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FULL/LONG TITLE OF THE TRIAL

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.

SHORT STUDY TITLE / ACRONYM

Morphine And BrEathLessness trial (MABEL)

This protocol has regard for the HRA guidance and order of content (version 1.1 January 2015)

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PROTOCOL VERSION NUMBER AND DATE

Version 1.10 10.10.2023

SPONSOR / CO-SPONSORS / JOINT-SPONSORS

Hull University Teaching Hospitals NHS Trust

RESEARCH REFERENCE NUMBERS

IRAS Number: 263087

REC Number: 19/NE/0284

EudraCT Number: 2019-002479-33

ISRCTN Number: 87329095

SPONSORS Number: R2377

FUNDERS Number: 17/34/01

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SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: DocuSigned by: James Illingworth 3DDA0F96873F430... Date: ...../...../.....

Name (please print): James Illingworth 16-Oct-2023 | 16:15 BST

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Chief Investigator: Professor Marie Fallon

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Position: Statistician

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Protocol V1.8 31/01/2022 changes

Page 29:	Amended text: "*physical activity*"
Page 32:	Amended text from "*research nurse*" to "*study team*"
Page 37:	Amended text from "*month*" to "*quarter*"
Page 37:	Added text: "*are approached but not consented and those who are consented but not randomised*"
Page 37:	Amended text to clarify consent process and responsibilities *"or delegated study doctor. If eligible, the study doctor will proceed to obtain written informed consent from the patient in accordance with GCP. With Sponsor approval, … may be permitted to consent. However, Sponsor approval must be sought before a PI can delegate informed consent responsibility to a non-GMC registered team member. If the Independent Prescriber is also the site PI, this must be approved by the Sponsor in the site set up stage.*
Page 38:	Amended text to clarify consent process and responsibilities: "...*study doctor or Sponsor approved Independent prescriber listed on the Delegation Log who has received GCP training. See section 7.1.2.1 for more details on who else may be permitted to take consent.*"
Page 38:	Amended text from "*PI*" to "*person taking consent*"
Page 47:	Added text "*or sponsor approved registered independent prescriber*"
Page 49:	Added text "*Only a study doctor listed on the delegation log can make the decision to dose escalate IMP to 10mg (or not) on Day 7*"
Page 50:	Changed text in flow diagram – SN replaced with study doctor
Page 52:	Amended text from "*morphine sulfate immediate release solution*" to "*an opioid (either weak or strong), for breathlessness, cough or pain…*"
Page 53:	Amended text "*study team*"
Page 53:	Added text: " *If the participant or carer returns the bottles directly to the dispensing pharmacist, the trial pharmacy team will count the number of returned unused capsules and inform the study team so that the drug accountability form can be completed in the e-CRF"*

Protocol V1.9 30.04.2023 changes

Page 14	*Added text: "(use the difference between baseline and Day 7 NRS worse breathlessness scores)"*
Page 42	*Added text: "for 18 months …whichever is earliest"*
Page 49	*Added text: "at Day 7 from the baseline measure"*

Protocol V1.10 10.10.2023 changes

Page 6	*Amended text: Co applicant and Trial Coordinator details updated*
Page 67	*Amended text: "25 years"*

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STUDY LAY SUMMARY

WHY THIS IS IMPORTANT?

Chronic breathlessness affects most people with advanced lung cancer, lung fibrosis, COPD (chronic obstructive pulmonary disease; 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.

WHAT WE PLAN TO DO

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 & 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.

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 from their GP or usual hospital doctor, 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), 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.

WHAT WILL WE ACHIEVE?

If the study shows that morphine helps, and doesn’t harm, we want all suitable patients to be able to have access to it. However, we know some doctors, nurses, patients and carers may have concerns about morphine, so we will find out what support is needed to make sure morphine is available, and used carefully and in accordance with the evidence.

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TRIAL SUMMARY

Trial Title	Morphine And BrEathLessness trial	
Short title	MABEL	
Clinical Phase	3	
Trial Design	Double blind, placebo controlled	
Trial Participants	Patients with chronic breathlessness due to cardio-respiratory disease, post COVID-19 breathlessness or cancer	
Planned Sample Size	158	
Treatment duration	56 days	
Follow up duration	Follow-up is 3 monthly until last recruit has reached Day 56. After which optional open label morphine will be offered to those participants interested. There will be 3 monthly data collection of symptoms and side effects for these participants	
Planned Trial Period	30 months	
	Objectives	Outcome Measures
Primary	Evaluate the effectiveness of low dose oral modified-release morphine on worst breathlessness / 24 hours at Day 28.	Breathlessness (NRS worst breathlessness / 24 hours at 4 weeks) measured at baseline, Days 7, 14, 20 and 28
Secondary	i) Placebo-controlled net effects (benefits-side-effects balance) beyond 7 days with blinded side-effects data up to 2 months ii) Net benefit in the population in addition to people with COPD iii) Net effect on longer term changes in physical activity, function and quality of life if chronic breathlessness is reduced iv) Longer term impact on health service use, especially days as a hospital inpatient unplanned health service contact and to assess any potential re-distribution of resource consumption between provider organisations v) Cost consequence and cost-effectiveness vi) Any survival differential between groups vii) To identify influences affecting trial equipoise (especially with regard to morphine side-effects) and safe prescribing, and develop a clinically usable process for safe prescribing and monitoring of morphine in specialist and generalist settings viii) to identify impact on informal carers	Distress due to breathlessness (NRS distress past 24 hours); quality of life (SF-12; EQ-5D-5L); sleep (Epworth); side-effects (respiratory, sedation, delirium, hallucinations, vivid dreams, nausea, constipation); function (Australian Karnofsky Performance (AKPS) Scale); capability (ICECAP-SCM); Health Resource and Utilisation, costs and cost-effectiveness; survival; carer burden (ZBI-12); adherence to safe prescribing plan Carers: ZBI-12; VOICES survey for those who are bereaved during the trial

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Investigational Medicinal Product(s)	Morphine Sulfate modified release or placebo
Non-Investigational Medicinal Product(s)	Docusate Sodium laxative or placebo
Formulation, Dose, Route of Administration and dispensing	Morphine Sulfate modified release 5mg oral, twice daily increasing to 10mg oral, twice daily if insufficient response and tolerated Docusate Sodium laxative – 100mg oral, twice daily Day 0 following randomisation (one bottle of 14 days) Day 14 (two bottles of 14 days) Day 42 (one bottle of 14 days)
Main inclusion / exclusion criteria	Main Inclusion criteria: 1. Ambulant people with chronic breathlessness due to cardiac, respiratory disease, post COVID chronic breathlessness or cancer 2. Modified Medical Research Council (mMRC) breathlessness grade ≥3 3. Male or female aged ≥ 18 years old 4. Management of the underlying condition unchanged for the previous 7 days 5. Australia-modified Karnofsky Performance Scale (AKPS) ≥40 6. eGFR of 25 mls/min/1.73^2 or more, unless the primary diagnosis is heart failure (≥30 mls/min/1.73^2) 7. If female and of child-bearing potential, must agree to use adequate contraception 8. Able to complete questionnaires and trial assessments 9. Able to provide written informed consent Main Exclusion criteria: 1. Have co-existing malignant disease only if this would affect the study in the investigators' opinion 2. Have used opioid medications >5mg morphine-equivalents daily for >7 out of last 14 days 3. Have known true morphine allergies or hypersensitivity to any of the tablet constituents as assessed by a clinician 4. Have known central hypoventilation syndrome 5. Have been involved in another medicinal trial (CTIMP) within the past 28 days 6. Are pregnant or lactating 7. Have respiratory depression, head injury, paralytic ileus, 'acute abdomen', acute hepatic disease 8. Have concurrent administration of monoamine oxidase inhibitors or are within 14 days of discontinuation of their use 9. Are within the first 24 hour post-operatively 10. Are taking more than 20mg Diazepam equivalents per day or are not able or willing to safely reduce dose to less or the same as 20mg / day for the duration of the study 11. Persons who cannot / do not wish to take gelatin (used as a medication encapsulation ingredient)

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Investigations performed	Baseline: Demographics, clinical exam, disease stage, Australian-modified Karnofsky Performance Scale (AKPS), Comorbidity Checklist, modified Medical Research Council Breathlessness Scale (mMRC-BS), Body Mass Index (BMI), Clinical exam, Numerical Rating Scale ([NRS] breathlessness severity/distress/pain/ cough), Epworth Sleep Scale (ESS), Karolinska Sleepiness Scale (KSS), St Louis University Mental Status (SLUMS) cognitive test, Short form-12 (SF-12 quality of life), Euroqol health status and visual analogue scale (EQ-5D-5L and EQ-VAS), ICE CAPability measure (ICECAP-SCM), Health Resource and Utilisation (HRUQ), Concomitant medications, Side-effects, adverse events (AEs), ActiGraphy (Day -8 to day 0), ZBI-12 (carers) Day 1,2,4,7,14 & 20: NRS Severity, KSS, side-effects, AEs, NRS Pain, cough (Day 7) and distress (Day 7, 14, 20) Concomitant medications (Day 7, 14, 20) Day 28: Clinical exam, AKPS, NRS Severity, distress, pain, cough, ESS, KSS, SLUMS, EQ5D-5L and EQ-VAS, SF-12, ICECAP-SCM, HRUQ, Concomitant medications, Side-effects, AEs, Actigraphy (Day 20 to Day 28), ZBI-12 (carers) Day 56: AKPS, NRS severity, distress, pain, cough, ESS, KSS, EQ5D-5L and EQ-VAS, SF-12, ICECAP-SCM, HRUQ, Concomitant medications, Side-effects, AEs, ZBI-12 (carers) Day 60: Subjective Opioid Withdrawal Scale (SOWS), Adverse Events 4 months post bereavement (carers if applicable) – VOICES survey
Biological samples from patients	Routine bloods (renal function only) at baseline (to ensure inclusion criteria met)
Planned trial sites	Multicentre within the UK

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MABEL Trial

ASSESSMENT AND ACTIVITY SCHEDULE	**Clinic / Home**	**Clinic / Home / Phone / Video**								**Clinic / Home / Phone / Video**	**Clinic / Home /**	**Clinic / Home / Phone / Video**	**Clinic / Home / Phone / Video**	**Clinic / Phone / Video**	**Clinic / Phone / Video**
Assessment (D = day)	**Baseline between D-8 and D0**	**after baseline measures**	**D1 ***	**D2**	**D4**	**D7 ****	**D14**	**D16 *****	**D18 *****	**D20**	**D28**	**D42**	**D56**	**D60**	**3-monthly to last recruit at D56**
Allowed variation in days			0	0	-/+ 1	-/+ 1	-/+ 2	0	-/+ 1	-/+ 2	-/+ 3	-/+ 1	-/+ 3	-1	
Eligibility screen and consent	Before D -8														
ActiGraph monitor (x = step count)	On D −8	X Off								X On	x Off				
AKPS status	x										x		x		
Age, sex, ethnicity, disease stage**** Comorbidity checklist, mMRC **B**S, BMI	x														
Clinical Exam: Pulse, BP, Respiratory Rate, Pulse Oximetry, CO_2	x										x				
Urine dipstick pregnancy test*****	x										x				
Randomisation		**x D0**													
NRS breathlessness severity (Primary outcome = NRS worst / 24 hours)	x			x	x	x	x	x	x	x	x		x		x
NRS breathlessness distress	x					x	x			x	x		x		x
NRS pain	x					x					x		x		
NRS cough	x					x					x		x		
Epworth sleep (ESS)	x										x		x		
Karolinska sleepiness (KSS)	x			x	x	x	x	x	x	x	x		x		
SLUMS cognitive test	x										x				
EQ5D-5L, EQ-VAS, ICECAP-SCM, SF-12	x										x		x		
Health Resource and Utilisation questionnaire	x										x		x		
Concomitant medication	x					x	x			x	x		x		
Dose escalation assessment						x									
Medication dispensing			x				x					x			
Side-effects / Toxicity Assessment	x			x	x	x	x	x	x	x	x	x	x		x
Subjective Opioid Withdrawal Scale														x	
Adverse events	x			x	x	x	x	x	x	x	x	x	x	x	
ZBI-12 (carers)	x						x				x		x		
VOICES (bereaved carers)															4 months post bereavement

