) (UK)

Who is the main contact?
Professor Marie Fallon, marie.fallon@ed.ac.uk

Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2019-002479-33

Integrated Research Application System (IRAS)
263087

Protocol serial number
R2377

Study information

Scientific Title
A parallel group, double-blind, randomised, placebo-controlled trial comparing the effectiveness and cost effectiveness of low dose oral modified release morphine versus placebo on patient-reported worst breathlessness in people with chronic breathlessness.

Acronym
MABEL

Study objectives
The null hypothesis is that there is no difference in the relief of chronic breathlessness in people with heart or lung disease or cancer provided by morphine or placebo.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 03/12/2019, North East – Tyne & Wear South Research Ethics Committee (NHSBT Newcastle Blood Donor Centre, Holland Drive, Newcastle upon Tyne, NE2 4NQ; +44 (0)207 1048084; nrescommittee.northeast-tyneandwearsouth@nhs.net), ref: 19/NE/0284

Primary study design
Interventional

Allocation
Randomized controlled trial

Masking
Blinded (masking used)

Control
Placebo

Assignment
Parallel

Purpose
Treatment

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Chronic breathlessness due to heart disease, lung disease or cancer or post-COVID breathlessness

Interventions
Randomised patients will receive either modified release morphine 5 mg capsules twice daily with docusate laxative 100 mg capsules twice daily (intervention arm 1) or placebo “5mg” morphine capsules twice daily and placebo docusate laxative capsules twice daily (intervention arm 2). To maintain blinding active drug and placebo capsules and their packaging will look the same.
The dose may be increased to 10 mg twice daily if the participant does not achieve an improvement (reduction) from baseline in the primary outcome measures (worst breathlessness over the past 24 hours – 0 to 10 numerical rating scale (NRS)) and the participant had acceptable side-effects (see definition of acceptable side-effects below). The decision to dose escalate will

be made if the NRS measure has not improved by at least one point at the day 7 assessment. The dose increase will start on day 15 to allow time for the prescription to be issued, dispensed and new dose to be supplied to the participant in a manner which ensures continuous drug supply. Whilst awaiting the new dose, the participant will continue on 5 mg twice daily.

Dose titration applies only if the participant has acceptable side-effects

The morphine preparation is MST Continus, encapsulated for blinding purposes.

Each participant will take the study medication for two months.

Acceptable side-effects in this trial are defined as:
1. No side-effects (all CTCAE grades 0)
OR
2. i) Gastro-intestinal effects acceptable (nausea, vomiting, constipation CTCAE grades ≤2) AND neuro-cognitive effects acceptable (cognition, memory, hallucinations CTCAE grade 0 AND no vivid dreams; grade 1 symptoms acceptable if present at the same grade at baseline);
ii) AND there is ongoing side-effect management and monitoring;
iii) AND both clinician and participant are happy to continue or increase IMP as appropriate

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Modified-release morphine, sodium docusate

Primary outcome(s)
The amount of breathlessness at its most over the previous 24 h (worst breathlessness) measured at day 28 using a 0–10 numerical rating scale (NRS) where 0 = no breathlessness and 10 = the most imaginable breathlessness).

Key secondary outcome(s)
Current secondary outcome measures as of 19/02/2021:
All measured at baseline, and day 2, 4, 7, 14, 28, 56
1. Distress due to breathlessness using 0-10 NRS distress/past 24 h
2. Assessment of related symptoms using 0-10 NRS (pain, cough) and quality of sleep (Epworth Sleepiness Scale); sleepiness using the Karolinska Sleepiness Scale (KSS)
3. Assessment of physical activity (daily steps Actigraphy monitor); performance status (Australia modified Karnofsky Performance Status (AKPS) and cognitive function (St Louis University Mental Status (SLUMS)
4. Quality of life (SF-12)
5. Health economic assessment (EQ5D; EQVAS; ICECAP; service utilisation)
6. Harms, including survival
7. Carer burden (Zarit 12; VOICES survey for those bereaved during the study time course
8. Opioid withdrawal: Subjective opioid withdrawal scale (SOWS)

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6. Harms, including survival
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8. Opioid withdrawal: Subjective opioid withdrawal scale (SOWS)