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Key and notes to Assessment Activity Schedule

*** Day 1: The participant takes the first dose of study drug. In practice this may be the same as Day 0 if participants received study drug the same day as randomisation. The first dose should be taken in the evening of Day 1 and within 4 days of randomisation (to allow for weekend / Bank Holiday weekends).**

**** Day 7: Decision to dose increase to 10mg Morphine Sulfate modified release/placebo twice daily or stay at 5mg Morphine Sulfate modified release/placebo twice daily (use the difference between baseline and Day 7 NRS worse breathlessness scores)**

***** Day 15: The participant takes the first dose of 10mg Morphine Sulfate modified release/placebo twice daily. The first dose should be taken in the evening of Day 15**

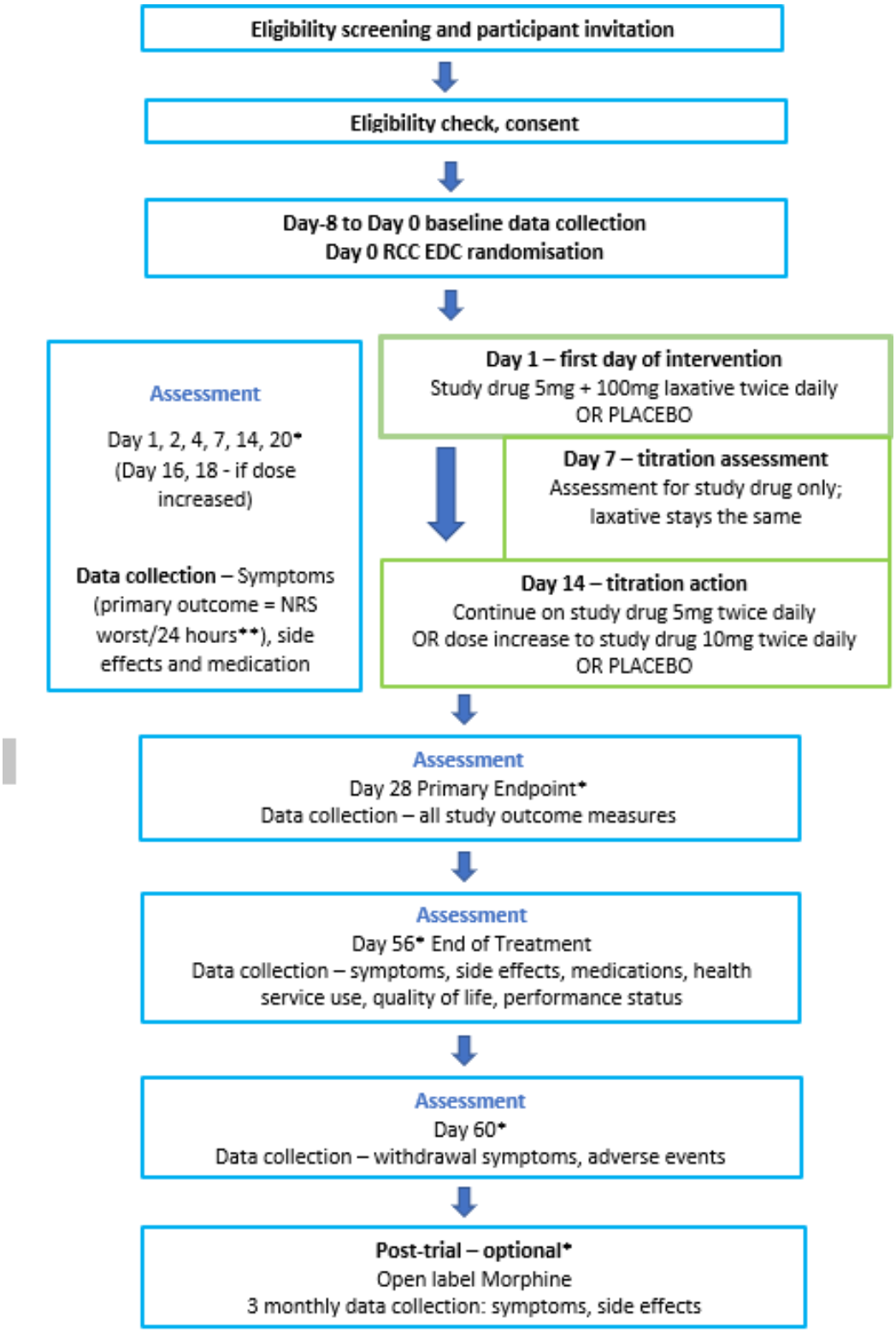
***** Day 16 and Day 18: Study measures are ONLY conducted if the participant dose increases to 10mg Morphine Sulfate modified release/placebo twice daily**

******e.g. NYHA for heart failure, GOLD for COPD, cancer staging**

*******or serum pregnancy tests if it is the site's policy for female participants with child bearing potential**

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MABEL Trial



* For details of data collection – see study assessment schedule
** Numerical rating scale worst breathlessness over the previous 24 hours

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ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITTEES/GROUPS AND INDIVIDUALS

The Sponsor will have overall responsibility for the trial. The trial will be managed by the HHTU, on behalf of Professor Marie Fallon (Chief Investigator). The Sponsor of the trial will be Hull University Teaching Hospitals NHS Trust (HUTH). The study will be monitored by HHTU in accordance with HUTH and HHTU Standard Operating Procedures to ensure compliance with UK Clinical Trial Regulations. All trial related documents will be made available upon request for monitoring by HHTU monitors and for inspection by the MHRA.

Chief Investigator(s) - The Chief Investigator(s) will have responsibility for the design, coordination and management of the study.

Clinical Trials Unit -The Sponsor, Chief Investigator(s) and HHTU will be stipulated clearly in the Sponsor-University of Hull contracts respectively.

Statistical Analysis – Dr Catriona Keerie, employed by the University of Edinburgh, will oversee the statistical aspects of this study including the drafting of the analysis plan, the conduct of analyses and reporting of results.

Health Economic Analysis – Dr Peter Hall, employed by the University of Edinburgh, will oversee the health economic aspects of this study including the drafting of the analysis plan, the conduct of analyses and reporting of results.

The Site Principal Investigator at each participating centre will be responsible for local site-specific assessment approval, and for the local conduct of the study.

Local Project Teams – These will consist of Physicians or registered Independent Prescribers (nurses who are registered with the Nursing and Midwifery Council (NMC) as an Independent Prescriber and are permitted to prescribe controlled drugs) (responsible for introducing the patient to the trial and ensuring eligibility and consent) and Study Nurses (responsible for patient recruitment, supporting the consent process and co-ordination of all aspects of data collection). Sites are specifically responsible for conducting the trial in accordance with the protocol, Standard Operating Procedures (SOPs), trial agreement, the UK Clinical Trial Regulations and GCP.

Independent Data Monitoring and Ethics Committee (DMEC)
The DMEC will review the safety and ethics of the trial by reviewing interim data approximately every 6 months from the start of recruitment, and membership to this group will include an independent statistician.

Trial Steering Committee (TSC)
The TSC will provide overall supervision of the trial, in particular trial progress, adherence to protocol, patient safety and consideration of new information.

Trial Management Group (TMG)
The TMG will comprise of the Chief Investigator, other lead investigators (clinical and non-clinical), members with a specific interest (e.g. nurses; patient representatives [two]), and members of HHTU and a Sponsor representative.

KEY WORDS: Morphine; chronic breathlessness; randomised controlled trial; placebo; dyspnoea

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LIST OF ABBREVIATIONS

Define all unusual or 'technical' terms related to the trial. Add or delete as appropriate to your trial. Maintain alphabetical order for ease of reference.

AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trial Authorisation
CTCAE	Common Terminology Criteria for adverse events
CTIMP	Clinical Trial of Investigational Medicinal Product
DMEC	Data Monitoring and Ethics Committee
DSUR	Development Safety Update Report
EC	European Commission
EDC	Electronic Data Collection
EMEA	European Medicines Agency
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance
GCP	Good Clinical Practice
GDPR	General Data Protection Regulations
GMP	Good Manufacturing Practice
HHTU	Hull Health Trials Unit
HUTHT	Hull University Teaching Hospitals NHS Trust
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
MA	Marketing Authorisation

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MHRA	Medicines and Healthcare products Regulatory Agency
MS	Member State
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHS R&D	National Health Service Research & Development
NIMP	Non-Investigational Medicinal Product
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
RCC	RedCAP Cloud (Electronic Database)
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SSI	Site Specific Information
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Events
TMG	Trial Management Group
TSC	Trial Steering Committee
TMF	Trial Master File
UoH	University of Hull

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STUDY PROTOCOL

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 breathlessness in people with chronic breathlessness.

1.0 BACKGROUND AND RATIONALE

CHRONIC BREATHLESSNESS is frightening and devastating, prevalent in chronic progressive illnesses. It affects >90% of people with advanced lung cancer,[1] chronic obstructive pulmonary disease (COPD) [2], interstitial lung disease (ILD)[3] and >80% with heart failure.[4] Breathlessness is mostly triggered or worsened by exertion or anxiety. Despite treatment of underlying disease(s), chronic breathlessness often persists - *Chronic Breathlessness Syndrome*[5] – and is neglected despite evidence that non-pharmacological interventions can help and pharmacological interventions have potential.[6-8]

RATIONALE FOR MORPHINE USE IN CHRONIC BREATHLESSNESS

There is good rationale to use opioids. Breathlessness perception is processed in brain areas [9] rich in opioid receptors.[16] Endogenous opioids reduce breathlessness and the opioid antagonist, naloxone, increases exertion-induced breathlessness.[10;11] Opioids appear to centrally modulate breathlessness perception to be less intense and unpleasant. As physical exertion generates breathlessness, central "blunting" of breathlessness perception may allow more physical exertion. Conversely, opioids may reduce both breathlessness and activity due to opioid-related somnolence, although this is usually short-term. Thus breathlessness and physical activity are closely related.

CLINICAL STUDIES FOR BREATHLESSNESS

There are four meta-analyses of placebo/opioid RCTs showing evidence of benefit.[8;12-14] One (COPD only), showed benefit was best in steady state (standard mean difference [SMD]: steady state -0.44 [95% CI, -0.68 to -0.19] *vs* all studies - 0.30 [95% CI, -0.59 to -0.02]).[14] A 2016 Cochrane update,[13] found only low level, imprecise evidence. That analysis did not account for cross-over design (11/12 studies), used a fixed effects model despite study heterogeneity, and added a sample-size limit of 50 to the risk of bias tool irrespective of study power. A fourth[8] re-analysed the data using standard techniques for cross-over data,[15] showing improved precision and moderate evidence of clinically significant benefit.[16] However, data are only available *for short term use*.

A recent phase 3 RCT of morphine, oxycodone and placebo (ANZCTN 12609000806268) for chronic breathlessness due to various aetiologies showed morphine helped people with COPD and those with more intense breathlessness (mMRC 3 or 4)(conference abstract).[17]

DOSING AND DOSE TITRATION

The repeat dose studies all used oral morphine; modified release morphine (MRM) in the larger studies [18;19] due to lower peaks and higher troughs, more convenience for patients and the most predictable pharmacokinetics.

An open label, dose ranging study was conducted with MRM[19] starting on 10mg daily for 7 days. Those responding (>10% reduction over baseline) went to extension phase at that dose. If no response, the dose was increased to 20mg for a week. The algorithm was repeated up to 30mg. Out of 83 people, 2/3 had benefit: 70% at 10mg, 20% at 20mg and 8% at 30mg. Tachyphylaxis, opioid-related admission and respiratory depression were not seen in up to 22 months follow up. A secondary analysis of successful

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people titrated to a clinically significant benefit showed maximal benefits may not occur for 7 days following the dose titration with benefit.[20]

SAFETY

The safety and harm profile of morphine is well described. Respiratory compromise is seen as a contra-indication to using morphine in people with COPD and interstitial lung disease (ILD).[21] A meta-analysis showed no clinically relevant changes in oxygen nor carbon dioxide levels.[22] However, safety remains a concern for clinicians, with some indicating they would not prescribe morphine,[23;24] although a recent survey of junior doctors indicates a greater willingness to prescribe.[25]

A long-term oxygen-dependent COPD cohort (reflecting the severity of their COPD and also the length of time that people may have disabling chronic breathlessness) with 4 years' follow up showed no increase in admissions nor mortality with a morphine equivalent daily dose of ≤30mg.[26] A recent study has failed to find a relationship between opioids and either admissions or mortality at any dose in ILD.[27] A Canadian population-based COPD study shows a small absolute excess in respiratory adverse events within 30 days of opioid prescription but no causality can be ascribed and no clinical information was available about why opioids were initiated, the overall point on the disease trajectory where opioids were initiated, nor the respiratory function of people in the study.[28]

EVIDENCE GAPS

Most study participants to date have COPD. Some have cancer and heart failure but very few have ILD or other conditions. The longest reported placebo-controlled follow up is 7 days. Current ongoing studies are described above.

CURRENT CLINICAL PRACTICE

Until very recently there has been no medication registered for chronic breathlessness in any jurisdiction globally. However, in January 2019, the Therapeutics Goods Administration of Australia approved an extension of the license for Kapanol® 5mg and 10mg capsules (oral sustained-release morphine) for chronic breathlessness. The evidence to date supports regular, low dose, modified release morphine as safe and efficacious *in the short term*.[8] However, it does not inform clinical practice which is mostly for longer term use. Current clinical guidelines from a number of professional bodies internationally include opioids as a treatment option to be considered when the underlying disease treatments and non-pharmacological measures have been optimised but the symptom remains troublesome. [29-32] People with advanced cardio-respiratory disease, particularly non-cancer, are among those most likely to have such chronic breathlessness, living with relatively stable, albeit advanced disease. Importantly, they may live with the palliative needs resulting from breathlessness for months, even years, prior to death.[33] We must, therefore, evaluate the *net* long term effects (benefits and side-effects) of any intervention for patients and carers, including into bereavement. Even small reductions in breathlessness help patients' wellbeing and function, and reduce carers' distress.[7;16] These benefits could be experienced over months and years for many people living with advanced cardio-respiratory conditions. Many of these patients will receive their palliative care from their usual care team (e.g. primary care, respiratory, cardiology, etc.) albeit with access to support from specialist palliative care as needed. This integrated palliative care model[34] contrasts with the traditional model of curative treatments then palliative care at the very end of life, and palliative interventions deliverable by generalists, albeit supported by specialist palliative care (SPC) are highly pertinent.

However, even amongst specialist palliative care providers, wide practice variation exists in willingness to prescribe, dosing and quality of monitoring. Potential problems therefore are; i) patients may be denied a helpful medication (due to unfounded fears about respiratory side-effects),[24] ii) they may have

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a poorly monitored, suboptimal regime, iii) there may be no net-benefit in the longer term, and it may cause net harm.

THERE IS AN URGENT NEED to identify if MRM improves chronic breathlessness, and, if so, to identify the clinical care pathway that will become the new standard of care.

2.0 ASSESSMENT AND MANAGEMENT OF RISK

This section describes the risk associated with IMP. A full risk assessment of the trial as a whole will be completed by the Sponsor.

2.1 The known and potential risks and benefits to human subjects

As described in the background and rationale, morphine is an old drug with a well-known safety and harm profile.

In this clinical situation of chronic breathlessness, the evidence to date supports the safety of the route of administration, dose, dosing and monitoring schedule employed in this trial. Although we do not have access to a once daily administered preparation, we do have a twice daily Morphine Sulfate modified release preparation which allows the same daily dose and provides steady state. The Therapeutics Goods Administration in Australia has recently approved a preparation of sustained release morphine (Kapanol 10mg, 20mg capsules for once daily use) for the indication of chronic breathlessness. Kapanol is not available in the UK and so we will use MST Continus at the same daily dose although this preparation's MHRA licence is for moderate to severe pain rather than for chronic breathlessness.

The extensive systematic review and meta-analysis of respiratory side-effects related to the use of opioids for breathlessness in 1064 participants found only one case report of respiratory depression needing short-term ventilator support.[22] Respiratory depression (defined as a respiratory rate of 4-5 breaths/minute, very poor respiratory effort and minimal wheezing over both lung fields) was reported after administration of 4mg nebulized morphine and 4mg dexamethasone for breakthrough breathlessness in a patient already using 10mg oral slow-release morphine three times *per* day and 10mg oral immediate release morphine when required for cancer-related pain.

In clinical trials and other studies using the dose and monitoring employed in this trial, there were no episodes of respiratory depression, opioid-related hospital admissions, obtundation or deaths.

In practice, with the doses and schedule used in this trial, the expected profile of potential side-effects is of gastro-intestinal symptoms (constipation, nausea with or without vomiting), and neuro-cognitive symptoms (sedation, cognitive disturbance). Apart from constipation which needs proactive and continued management with laxative, the other symptoms are expected to i) arise within the first week of any dose level and ii) be mild and settle either spontaneously or with simple management (such as anti-emetics) for most. For those experiencing moderate to severe side-effects, these are expected to resolve completely on stopping morphine within a few days only.

The SmPC states that the only preclinical safety data are in relation to male rats where reduced fertility and chromosomal damage in gametes have been reported. There are risks in late pregnancy due to the risk of neonatal respiratory depression in the event of delivery of the baby.

2.2 How high the risk is compared to normal standard practice

The use of morphine for breathlessness is recommended by a number of current international clinical guidelines for patient populations relevant to this trial. Opioids are also currently prescribed by an

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increasing body of clinicians for chronic breathlessness in usual clinical practice despite the lack of robust longer-term clinical trial data for morphine, and a lack or absence of clinical study data for other opioids, routes of administration and dosing schedules.

In current practice no standard dose or monitoring schedule is described and thus practice varies with different opioids, different preparations (immediate release given *ad libitum* and modified release) and different dose schedules and different routes of administration (oral, injectable, transmucosal) according to individual prescriber's preference and despite a lack of evidence for approaches other than that used in this trial. No standard monitoring schedule exists and this is left to individual clinical experience and practice.

In clinical practice there are regulations in relation to the storage, prescription, dispensing and destruction of controlled drugs such as morphine. These will be adhered to in this trial. In addition, we will have standard trial procedures for i) IMP and nIMP storage, prescription and dispensing, ii) study nurses or informal carers picking up IMP and nIMP and taking to a patient in the event they cannot pick them up themselves, iii) dose titration, and iv) for compliance assessment.

Therefore, the risk to human subjects in this trial is expected to be lower because we are using evidence-based best practice, are developing a safe monitoring protocol and are training clinicians to use it. At the most, the risk will be no higher than in normal standard practice.

The risk with regard to pregnancy in this trial is very low as very few, if any, potential participants will be at risk of pregnancy.

2.3 How the risk will be minimised/managed

We will use the dose, preparation, route of administration, and dose schedule which has the best evidence-base to date.

We will develop a monitoring schedule which will be included in the site clinical training (in addition to the site initiation visit regarding trial conduct) for clinicians. This will form part of a parallel normalisation process theory based study (related ethics application) in order to identify and manage morphine-related side-effects early in order to maximise safety, and the number of participants tolerating morphine, and thus allowing a better evaluation of net-benefit. The site clinical training will be led by Co-investigator Sabrina Bajwah supported by Miriam Johnson and Marie Fallon. Six co-investigators are consultant palliative physicians and are very experienced in the use of opioid medication, and each will be responsible for the site clinical training. Between them, they will also provide clinical support to site teams in the event of morphine-related side-effects and the need for further advice. Where independent prescribers are to take consent, the Sponsor will review registration and the level of competence prior to "green light" approval for a site.

We have a detailed and systematic plan to identify and manage adverse events, identifying treatment-emergent side-effects by including the most likely morphine-related side-effects in the clinical record form (CRF); using the relevant CTCAE (Common Terminology Criteria for Adverse Events) at baseline and every patient contact and focussing on the first 7 days of any dose level in addition to routine trial adverse event reporting.

The risk management in relation to IMP and nIMP storage, prescription, dispensing and compliance is as above.

The very low, but possible, risk with regard to fertility and pregnancy will be managed through eligibility criteria. In the absence of teratogenicity data in humans, we will require that reliable contraception is

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used. Because of the risk to the neonate, pregnancy and lactation are trial exclusions, and participants of child-bearing age are required to agree to use reliable contraception.

2.4 COVID-19 AND PARTICIPANT RISK

There is no current evidence that the risk of taking the MST IMP at either 5mg or 10mg doses in event of a positive COVID-19 infection will have a negative impact on the safety of participants; indeed, this is included in a number of guidelines for the palliation of COVID-19 breathlessness as for other causes of breathlessness. We will not be testing for COVID-19 in this study but will advise participants who become symptomatic to follow national guidance on testing. We will report COVID-19 positive cases as an AE /SAE and cases will be monitored by the TMG, TSC and DMEC committees throughout the study. Post-COVID-19 chronic breathlessness is a recognised consequence of COVID-19 infection and such patients will be eligible for the study if they fit the other eligibility criteria. Participants will not be withdrawn from study medication in the event of COVID-19 infection. However, treating clinicians should follow clinical management guidelines and make local decisions regarding patient care as for any intercurrent illness including stopping study medication, or withdrawal from the trial, if deemed appropriate. In order to protect study integrity, as with any intercurrent medical condition, treating clinicians should treat study participants as being on active study IMP. Unblinding of participants to study treatment allocation will only be conducted after discussion with the CI and if absolutely essential for participants safety. See section 7.5 Page 39 for further details on the unblinding process.

All participants will be provided with a card with trial information, and emergency contact details.

3.0 OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

3.1 Primary objective

AIM: The overarching aim is to test the effectiveness, cost consequence and cost-effectiveness of regular low dose oral modified release morphine for patient-reported worst breathlessness in people living with and needing palliation for chronic breathlessness due to advanced disease compared with placebo.

OBJECTIVES. Specific objectives are as follows:

Embedded pilot

To identify whether recruitment rate after 6 months is sufficient to allow progression to the full trial. After 6 months, we will observe the stop-go rules as shown in Table 1 allowing that sites may not recruit during their first month open.

Table 1. Stop-Go rule

Recruitment Target by end of 6 month pilot; 36 (23% total)		
Green	≥75%	Action: Proceed. Sites open for >3 months without recruits may be closed
Amber	≥50% to <75%	Action: examine and address recruitment blocks per site including protocol amendments if appropriate, consider either more sites or more time or both. Sites open for >3 months without recruits may be closed
Red	<50% expected	Action: the trial does not look feasible, options to be discussed with TSC, DMC and funder including termination of trial

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We will also use the pilot phase to check data and treatment completion rates and refine the design of the health resource use questionnaire.
Full trial
Primary Objectives
(i) To evaluate the effect of low dose oral modified-release morphine on worst breathlessness over 28 days in people with chronic breathlessness
(ii) To assess whether any benefit, found in (i), is cost-effective

The null hypothesis is that there is no difference in the relief of chronic breathlessness provided by morphine or placebo where a clinical meaningful difference is defined as a 1 point improvement in the amount of breathlessness at its most over the previous 24 hours (worst breathlessness) measured by a 0 to 10 numerical rating scale (NRS).
In order to achieve these objectives the trial will measure breathlessness in eligible, recruited patients. The primary outcome is patient-rated worst breathlessness in the past 24 hours as defined in Section 3.3.1.