Completion date
31/01/2024

Eligibility

Key inclusion criteria
Current participant inclusion criteria as of 19/02/2021:
1. Ambulant people with chronic breathlessness due to the following conditions. Chronic breathlessness is defined as those with persistent disabling breathlessness despite optimum treatment (as described) of their underlying disease in the opinion of the identified clinician.
1.1. Chronic heart failure (New York Heart Association (NYHA) class III or IV) [HFPEF or HFNEF] with left ventricular dysfunction only and meets all of the following:
1.1.1. Reached target dose (or be on maximally tolerated dose, or be intolerant) of an inhibitor of the renin-angiotensin system (including ARNIs) shown to improve prognosis
1.1.2. Reached target dose (or be on maximally tolerated dose, or be intolerant) of a beta adrenoceptor antagonist shown to improve prognosis
1.1.3. Reached target dose (or be on maximally tolerated dose, or be intolerant) of an aldosterone antagonist
1.2. Chronic obstructive pulmonary disease (COPD) or interstitial lung diseases (ILD) and receiving optimum treatment as follows (based on NICE idiopathic pulmonary fibrosis (IPF) /pirfenidone/nintedanib guidelines, British Thoracic Society ILD guidelines [includes CTD-associated ILD], American Thoracic Society (ATS)/European Respiratory Society (ERS) guideline for IPF):
1.2.1. On optimal immunosuppression for connective tissue disease (CTD) ILD
1.2.2. On anti-fibrotic drug therapy (pirfenidone or nintedanib) for IPF if suitable.
1.2.3. On oxygen therapy (long term or ambulatory) if they fulfill guideline criteria 6
1.2.4. On appropriate treatment for pulmonary hypertension, if applicable
1.3. Post-COVID chronic breathlessness
1.4. Cancer. People with cancer, of any stage (0-4) may be included only if they are opioid naïve (as defined in the exclusion criteria) as there are insufficient data to guide dosing of opioids for breathlessness in people already taking opioids for pain.
2. Breathlessness severity defined as modified Medical Research Council (mMRC) breathlessness scale grade 3 or 4 (i.e. stops for breath after walking about 100 yards or after a few minutes on level ground, or is too breathless to leave the house or is breathless when dressing). A pooled data study shows that people with worse baseline breathlessness are more likely to respond to opioids. A phase 3 trial in people with COPD showed that those with mMRC grade 3 or 4 were more likely to respond to opioids. This approach also concurs with clinical recommendations.

3. Male or female aged ≥18 years
4. Management of the underlying condition unchanged for the previous 7 days. This, and criterion 5, excludes the very unstable patient who is unlikely to complete the 56-day RCT phase.
5. Australia-modified Karnofsky Performance Scale (AKPS) ≥40. This, with criterion 4, is to identify patients most likely to complete the 2 months RCT phase.
6. Estimated Glomerular Filtration Rate (eGFR) of 25 ml/min or more, unless the primary diagnosis is heart failure (≥30 ml/min). Renal clearance of eGFR ≥25 ml/min is adequate for the study doses of morphine, however, in heart failure patients are more likely to have fluctuations in renal function for which the higher level will allow.
7. If female and of child-bearing potential, must agree to use adequate contraception when taking IMP and for 7 days following cessation. Contraceptive methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include:
7.1. Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
7.1.1. Oral
7.1.2. Intravaginal
7.1.3. Transdermal
7.2. Progestogen-only hormonal contraception associated with inhibition of ovulation:
7.2.1. Oral
7.2.2. Injectable
7.2.3. Implantable
7.3. Intrauterine device (IUD)
7.4. Intrauterine hormone-releasing system (IUS)
7.5. Bilateral tubal occlusion
7.6. Vasectomised partner
7.7. Sexual abstinence
8. Able to complete questionnaires and trial assessments
9. Able to provide written informed consent

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Previous participant inclusion criteria:
1. Ambulant people with chronic breathlessness due to cardiac, respiratory disease or cancer*. Chronic breathlessness is defined as those with persistent disabling breathlessness despite optimum treatment** of their underlying disease in the opinion of the identified clinician.
2. Breathlessness severity defined as modified Medical Research Council (mMRC) breathlessness scale grade 3 or 4 (i.e. stops for breath after walking about 100 yards or after a few minutes on level ground, or is too breathless to leave the house or is breathless when dressing). A pooled data study shows that people with worse baseline breathlessness are more likely to respond to opioids. A phase 3 trial in people with COPD showed that those with mMRC grade 3 or 4 were more likely to respond to opioids. This approach also concurs with clinical recommendations.
3. Male or female aged ≥ 18 years old
4. Management of the underlying condition unchanged for the previous 1 week. This, and criterion 5, excludes the very unstable patient who is unlikely to complete the 8 week RCT phase.
5. Australia-modified Karnofsky Performance Scale (AKPS) ≥40. This, with criterion 4, is to identify patients most likely to complete the 2 months RCT phase.
6. Estimated Glomerular Filtration Rate (eGFR) of 25 ml/min or more, unless the primary diagnosis is heart failure (≥ 30 ml/min). Renal clearance of eGFR ≥25 ml/min is adequate for the study doses of morphine, however, in heart failure patients are more likely to have fluctuations in renal function for which the higher level will allow.
7. If female and of child-bearing potential, must agree to use adequate contraception when

taking IMP and for 7 days following cessation
8. Able to complete questionnaires and trial assessments
9. Willing to stop wearing any personal activity meter during the actigraphy attachment period.
10. Able to provide written informed consent