3.2 Secondary objectives

To assess the benefit of modified-release morphine on:
i) Placebo-controlled net effects beyond 7 days with blinded side-effects data up to 2 months;
ii) Net benefit in the population in addition to people with COPD;
iii) Net effect on longer term changes in physical activity if chronic breathlessness is reduced;
iv) Longer term impact on health service use, especially days as a hospital inpatient; unplanned health service contact and to assess any potential re-distribution of resource consumption between provider organisations; patient and carer financial implications / out of pocket expenses.
v) Cost consequence and cost-effectiveness;
vi) Any survival differential between groups; and
vii) To identify influences affecting trial equipoise (especially with regard to morphine side-effects) and safe prescribing/monitoring, and develop a clinically usable process for safe prescribing and monitoring of morphine in specialist and generalist settings;
viii) To identify informal carer burden;
ix) To explore impact on bereavement on the carer if relevant

Secondary objectives will be met through the measurement of the outcomes listed in Section 3.3.2.

3.3 Outcome measures/endpoints

3.3.1 Primary endpoint/outcome

The primary outcome will be the amount of breathlessness at its most over the previous 24 hours (worst breathlessness) measured at Day 28. Patient-rated *worst* breathlessness over the previous 24 hours will be measured using a 0 – 10 numerical rating scale [NRS] where 0 = no breathlessness and 10 = the worst imaginable breathlessness) [35-38]. This measure is highly correlated with visual analogue scores (VAS), has better test-rest reliability[39], and research in pain shows that patients find them easier to use than VAS scales [40;41]. A clinically important moderate improvement in chronic breathlessness has been shown to be 11.3mm VAS or 1 point on the NRS (which can also be reported by phone) [16].

The primary endpoint is at Day 28 of study.

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3.3.2 Secondary endpoints/outcomes

3.3.2.1. Further measures of breathlessness

We will also use a NRS to assess:

- Distress due to breathlessness. Distress is a distinct domain of breathlessness which can be discerned by patients and contribute to the experience of the symptom[42]. Distress has been used as a primary outcome in trials of breathlessness complex intervention services,[12] but not in trials of opioids which have used the amount of breathlessness variably described as severity or intensity.
- At Day 56, participants will be asked whether the changes in breathlessness they experienced are sufficient to warrant ongoing therapy with the arm to which they were allocated.

3.3.2.2 Assessment of functional and performance status

- Physical activity: daily step count and physical activity: We will use ActiGraph for ease of wear (wrist has highest compliance), ease of site management, and the ability to provide step counts and activity level measurements. There are emerging activity data in patient populations with limited mobility, but there are no agreed standards for activity data collection in clinical trial protocols.[44] Recent recommendations for trials in COPD include: a 7 day wear period to allow 5 days' valid days; at least 10 hours' wear for a "valid day" (24 hours would be preferable); suggested definitions for a non-wear episode; suggested outcome measures to include sedentary, light physical activity and total activity.[44] Light/moderate activity will be based on a cadence of 60 steps/min or greater for minimum intervals of 2 min and 5 min to distinguish "pottering activity".[44]

- Cognitive function: Cognitive function will be assessed at baseline and Day 28) using the St Louis University Mental Status (SLUMS) questionnaire. This is an 11-item questionnaire scored out of 30; testing memory, orientation, attention and executive functions. The score is adjusted for school education.[45]

- Australia modified Karnofsky Performance Status (AKPS)[46]: The AKPS[46] can measure longitudinal changes in the palliative care population and represents a global measure of functional status across all domains.[47] It is a measure of functional status with 10% gradations from 0 (dead) to 100 (fully functional). The AKPS blends the original KPS and is more useful in advanced disease.[46] It can be used across palliative care settings; patient's home, hospital/hospice inpatient and nursing/care homes. AKPS predicts survival, can reflect longitudinal changes and is easier to use than previous versions.

- Carer burden: The Zarit Burden Interview (ZBI) 12 is a short questionnaire to assess the burden of disease as experienced by the informal carer.[48]

- Impact on bereavement: Where a patient participant dies during the study, a shortened version of the VOICES-short form questionnaire (a validated survey used National Survey for the Bereaved since 2010) will be sent by post 4 months into bereavement (this is the earliest time after death the National Survey sends the survey[49]).

3.3.2.3. Quality of life assessments

As we will be including people with different underlying symptomatic conditions, we will use the SF-12; a generic and short quality of life tool.[50] As chronic breathlessness worsens across the population, so do the physical and mental component summary scores of health-related quality of life at clinically and

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statistically significant levels in every age group.[51] Responses will be compared to population normative data.

The EuroQoL EQ-5D [52] is a self-administered, validated, measure of health status and consists of a 5-question multi-attribute questionnaire and a visual analogue self-rating scale (the EQ-VAS). Respondents are asked to rate severity of their current problems (level 1 = no problems, level 2 = slight problems, level 3 = moderate problems, level 4 = severe problems, level 5 = unable [or extreme]) for five dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.

3.3.2.4 Health economic assessment

The SF-12 (SF-6D) and the EQ-5D (tariff and VAS) will be used to provide alternative utility weights as a basis for estimations of Quality Adjusted Life Years (QALYs). Utility weights will be estimated from the ICECAP-SCM capability measure.

Health Service use will also be collected using patient Health Resource and Utilisation questionnaires (HRUQ), combined with information collected on the CRF. Respondents will be asked to recall the amount of use they have made of the specified service over the past month along with any out of pocket expenses incurred by themselves and their carers, measured at baseline, Day 28 and Day 56 and completed with assistance from carers and the research team. The Health Service use questionnaire will be based on an adaptation of the UK Cancer Costs Questionnaire (https://blogs.ed.ac.uk/ukcc/).

Health service use, costs and health/service consequences will be presented descriptively. The primary outcome measure for the cost-effectiveness analysis will be the Incremental Cost Effectiveness Ratio (cost per QALY) expressed as the Incremental Net Benefit.[53]

3.3.2.5 Assessment of related symptoms

- Average pain over previous 24 hours (NRS): a 0-10 NRS of average pain over the previous 24 hours will be used. NRS-pain is a simple, validated tool to assess pain severity.[40;54 55] so this symptom, if present, may also respond to morphine.
- Most severe cough over previous 24 hours (NRS): a 0-10 NRS of severity of cough over the previous 24 hours will be used as this may respond to morphine.[56;57]
- Epworth Sleep Questionnaire: a screening tool for sleep-disordered breathing, also used to assess daytime sleepiness.[58]

3.3.2.6 Side-effects

- Opioid related symptoms will be identified during each assessment using criteria established by the National Cancer Institute (version 5.0) and will be graded accordingly. Constipation, confusion, nausea, vomiting, memory, hallucinations and cognitive impairment will be specifically included on the CRFs.
- Karolinska sleepiness scale: a 1-9 numerical scale with verbal descriptors for self-reported sleepiness [59].
- Onset of vivid dreams.
- Cognitive function will be assessed in more detail using the St Louis University Mental Status Examination (SLUMS) tools.[45]
- Opioid withdrawal will be assessed with the Subjective Opioid Withdrawal Scale (SOWS).[60] SOWS is a 16-point questionnaire rating the presence of signs and symptoms of opioid withdrawal on a five-point Likert Scale. Higher scores indicate increasing severity of opioid withdrawal. At 10 to 20mg per day for 56 days, we anticipate troublesome withdrawal will be highly unusual. The added complexity of a reducing dose post-trial is therefore not justified. The

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study nurse will remain blinded at this point and thus all patients will be contacted to check that all has been well for the first three days since leaving the study (Day 60).

TEAE (Treatment Emergent Adverse Events) are those which, compared to baseline measures either appear or worsen. Severe TEAEs are defined as grade 4 (life-threatening/urgent intervention needed) or 5 (death), or grade 3 events *which do not improve with appropriate management (includes but does not necessitate IMP withdrawal).*

"Acceptable side-effects (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.

In view of the potential of gastro-intestinal effects in particular to cause unblinding, the site PI will be asked to state whether they believe the participant to be randomised to active, placebo or "don't know".

3.4 Clinical Assessments

The following clinical assessments will be undertaken:

- Standard blood renal biochemistry (serum Urea, Electrolytes and Creatinine) if not done within the previous 3 weeks will be performed as part of the eligibility screening process. Renal clearance will be assessed using eGFR **or** Cockroft and Gault calculation (estimated creatinine clearance = (140-age) x Mass(kg) x constant/serum creatinine (µmol/L), where *constant* is *1.23* for men and *1.04* for women)
- Standard examination to record:
  - resting pulse rate and blood pressure,
  - resting respiratory rate
  - pulse oximetry
  - CO_2 measure
- Comorbidity Checklist: This is adapted from the validated Charlson Comorbidity Index used to estimate relative risk of death from prognostic clinical covariates, and useful in studies with 1 to 2 year follow up.
- Urine dipstick pregnancy test (or serum pregnancy tests if it is the site's policy) at baseline and Day 28, for female participants with child-bearing potential. Women of childbearing potential must have a negative pregnancy test within 7 days prior to treatment initiation.
- Used study medication packages (IMP and nIMP) will be returned to the site trial pharmacy for compliance check and unused medication destroyed according to legal requirements.

3.5 Timetable of assessments

The timetable of assessments is given at the beginning of this protocol on Page 12 (Assessment and Activity Schedule).

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1. Home or phone visits for all activities is an option for participants who are unable or unwilling to travel to clinic, for whatever reason.

2. It is possible that baseline D0 and D1 could be the same day. D1 merely denotes the first day that the participant starts the IMP and nIMP.

3. D1 should fall on Sunday to Thursday so the participant has had at least one safety check before a weekend.

4. Assessments at Day 28 and Day 56 can be completed +/-3 days of schedule to allow for difficulties in timing appointments.

5. The study team telephones to check toxicity and adverse events in the first week as part of the CRF requirements. This will include a call within 24 hours of the participant's first study dose (Day 2), midweek (Day 4), and at the end of the week (Day 7). The calls on Day 4 and Day 7 can be flexible to −/+ 1 day.

6. In the event of dose increase (decision Day 7), the participant should be supplied with a bottle containing the new dosage (10mg capsules IMP twice daily) to start on Day 15. The participant will then receive a call from the study nurse within 24 hours of the participant's first dose of the increased dose of IMP (Day 16), and another 2 days later (Day 18). Day 18 can be flexible to -/+1 day. The overall timeline of the study will not be affected by the flexibility in the timing of the dose titration and the study is designed to mirror clinical practice in this matter.

At the end of the Day 56 telephone assessment the study nurse will ask patients whether or not they wish to take open label morphine. If patients have been on morphine, but wish *not* to take open label morphine, there is a small risk of physical withdrawal. At 10 to 20mg per day for two months we anticipate this will be highly unusual and do not feel it justifies the added complexity of a reducing dose in this first week as a routine.

Participant and study team remain blinded at this point and thus all participants will be contacted on Day 60 (-1 day) to check that all has been well for the first three days since leaving the study and to complete the SOWS questionnaire; appropriate management will be arranged if need be. If a participant wishes to take open label morphine, they will be referred to their usual clinician (either GP or hospital doctor) who will make that clinical judgement and prescribe if appropriate. Participants may have been on placebo and would be starting active morphine. Their usual clinician will be advised to monitor such patients *as if* they are opioid naive. Patients and their General Practitioners will receive written information at the end of the 56-day RCT to outline these issues. Participants who agree to continue providing longer term study assessment data, and who take open label morphine will be requested to start this within two weeks of the end of the RCT. Participants who wish to take open label morphine will be contacted by the study team within the first three days of last dose of IMP to check all is well.

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4.0 TRIAL DESIGN

We will use an experimental paradigm (parallel group, placebo controlled superiority RCT) to test effectiveness but with an embedded qualitative study ("implementation study") using Normalisation Process Theory to explore implementation issues (see Section 12.0).

Trial: The phase 3 trial is a 2-month, parallel group, randomised, double-blind, placebo-controlled trial comparing the effect of 10mg or 20mg daily oral Morphine Sulfate modified release (IMP) *versus* placebo on the amount of chronic breathlessness due to cardio-respiratory disease, post COVID-19 chronic breathlessness or cancer. Patients will be randomly allocated in a 1:1 ratio using permuted blocks to active or placebo treatment. Morphine Sulfate modified release and placebo IMP capsules prepared by St Mary's Pharmaceutical Unit (SMPU) will be identical in appearance, taste and smell to ensure blinding.

Recruitment will be reviewed after a 6-month embedded pilot.

As constipation is a common side-effect of morphine, corresponding laxative (docusate) or placebo laxative will be given as a non-investigational medicinal product (nIMP). Again, these will be prepared as identical capsules by SMPU to ensure blinding is maintained.

The primary efficacy analysis will be at Day 28 after start of treatment (Day 1). After the 56-day placebo-controlled study period, all participants will be offered 5mg twice daily oral modified-release morphine and laxative at the discretion and responsibility of their usual treating physician. A schedule of assessments can be found on Page 12 (Assessment and Activity Schedule).

All willing participants, whether they continue with modified-release morphine or not after the 56-day trial period, will be followed up with regard to amount of breathlessness, survival and morphine-related adverse events until the last recruit has completed the 56-day placebo-controlled study period. We have attempted to minimise patient burden with regard to required study measures. In keeping with ICH Good Clinical Practice guidance (4.3.4) we will encourage participants to inform us of reasons for incomplete outcome data, while respecting their right not to discuss this if they do not wish to.

Implementation study: Although the intervention is a drug, rather than a complex intervention, nevertheless, complex implementation issues surround its use for people with breathlessness. It is important to understand these issues both in the conduct of the trial and potentially at the point of delineating a new standard of care, should the trial be positive. Despite an evidence base which does not inform adequately the practical use of morphine for *chronic* breathlessness (that is, longer term use) the evidence so far has led to morphine use in current clinical practice and is recommended in international guidelines.[29-32] Further, it is implemented in a very variable way, with justified concerns about lack of safety monitoring and management. There is a need for a process for prescription of morphine, monitoring and management of related harms which we will be able to develop for this trial. This will be directly clinically translatable should the trial be successful.

We will therefore conduct an implementation study alongside the RCT. Data will be synthesised when both datasets are complete.

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5.0 STUDY SETTING

This is a multi-centre trial being conducted across the UK. It is anticipated that approximately 14 centres will be recruited with each centre recruiting 1-2 patients per month. Further centres may be contacted depending on recruitment rates which will be monitored by the Trial Manager and reviewed by the Trial Management Group.

Centres with large cohorts of eligible patients and/or where there are established integrated services with the palliative care team will be prioritised for trial collaboration.

The list of documentation and approvals required before a centre can enroll patients will be in accordance with the Sponsor Greenlight process and HHTU Standard Operating Procedures.

6.0 ELIGIBILITY CRITERIA

6.1 Inclusion criteria

6.1.1 Patient participants

1. Ambulant people with chronic breathlessness due to cardiac, respiratory disease, post-covid-19 chronic breathlessness 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[5]
2. Breathlessness severity
   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 opoids[62]. A phase 3 trial in people with COPD showed that those with mMRC grade 3 or 4 were more likely to respond to opioids.[17] This approach also concurs with clinical recommendations[29;30]
3. Male or female aged ≥ 18 years old
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. eGFR of 25 mls/min/1.73^2 or more, unless the primary diagnosis is heart failure (≥30 mls/min/1.73^2) within 21 days of consent. Renal clearance of eGFR ≥25 mls/min/1.73^2 is adequate for the study doses of morphine, however, 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. Able to provide written informed consent

***** People with cancer, of any stage (0 to 4) may be included only if they are opioid naïve 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); post COVID-19 chronic breathlessness; chronic heart failure (New York Heart Association (NYHA) class III or IV) [HFPEF or HFNEF]

****** Optimum tolerated treatment is defined according to condition:

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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:***

   - On optimal immunosuppression for Connective Tissue Disease (CTD) ILD
   - On anti-fibrotic drug therapy (Pirfenidone or Nintedanib) for IPF if suitable
   - On oxygen therapy (long term or ambulatory) if they fulfil guideline criteria[63]
   - On appropriate treatment for pulmonary hypertension, if applicable

2. For heart failure (*left ventricular dysfunction* only):

   - 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

   - Reached target dose (or be on maximally tolerated dose, or be intolerant) of a beta adrenoceptor antagonist shown to improve prognosis;

   AND

   - 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.

**** 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:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation
  - oral
  - injectable
  - implantable
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner
- sexual abstinence

6.1.2 Carer participants

1. Family or friend providing care for a patient participant (consented) as identified by the patient participant
2. Male or female ≥18 years old
3. Able to complete study carer assessments
4. Able to provide written informed consent

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6.2 Exclusion criteria

6.2.1 Patient participants

1. Are unable to provide informed consent
2. Are unable to complete baseline study questionnaires even with the assistance of the study nurse
3. Have co-existing malignant disease only if this would affect the study in the investigators' opinion
4. Have used opioid medications >5mg morphine-equivalents daily for >7 out of last 14 days
5. Have known true morphine or docusate allergies or hypersensitivity to any of the tablet constituents as assessed by a clinician
6. Have known central hypoventilation syndrome (e.g. Ondine's curse post stroke)
7. Have been involved in another medicinal trial (CTIMP) within the past 28 days
8. Are pregnant or lactating
9. Have respiratory depression, head injury, paralytic ileus, 'acute abdomen', acute hepatic disease
10. Have concurrent administration of monoamine oxidase inhibitors or are within 14 days of discontinuation of their use
11. Are within the first 24 hours post-operatively
12. Are taking >20 mg diazepam or equivalent/day, or are unable to reduce dose before randomisation to <20mg/day for the duration of the study treatment period
13. Persons who cannot / do not wish to take gelatin (used as a medication encapsulation ingredient)

6.2.2 Carer participants

1. Does not meet inclusion criteria

7.0 TRIAL PROCEDURES

7.1 Recruitment

Sites have been chosen on the basis of track record, access to relevant patient populations and research infrastructure, and a range of settings (hospital, community/hospice based) and diseases (respiratory, cardiology, oncology) to ensure external validity. Whilst most site principal investigators "sit" in secondary care, they work in integrated cross setting teams with community colleagues. The vast majority of identified patients will be those living in the community. Recruitment rate will be monitored closely per site. Persistently poor recruiting sites will be closed and replaced if necessary.

A Study Within A Trial (SWAT) has been added to this trial protocol. It will not change existing trial interventions, processes or outcomes. An Infographic Sheet will be attached to the existing study PIS at the approach stage of the main study in sites randomised to Infographic Sheet plus existing PIS versus existing PIS only. Please see section 13 for further information about the SWAT intervention.

7.1.1 Identification

7.1.1.1 Patients

The flow of patients through this trial is illustrated at the beginning of this protocol in Study Flow Chart on page 14. It is planned that 158 patients will be recruited into the study over a period of 18 months. Participating centres should have large cohorts of eligible patients, who are already receiving long term cardio-respiratory or cancer care, who may be identified using screening of lists of clinics and nurse specialists, technicians, and auditors. Patients may also be detected incidentally, through clinic attendance, through multi-disciplinary team meetings, or through inpatient admissions. It is anticipated

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that the bulk of patients will be identified through clinic-based case-finding of existing patient cohorts. Some sites will also have registers of patients who have indicated willingness to be approached with regard to relevant clinical trials. In the latter case, patients have provided written consent to have their contact details kept by the clinical team for this purpose and data are kept in accordance with GDPR (2018).

Most breathless patients considered for opioids will be living independently in their own homes. Therefore participants will be recruited from out-patient clinics and primary care settings. Recruitment strategies will be tailored to sites according to service configuration e.g. services may be led from community or hospital based teams but liaise across settings. Clinical pathways will also be used to identify the most efficient recruitment strategy, e.g. patients with ILD will all be known to the tertiary centre.

7.1.1.2 Carers

Patient participants will be invited to identify whether they have a family member or friend who provides care for them. If they nominate such a person, he or she will be invited to participate to provide carer burden (ZBI-12) data at baseline, at the primary endpoint and study end.

7.1.2 Screening and eligibility

Eligibility Criteria are listed in section 6

7.1.2.1 Patients

Anonymised screening logs will be kept at each site and a copy sent to HHTU every quarter through an agreed secure route.

In order to demonstrate whether our included population are representative of the population of interest, we will collect anonymised information on participants who are approached but not consented and those who are consented but not randomised for CONSORT reporting including the reason not eligible for trial participation, or if they are eligible but declined.

The study nurse or doctor will complete the paper Eligibility Form. This will be checked and signed by the site Principal Investigator (PI) or delegated study doctor. If eligible, the study doctor will proceed to obtain written informed consent from the patient in accordance with GCP. With Sponsor approval, a registered independent prescriber (nurses who are registered with the Nursing and Midwifery Council (NMC) as an Independent Prescriber and are permitted to prescribe controlled drugs) may be permitted to consent. However, Sponsor approval must be sought before a PI can delegate informed consent responsibility to a non-GMC registered team member. If the Independent Prescriber is also the site PI, this must be approved by the Sponsor in the site set up stage. Eligibility details, including confirmation of consent, will be entered into the eligibility page of the e-CRF (RCC). At the point of creating a new subject on RCC, the participant will be given a Subject ID number. This will be used to identify the participant for the rest of the trial. If eligibility is confirmed, the study team will proceed to on the RCC to randomisation (see Section 7.3 for details on Randomisation).

In the event of a patient being initially ineligible, but subsequently re-screened, they will be given a *de novo* Subject ID number and treated as a new patient.

For patients who do not have a sufficiently recent renal function test, consent (see section 7.2) will be taken before this test is carried out to comply with the requirement to have eligible renal function confirmed within 21 days of consent. In the event of outstanding tests of renal function, the study team

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should advise patients that signing consent does not guarantee participation in the trial. However, if renal function is found to be within the eligible range, a further consent to participate in the trial is not needed.

Transport will be provided for patients, or expenses reimbursed if the visit is required outside routine appointments for clinical care. Most of the clinical assessments and tests are routine, meaning the patient would undergo them whether they were in the trial or not.

7.1.2.2. Carers

Patients will be asked to identify carers and provide contact details, or carers may be approached at the appointment if accompanying patients. A carer information sheet will be provided to the carer, and if they agree to participate, informed consent will be taken. Data will be collected from the carers at the specified time-points and data entered into the e-CRF.

7.2 Consent

7.2.1 Face to Face consent: All consent forms will be stored in accordance with local requirements. A copy of the consent form will be given to the participant, a copy entered into the patient's hospital notes and the original signed copy kept in the Investigator site file. A copy will be uploaded onto the e-CRF for central monitoring purposes.