* People with cancer may be included only if they are opioid naïve (as defined in the exclusion criteria) as there are insufficient data to guide dosing of opioids for breathlessness in people already taking opioids for pain.
Eligible cardio-respiratory diseases: chronic obstructive pulmonary disease (COPD); interstitial lung diseases (ILD); chronic heart failure (New York Heart Association (NYHA) class III or IV) [HFPEF or HFNEF]
**Optimum tolerated treatment is defined according to condition:
The assessment of whether the participant is receiving optimal treatment for their underlying disease is to be made by the identifying clinician and should be based on the following guidance (unless specific contra-indications):
1. For COPD or ILD***
2. For COPD or ILD***
2.1 On optimal immunosuppression for Connective Tissue Disease (CTD) ILD
2.2 On anti-fibrotic drug therapy (Pirfenidone or Nintedanib) for IPF if suitable.
2.3 On oxygen therapy (long term or ambulatory) if they fulfill guideline criteria 61
2.4 On appropriate treatment for pulmonary hypertension, if applicable
3. For heart failure (left ventricular dysfunction only):
3.1 Reached target dose (or be on maximally tolerated dose, or be intolerant) of an inhibitor of the renin-angiotensin system (including ARNIs) shown to improve prognosis;
AND
3.2 Reached target dose (or be on maximally tolerated dose, or be intolerant) of a beta adrenoceptor antagonist shown to improve prognosis;
AND
3.3 Reached target dose (or be on maximally tolerated dose, or be intolerant) of an aldosterone antagonist.
*** Based on NICE Idiopathic Pulmonary Fibrosis (IPF) / pirfenidone/ nintedanib guidelines, British Thoracic Society ILD guidelines (includes CTD assoc ILD), American Thoracic Society (ATS) / European Respiratory Society (ERS) guideline IPF.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 Years

Upper age limit
100 Years

Sex
All

Total final enrolment
143

Key exclusion criteria
Current participant exclusion criteria as of 19/02/2021:
1. Unable to provide informed consent
2. Unable to complete baseline study questionnaires even with the assistance of the study nurse
3. Presence of co-existing malignant disease, only if this would affect the study in the investigator's opinion
4. Used opioid medications >5 mg morphine-equivalents daily for >7 out of last 14 days
5. Morphine or docusate allergies or hypersensitivity to any of the tablet constituents as assessed by a clinician
6. Central hypoventilation syndrome (e.g. Ondine’s curse post-stroke)
7. Involved in another medicinal trial (CTIMP) within the past 4 weeks
8. Pregnant or lactating
9. Respiratory depression, head injury, paralytic ileus, 'acute abdomen', acute hepatic disease
10. Concurrent administration of monoamine oxidase inhibitors or are within 2 weeks of discontinuation of their use
11. Within first 24 h post-operation
12. Are taking >20 mg diazepam or equivalent/day, or are unable to reduce dose before randomisation to <20 mg/day for the duration of the study treatment period
13. Persons who cannot or do not wish to take gelatin (used as a medication encapsulation ingredient)

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5. Morphine or docusate allergies or hypersensitivity to any of the tablet constituents as assessed by a clinician
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Date of first enrolment
01/03/2021

Date of final enrolment
31/10/2023

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Hull and York Medical School
University of Hull
Hull
England
HU6 7RX

Sponsor information

Organisation
Hull University Teaching Hospitals NHS Trust (UK)

ROR
https://ror.org/01b11x021

Funder(s)

Funder type
Government

Funder Name
Health Technology Assessment Programme

Alternative Name(s)
NIHR Health Technology Assessment Programme, Health Technology Assessment (HTA), HTA

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary

Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		28/09/2025	07/10/2025	Yes	No
Protocol article		15/06/2023	07/10/2025	Yes	No
Abstract results		10/10/2024	07/10/2025	No	No
HRA research summary			28/06/2023	No	No
Other publications	Health economic evaluation	04/11/2025	18/11/2025	Yes	No
Participant information sheet	version V1.2	04/06/2020	23/02/2021	No	Yes
Participant information sheet	version V1.2	04/06/2020	23/02/2021	No	Yes
Protocol (other)	V1.10	10/10/2023	26/11/2026	No	No
Protocol file	version V1.4	08/12/2020	23/02/2021	No	No