Eligible patients will be approached and introduced to the study by a member of the clinical team responsible for their treatment, and have the opportunity to discuss the trial fully with both the clinician and the study nurse. Each participant will be informed of the aims, methods, anticipated benefits, and potential hazards and discomforts of the study, both through the Patient Information Sheet (PIS) and verbally. Patients will have at least 24 hours between receiving the PIS and giving their informed consent. Written informed consent may then be taken by a study doctor or Sponsor approved Independent prescriber listed on the Delegation Log who has received GCP training and the process of obtaining consent will be documented in the patient's medical notes. See section 7.1.2.1 for more details on who else may be permitted to take consent. Written informed consent will be taken before the baseline assessment is undertaken. Witnessed verbal consent for this trial will be allowed in the case of poor literacy or insufficient English language skills. Where necessary, verbal translation via a hospital or personal interpreter or telephone translation service (depending on availability) will be accessed to enable as broad a representation of patients as possible to participate.

7.2.2. Remote consent: If a participant is unable or unwilling to travel to clinic, due to COVID-19 or any other reason, they will be able to provide electronic consent remotely via DocuSign. The same pre-consent process will be followed as for face to face consent. However, the participant should only sign the electronic consent form after a full discussion with the person taking consent on the phone or video call. If the participant would like to proceed to consent, HHTU will send the Informed Consent form via DocuSign to the participant. The participant where possible, will sign the DocuSign form whilst still on the phone / video call.

If a paper consent form is to be posted to the participant, once signed, the participant must send it back to the site research team immediately so the person taking consent (who must be the same person who had the discussion on the phone/ video call) can sign it, taking the shortest amount of time possible between signatures. Confirmation of participant identity and signature must also be provided to comply with the MHRA Joint Statement on seeking consent by e-methods for a Type B study (Sept 2018).

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The site Principal Investigator (PI) will hold overall responsibility for the informed consent of participants at their site in an environment free from coercion or undue influence. The site PI may delegate responsibility to participate in the informed consent process to medical practitioners or independent prescribers at the site. Such personnel will be duly authorised, trained and competent to participate according to the ethically approved protocol. Where independent prescribers are to take consent, the Sponsor will review registration and the level of competence prior to “green light” approval for a site. See section 7.1.2.1 for further detail. **This trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirements.**

The participant will remain free to withdraw at any time from the trial without giving reasons and without prejudicing his/her further treatment, and will be provided with a contact point where he/she may obtain further information about the trial. Where a participant is required to re-consent or new information is required to be provided to a participant, the site PI will ensure this is done in a timely manner.

All personnel undertaking consent will make an assessment of capacity as part of the consent process. For this trial and for consent to be ethical and valid in law, participants must be capable of giving consent for themselves. A capable person will:

- understand the purpose and nature of the research
- understand what the research involves, its benefits (or lack of benefits), risks and burdens
- understand the alternatives to taking part
- be able to retain the information long enough to make an effective decision
- be able to make a free choice
- be capable of making this particular decision at the time it needs to be made (though their capacity may fluctuate, and they may be capable of making some decisions but not others depending on their complexity)

Where a participant is able to consent but later becomes incapacitated, they will be withdrawn from the trial, but we will collect data for survival. Consent at study entry will seek explicit permission for this. Data collected to that point of withdrawal will contribute to the analysis. Survival data will contribute to the specific survival analysis.

7.3 The randomisation scheme

The responsible statistician will prepare a randomisation schedule using the random permuted block method (1:1 ratio according to a computer generated sequence) stratified by causal disease (defined as COPD, OR heart disease, OR cancer OR other non-malignant lung disease) and site. Randomisation will be completed via an online system provided by the HHTU. Block size remains confidential. Full details of the randomisation scheme is not included in the trial protocol as knowledge of these details might undermine randomisation by facilitating deciphering of the allocation sequence. Instead, this specific information will be provided in a separate document with restricted access.

7.3.1 Method of implementing the allocation sequence

Once a site can proceed with randomisation for a consented patient, authorised trial staff with delegated responsibility for randomising patients should follow the instructions in the latest MABEL REDCap Cloud (RCC) User Manual, held in the local site file. This will involve logging onto the secure online randomisation system (RCC) administered by HHTU. RCC user accounts will be set up for delegated site staff by HHTU once all the necessary trial documentation and approvals for participation in the study

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have been received. Randomisation will not be activated at individual sites until the sponsor green light approval has been confirmed.

The online randomisation system will include an eligibility check before allowing randomisation to be completed. HHTU will receive an alert with confirmation of the site randomisation and assigned Subject ID number. The participant's Subject ID number should be added to the site screening log and participant register. The Subject ID number will be entered on all participant study documents and future correspondence from that point forward throughout the study. No other patient identifier will be used.

The online randomisation system will not automatically generate a study prescription form.

IMP and nIMPs will be supplied by SMPU to site pharmacy units arriving as bottles pre-packed and labelled according to the randomisation schedule supplied by HHTU. HHTU will request initial stock supplies for each site pharmacy following Sponsor permission. Subsequent orders will be placed by each site pharmacy in order to distribute timely and sufficient quantities of bottles of active drug or placebo. The IMP and nIMP will be supplied in tamper-evident, child-resistant, HDPE containers. Each IMP and nIMP bottle will have a unique identifier (i.e. a Kit Number). The Kit Numbers will identify the contents by the unique identifier but will not identify whether this equates to active or placebo. IMP and nIMP bottles will be dispensed from site pharmacy units according to the study prescription and dispensing logs completed. A Controlled Drug register will also be completed for receipt, dispensing and return of IMP and placebo. Treatment allocation will be concealed from the investigator, patients, the site research team, HHTU team and pharmacists for the full duration of the trial. The unblinding process detailed below enables clinicians to reveal treatment allocation in emergency situations.

In the event of SMPU informing about a required recall, the site pharmacy unit will check against the dispensing list for any affected IMP or nIMP, and patients will be contacted to return the medication. The details for this process will be in the site pharmacy manual.

7.4 Blinding

To maintain blinding, active drug and placebo capsules and their packaging are identical in appearance. Capsules are swallowed whole and appearance, taste, smell and consistency are identical.

As constipation is a common side-effect of morphine, corresponding laxative (Docusate sodium) or placebo laxative will be given as a non-investigational medicinal product (nIMP). Again, these will be prepared as identical capsules by SMPU to ensure blinding is maintained.

The side effects of the IMP and nIMP may lead to inadvertent unblinding of the treating clinician if the patient mentions symptoms during consultations. We will ask clinicians to record whether they think they knew the treatment allocation and review and report as part of the final analysis.

7.5 Unblinding

Reasons for unblinding include:

- Medical emergency where unblinding of the medication is necessary to inform clinical decision making
- In the event of a SUSAR needing expedited reporting
- Request by Data Monitoring Committee

In the latter two circumstances see 7.5.2

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7.5.1 This section outlines the process for emergency unblinding, the process is also described in the unblinding SOP in the Pharmacy Manual.

Routinely breaking the blind in double blind trials could compromise the integrity of the trial. The study code should only be broken for valid medical or safety reasons, e.g. in the case of a serious adverse event (SAE) where it is necessary for the investigator or treating health care professional to know which treatment the patient is receiving **before** the participant can be treated. This is also relevant to the period in the few days following the 56-day RCT where a clinician may need to know study allocation in the highly unlikely situation where a patient develops severe symptoms which could be due to morphine withdrawal.

Due to the low toxicity profile of low dose modified release morphine under appropriately monitored circumstances, the need for unblinding is very unlikely. The only envisaged emergency clinical scenarios are of anaphylaxis and respiratory depression requiring ventilator support. In both these cases, IMP would be stopped and the participant managed assuming that they are receiving active drug. Therefore emergency unblinding would be unnecessary. However, in the event of unforeseen circumstances warranting unblinding, the emergency unblinding process should be followed.

Emergency unblinding may be requested by the treating clinician (registrar level or above). The treating clinician will call the emergency trial phone number which will connect them to the Chief Investigator(s). This number will be accessible 24 hours a day every day of the year. The caller will be able to speak to the Chief Investigator(s) to discuss the clinical event and a decision will be made as to whether to unblind or not. Regardless of Chief Investigator(s) opinion, if the treating clinician still wishes to proceed to unblind there will be no barrier or veto of any decision made by the treating clinician. The Chief Investigator(s) will then enable access to the study code break via RCC and will email the treating clinician with a one-use-only access code to the randomisation system in RCC. After logging into RCC the treating clinician will be asked to enter the participant Subject ID Number and reason for unblinding. The treatment allocation (Active or Placebo, but not Group A or B) will be displayed to the treating clinician. An alert with the Site number and Subject ID Number (but not unblinded treatment allocation) will be sent to the HHTU. HHTU will notify the CI(s) and sponsor that the Subject was unblinded. The treating clinician will continue to deal with the participant's medical emergency as appropriate and document that emergency unblinding has occurred in the medical notes. HHTU will inform site staff of the unblinding event, but not the treatment allocation. HHTU will also remind the site research team that that only unblinded staff (direct care team) and/or authorised unblinded site research staff access the medical notes from this point forward in order to prevent unintentional unblinding. Unblinded site research staff must be authorised unblinded responsibilities on the delegation log). Summary information will be provided to the DMEC and reported as required in the final study analysis and report.

7.5.2 Non-emergency unblinding

In the event of a SUSAR, the Sponsor would request the CI to approve a one-use-only RCC access code. The same process as detailed above in 7.5.1 for emergency unblinding would apply, except the unblinded information (Active or Placebo, but not Group A or B) is sent to the Sponsor only.

The DMEC may request unblinded information for the closed part of the DMEC meeting to conduct safety and trend analysis in accordance with the DMEC Charter. An independent statistician will arrange access and transfer of unblinded reports/data to the DMEC in accordance with relevant SOPs.

7.6 Trial assessments

The participants will have baseline assessments between Day −8 and 0, and follow up assessments on Day 1, 2, 4, 7, 14, (16,18 dose escalation only), 20, 28, 42, 56 and 60. All assessments can be completed

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by the study nurse via a home, phone or postal visit, and most are short questionnaires only. The baseline and Day 28 assessments will require a face to face visit either via a home or clinic visit for vital sign measurements. The assessment schedule is tabled at the beginning of the protocol on page 12 and assessment details are given in Section 3.4.

7.6.1 Baseline data

Baseline study assessments will take place before randomisation, between Day −8 and Day 0, where Day 0 is the day of randomisation. The patient will then be randomised and receive their first packages of study medication. They will take the first dose within 4 days (to allow for Bank Holiday weekends) of Day 0, at night before going to bed, and the second dose in the morning on waking. The day of the first dose will be counted as Day 1 (even if this is the night of Day 0 for those who receive their prescription immediately on the day of randomisation). Thereafter, participants will be asked to complete study assessments in the morning if possible, although the study nurse phone call or face-to-face visit will be scheduled at a time arranged according to the participants' convenience.

NB. The letter informing the participant's GP that they have consented to the study will be sent through an agreed secure method to the GP surgery after consent and before the participant is randomised (Day −8 to Day 0). This will mean that the GP will have been informed before the patient takes their first dose of study medication.

7.6.2 Primary endpoint and primary outcome measure
This is described in Section 3.2.1.

7.6.3 Secondary outcome measures
These are described in Section 3.2.2.

7.7 Long term follow-up assessments

At the end of the 56-day assessment, the study nurse will ask patients if a) they would be willing to provide minimum benefit and harm data every three months from the end of the 56-day treatment period for 18 months or until the last participant has completed the 56-day treatment whichever is earliest and b) whether or not they wish to take open label morphine. Provision of data and open-label morphine are irrespective of each other; some may opt to do both, others neither, and still others only to provide data, or to take morphine and not provide data.

- Participants willing to provide minimum benefit and harm data will complete the following during telephone follow up:
    - Benefit: NRS worst breathlessness and NRS distress due to breathlessness
    - Side-effects: Morphine related symptoms (NCI CTCAE grading and presence/absence of vivid dreams)
- Participants agreeing to provide follow up but who are not contactable even through their GP (explicit consent sought in trial consent) for more than one consecutive data collection point will be considered "lost to follow up". We expect these instances will be rare as we should be able to establish if the patient is alive or dead, and if alive, where they are.
- If the participant indicates that they wish to take open label morphine, they will be referred to their usual clinician who will make that clinical judgement and prescribe if they consider appropriate and are willing to undertake clinical responsibility. Participants may have been on placebo and would be starting active morphine. Their usual clinician will be advised to monitor

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such patients *as if* they are opioid naïve. The advised starting dose would be 5mg MST Continus twice daily. Patients and their GP will receive written information at the end of the 56-day RCT to outline these issues.

Participants who agree to continue providing longer term study assessment data, **and** who take open label morphine will be requested to start this within 14 days of the end of the RCT.

Carers who are bereaved during the study period will be sent a VOICES survey 4 months after the bereavement if this is within the study data collection period.

7.8 Withdrawal criteria

Patient participation in the trial will be discontinued if:–

- the patient withdraws consent; reasons for withdrawal will be sought and recorded, whilst respecting the participants' right to give no reason
- the patient is withdrawn from the trial by the treating physician or medical researcher; reasons for withdrawal will be sought and recorded
- the trial is stopped on the recommendation of the DMEC.

Participants may withdraw fully from the trial (from the IMP, nIMP and from further data provision), or from the IMP and nIMP only *but continue to provide data.*

Participants withdrawing from IMP and nIMP will receive a study nurse phone call three days after stopping treatment to make general enquiry as to their wellbeing whether or not they are continuing to provide data. A SOWS assessment will be conducted.

In keeping with usual clinical care, if the participant stops IMP and the precipitating circumstances resolve to the satisfaction of both the participant and physician with responsibility for their care and both wish to restart the IMP, then the participant may do so. In this case, the date of IMP stop and recommencement will be documented as part of the adverse event reporting. Any events or reactions around this temporal relationship will be noted, and be helpful in attributing causality.

Subjects who withdraw from IMP, or from the trial, will not be replaced.

The study will be stopped, as guided by the TSC and DMEC, if:

- new literature indicates findings that can be applied to this question in terms of benefit or side effects
- reporting of AEs indicate that review of the study protocol is required, for the IMP
- there will be no interim analysis for effectiveness as the trial would not be stopped for this indication: even if a benefit was demonstrated, the side-effects data are very important in this clinical population, and recruitment to the full sample size would improve precision around the findings.

7.9 nIMP holiday

Should a participant experience loose stool, a temporary nIMP/Placebo holiday is permitted. The IMP/placebo must continue as prescribed and the nIMP/Placebo should be reinstated as soon as possible if clinically indicated. Prolonged interruption of Docusate/placebo dose is permitted but must be

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communicated to the Chief Investigator. A PI / CI decision will be made on whether the participant can continue in the study.

7.10 Storage and analysis of samples

Blood samples, checked in the preceding period (renal function within 21 days of randomisation), will be used for eligibility if the clinical situation is otherwise unchanged. If not available, whole blood venous blood samples will be drawn for eligibility screening. Samples will be analysed locally according to Trust procedures. The results will be held in the patient's medical notes as source data.

The site will adhere to and keep a copy of the site pathology service guidelines for obtaining, transporting and storing blood samples. Blood samples will be destroyed after analysis according to local Trust guidelines. The study nurse competency in blood sampling will be recorded at the study site, with a copy filed in each Investigator site file.

Biological samples collected from participants as part of this trial will be transported, stored, accessed and processed in accordance with national legislation relating to the use and storage of human tissue for research purposes and such activities shall meet the requirements as set out in the 2004 Human Tissue Act and the 2006 Human Tissue (Scotland) Act.

7.11 Study equipment

Blood pressure monitors, pulse oximetry and CO_2 measurement devices should be maintained / calibrated according to local Trust policy.

7.11.1 ActiGraph

The ActiGraph GT9X Link is an extensively validated, research grade activity monitor manufactured by ActiGraph. It weighs 14 grams, is 3.5 x 3.5 x 1cm and has a battery life of up to 14 days, depending on functions used. Linked with ActiGraph's own software, ActiLife, activity data from the GT9X Link is processed and analysed using independently developed and validated algorithms, capturing changes in free-living activity and sleep quantity. The ActiGraph GT9X Link can be used sequentially for multiple subjects.

In order to optimise subject compliance, the ActiGraph GT9X Link is worn on the non-dominant wrist using a Link wrist band. Wrist-worn devices also feature a wear time sensor which automatically senses when a device is removed. The device displays the date and time in 24-hour format, but all other subject feedback can be disabled for research purposes.

The ActiGraph Link is water resistant to 1 metre for 30 minutes, and can be worn when swimming and bathing.

ActiGraphs will be quarantined until cleaned with an alcohol-based solution in line with manufacturer guidelines between participants to minimise risk of exposure to COVID-19. User guides on how to clean the equipment will be provided to sites. Strict documentation will be maintained by sites to ensure that ActiGraphs are safe to distribute to participants.

7.12 End of trial

The end of the trial is defined as the date the last patient has completed their final clinic assessment for the 56-day RCT. Participants will also have the opportunity to take open label morphine after the end of the study if their usual clinician agrees. They will remain blinded to previous study allocation.

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An end of trial declaration form will be submitted to the MHRA, REC and HUTH R&D within 90 days from completion of the trial and within 15 days if the trial is discontinued prematurely. A summary of the trial final report/publication will be submitted to the MHRA, REC and HUTH R&D within 1 year of the end of trial. HUTH R&D will be notified immediately of any reason to halt the trial. The Chief Investigator(s) and HUTH R&D as sponsor will decide if the trial should be halted temporarily. The MHRA, REC and HUTH R&D will be notified within 15 days of a decision to temporarily halt the trial by submitting a substantial amendment notification.

8.0 TRIAL MEDICATION

8.1 Name and description of Investigational Medicinal Product

Opioids are available in various formulations and can be administered by a number of routes. We will use Morphine Sulfate modified release preparation as the IMP, with over-encapsulation to provide a blinded preparation. An initial dose of 5mg twice daily is required. The only preparation available as 5mg tablets in the UK is MST® CONTINUS®. Different modified release preparations of oral morphine do not have identical pharmacodynamics and pharmacokinetic profiles and switching from one preparation to another during titration is not recommended by the manufacturers. Thus MST® CONTINUS® will be used for both the 5mg and 10mg preparations.

The Morphine Sulfate modified release IMP will be over-encapsulated MST® CONTINUS® and will be identical in appearance, smell, taste and consistency to the placebo capsules.

The Morphine Sulfate modified release IMP will be provided as over-encapsulated MST® CONTINUS® 5mg tablets and 10mg tablets with matching placebo capsules. The 5mg and 10mg capsules will be different colours.

MST® CONTINUS® 5mg will be supplied by Cardiff and Vale University Local Health Board, St Mary's Pharmaceutical Unit (SMPU), 20 Field Way, Cardiff CF14 4HY, manufacturing authorisation number MIA(IMP) 35929.

Product information can be seen in the MHRA approved SmPC.

Morphine is rapidly metabolized to its active constituent in the liver, and is then predominantly excreted renally. Common side-effects (>10%) include constipation, (usually) transient drowsiness, nausea and difficulty concentrating when the medication is introduced or doses changed. Less common side-effects (1-10%) include anti-cholinergic effects such as urinary retention and acute confusion; itch; persistent nausea; dizziness and myoclonus.

Although concern about addiction is commonly expressed, the risk of addiction to opioids used for the treatment of breathlessness is extremely small. However, opioids can create a physical tolerance over time and sudden withdrawal may cause a physical withdrawal syndrome. This is not anticipated to be a concern with the dose or length of time in this study. In the event of a problem, symptoms are easily resolved with reducing doses of oral morphine for those who do not wish to continue opioids post-study. Opioids are widely used for the relief of pain and there is extensive knowledge regarding its safety in clinical practice even with frail patients. Modified release morphine is not licensed for the treatment of breathlessness despite its increasing off-license use for this indication in advanced illness. MHRA approval will be sought prior to study start.

8.2 Legal status of the drug

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MST® CONTINUS® (5mg, 10mg) is licensed for use in the UK for moderate to severe pain. It is a Schedule 2 Controlled Drug (CD), Prescription Only Medication.

A sustained-release preparation or oral morphine (Kapanol®, 10mg/24 hours, 20mg/24 hours) is licensed for chronic breathlessness by the Therapeutic Goods Administration in Australia. Kapanol® is not available in the UK. The use of morphine for breathlessness is recommended by a number of current international clinical guidelines for patient populations relevant to this trial. Therefore morphine can and is prescribed for chronic breathlessness by clinicians for this patient population in the UK as part of usual care but using preparations licensed for moderate to severe pain.

8.3 Reference Safety Information/Summary of Product Characteristics (SmPC)

The Summary of Product Characteristics (SmPC) will be used as the reference safety information (RSI). The current MHRA approved version will be clearly listed in the pharmacovigilance section of the site file.
The study will replace the RSI with updated versions as appropriate during the trial period, with new versions being formally reviewed as part of an updated risk assessment and implemented after a substantial amendment has been approved by the MHRA.

8.4 Drug storage and supply

Details will be given in the Study Pharmacy Manual.

The medicinal products will be manufactured and supplied by St Mary's Pharmaceutical Unit (SMPU) (MIA (IMP) 35929). Placebo preparations will be manufactured in accordance with Good Manufacturing Practice (GMP) by the SMPU. SMPU will store products until HHTU request supplies for sites. SMPU will arrange for transportation to site pharmacies according to Good Distribution Practice (GDP).

Study medication will be stored and dispensed by the site pharmacy department in accordance with Good Clinical Practice (GCP), and as detailed in the MABEL site pharmacy manual. The medication bottles will be dispensed (with the IMP or placebo bottles dispensed through the CD register) in accordance with SOPs for CTIMPs by hospital pharmacy units in the recruiting centres.
The pharmacy should use local Trust SOPs to cover each of the aspects of the safe management of CDs such as ordering, receipt, recordkeeping etc. SOPs will be kept up-to-date, reflecting current legal and good practice requirements for CDs and be clearly marked with the date of issue and review date.

8.4.1 Storage

MST® CONTINUS® is a CD and should be stored in accordance with the CD regulations and in accordance to the Trust's own standard operating procedures. Oral MST® CONTINUS® should be stored in the CD cabinet which should comply with the Misuse of Drugs (Safe Custody) Regulations, with medication packs dispensed through the MABEL trial CD register.

There is no supply of Morphine Sulfate modified release to participants after the 56-day treatment period, but participants will have the option of open label morphine. An End of trial letter will be sent to the participant's GP providing guidance about ongoing Morphine Sulfate modified release prescriptions.

8.5 Preparation and labelling of Investigational Medicinal Product

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The designated site clinical trials pharmacist/research team member will prepare the IMP and nIMPs for the participant on receipt of a legal prescription and in accordance with the Pharmacy Randomisation List, bottle allocation, Kit Number ID and Participant Log in accordance with the Pharmacy Manual.

Study medication will be labelled as described in Section 7.3.1. Participant Dispensing and Drug Return Logs will be maintained by the site pharmacy for each participant; one for IMP/placebo and one for nIMP/placebo.

Only an authorised study doctor or sponsor approved registered independent prescriber listed on the delegation log will prescribe study medication. The prescription will include all the legal requirements for a CD including quantity in words and figures in indelible ink.

The pharmacist will dispense the study medication to each participant upon receipt of a suitably signed trial specific prescription.

At randomisation, the participant will receive Bottle 1, containing 14 days' supply for Day 1 to Day 14.

Between Day 7 and Day 14 the participant will receive Bottles 2 and 3, each containing 14 days' supply, total 28 days' supply for Days 15 to 42.

Between Day 36 and Day 42, the participant will receive Bottle 4, containing 14 days' supply for Days 43 to 56).

Table 2 - Dispensing schedule

| Medication Dispensing / Administration Activity | Day | | |

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8.6 Dosage schedules

The dosing period for this trial is 56 days.

8.6.1 Intervention Arm 1:

Day 1 to Day 14:
5mg twice daily oral Morphine Sulfate modified release and 100mg twice daily oral Docusate Sodium
From Day 15 to Day 56:
EITHER
5mg twice daily oral Morphine Sulfate modified release and 100mg twice daily oral Docusate Sodium
OR
10mg twice daily oral Morphine Sulfate modified release and 100mg twice daily oral Docusate Sodium

8.6.2 Comparator Arm 2:

Day 1 to Day 14:
5mg twice daily oral *placebo* Morphine Sulfate modified release and 100mg twice daily oral *placebo* Docusate Sodium

From Day 15 to Day 56:
EITHER
5mg twice daily oral *placebo* Morphine Sulfate modified release and 100mg twice daily oral *placebo* Docusate Sodium
OR
10mg twice daily oral *placebo* Morphine Sulfate modified release and 100mg twice daily oral *placebo* Docusate Sodium
All participants will take one blinded opaque capsule each morning on waking and each night on going to bed containing either Morphine Sulfate modified release or placebo for 56 days. In addition, all participants will take one blinded opaque capsule each morning on waking and each night on going to bed containing either Docusate Sodium laxative or placebo for 56 days. In this pragmatic trial, the timing will not be more specific than this description. The Morphine Sulfate modified release/placebo capsules and the Docusate Sodium/placebo capsules will be different colours. The 5mg and 10mg Morphine Sulfate modified release/placebo capsules will be different colours. See pharmacy Manual.

Further possible dose changes are outlined in Section 8.7.

The medication will be administered by the participant themselves, their carer (informal or formal) or member of the research or clinical team as necessary. Each daily dose (morning and night) will be swallowed whole by the participant.

Product information can be seen in the MHRA approved SmPC.

8.7 Dosage modifications

8.7.1 Dose escalation

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The dose of IMP may be increased to 10mg 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 NRS scale) AND the participant has acceptable side-effects (see definition of acceptable side-effects). 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. As the vast majority, if not all, participants will be out-patients, and most assessments will be carried out in the community, the dose increase will start on Day 15 to allow time for the prescription to be issued, dispensed and new dose of IMP to be supplied to the participant in a manner which ensures continuous IMP supply. Whilst awaiting the new dose, the participant will continue on 5mg IMP twice daily. Only a study doctor listed on the delegation log can make the decision to dose escalate IMP to 10mg (or not) on Day 7.

Dose titration applies only if the participant has acceptable side-effects, defined in Section 3.3.2.6.

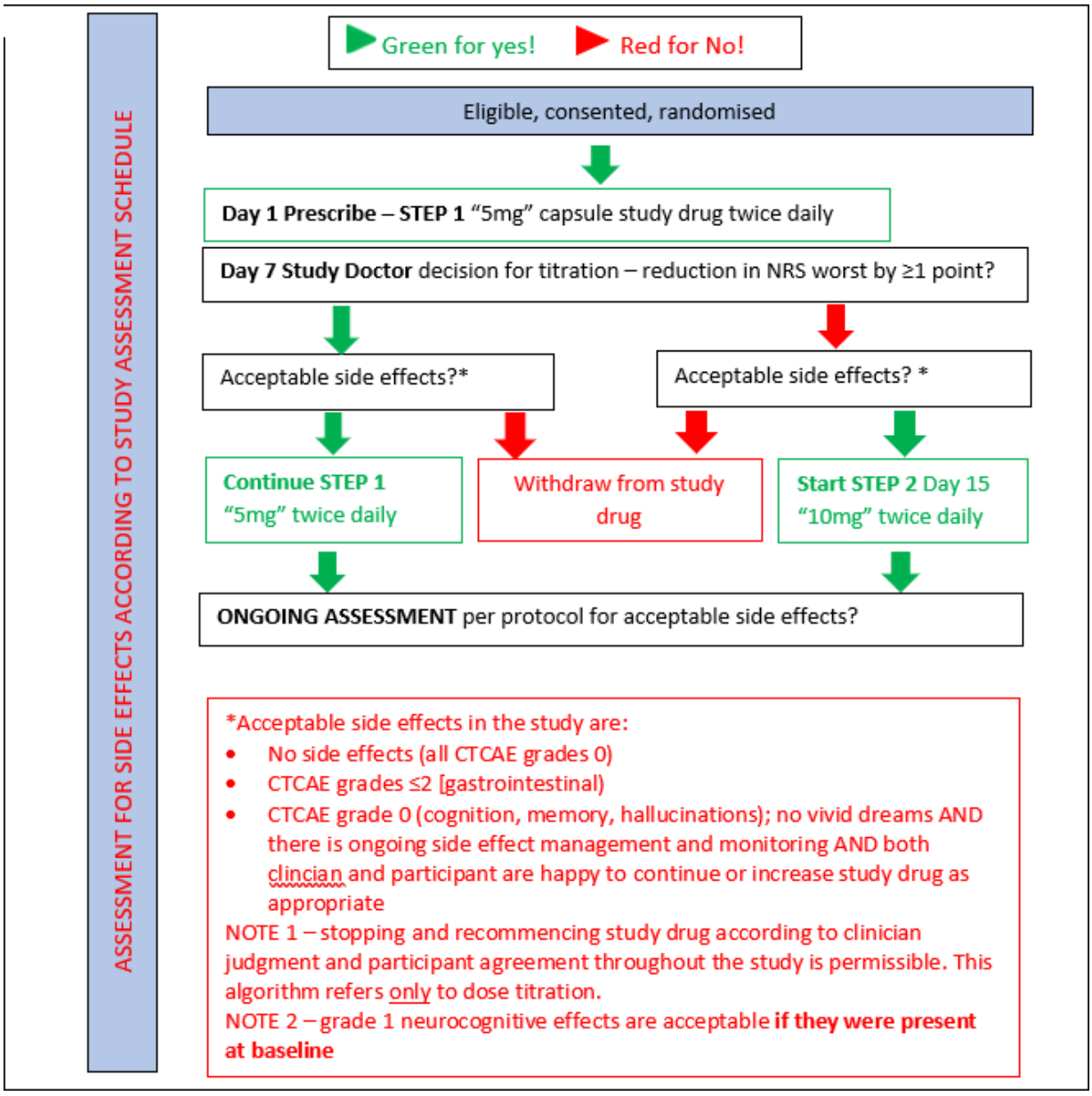
The process for dose titration will adhere to the following process (see Dose Titration Flowchart below). The titration only applies to IMP; the dose of nIMP stays the same:

a) On Day 7+/-1, the study nurse will complete Day 7 study assessments.
b) If the participant has achieved an improvement of at least one point on the NRS scale at Day 7 from the baseline measure and they have acceptable side-effects they will continue to take 5mg IMP/placebo twice daily. If they have unacceptable side-effects, they will withdraw from IMP and nIMP.
c) If they have not achieved an at least one point NRS improvement at Day 7 from the baseline measure and they have acceptable side-effects, the Principal Investigator (PI) / study doctor will consider the participant for dose titration to 10mg IMP twice daily starting on Day 15.
d) Participants dose titrating to 10mg will be reviewed for side-effects after 1, 3 and 7 days (Day 16, 18 and 20).

1. At any point during the study, in the event of side-effects leading to stopping of IMP, if these resolve to the satisfaction of the participant and the treating clinician, and the participant is willing to re-start the IMP, this will be allowed and documented in the CRF and clinical record.
2. Morphine is renally excreted. In keeping with routine clinical practice, routine renal function for the purposes of judging whether IMP should be continued will not be required as part of the protocol. Renal function may be tested during the 56-day treatment period if clinically indicated by their underlying medical condition and the results used in the participant's routine clinical care. In the event of such a test revealing a reduction of eGFR to below the trial's inclusion criteria, the IMP should be stopped. Should the renal function then improve again, the IMP may be restarted if participant and their clinician are in agreement.

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Dose Titration Flow Chart



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8.8 Management of morphine-related harms

Symptoms will be identified during each assessment using criteria established by the National Cancer Institute, and will be graded accordingly (see Section 3.3.2.6).

Specifically, for this study, the symptoms of interest will be:

- respiratory depression
- central nervous system (neuro-cognitive) effects
    - confusion
    - cognitive impairment
    - hallucinations
    - memory impairment
    - vivid dreams
    - drowsiness
- gastrointestinal
    - constipation
    - nausea, vomiting

Participants who develop signs and symptoms consistent with the following opioid-related harms will require clinical review:

- Any neuro-cognitive disturbance (cognition, memory, hallucinations CTCAE grade ≥1; presence of vivid dreams that are new or worse since baseline; somnolence ≥8 on the Karolinska scale). These will trigger an adverse event report.
- Constipation, nausea or vomiting grade ≥1 on the CTCAE. The attending physician should consider prescription of appropriate measures. A grade of ≥2 will trigger an adverse event report.
- Considered to have opioid side effects by the attending physician

A CTCAE grade of 3 *that has not responded to symptomatic treatment instituted by the treating physician* according to local protocols or grade 4 will additionally activate withdrawal of IMP.

8.8.1 Respiratory depression

If participants develop opioid toxicity in the form of respiratory depression (≤10 breaths/minute), associated with a fall in oxygen saturation (≤90%), the person will be assessed urgently by a medical practitioner. All other possible contributing factors assessed (e.g. acutely worsening renal function, infection screen, biochemical profile, drug error) should be considered.

8.8.2 Use of Naloxone for Respiratory Depression

If respiratory rate is ≥10/min and the participant is easily rousable and not cyanosed, with an oxygen saturation >90%, adopt a policy of careful ongoing monitoring. Consider reducing or omitting the next regular dose of study medication while other factors that may contribute to acute opioid toxicity such as acute renal impairment are assessed.

If respiratory rate <10/min, and a participant is cyanosed or with an oxygen saturation <90%:

- If the participant is in the community, then hospital admission is required
- Administer oxygen. If still cyanosed and oxygen saturation <90% then,
- Dilute a standard ampoule containing naloxone 400 microgram to 10 ml with saline for injection

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- Administer 2.5 ml (100 microgram) IV stat and review response. Doses may be repeated. Consider an intramuscular dose at the same time the intravenous dose is given. Continue to titrate naloxone until the participant's respiratory status is satisfactory
- Further boluses may be necessary because naloxone is shorter-acting than morphine (and other opioids)
- A continuous infusion of naloxone may be necessary in some cases for a short time

Caution: the use of higher dose boluses of naloxone may cause the participant to wake suddenly, but IV naloxone has a short half-life. If no cause is found, the participant should be withdrawn from the study medication and continue intensive monitoring until at least the next day. We would continue to collect outcome data.

8.8.3 Nausea and/or vomiting

Management of nausea and/or vomiting will be in accordance with local clinical protocols.

8.9 Concomitant medication

8.9.1 Permitted medications and treatments

All medications and treatments required for clinical care in the opinion of the clinician responsible for clinical care are permitted for the duration of the study except those identified below.

8.9.2 Medications and treatments not permitted:

In addition to the prohibited medications outlined in the exclusion criteria, participants should not:

- take an opioid (either weak or strong), for breathlessness, cough or pain, for the duration of the 56-day treatment period.
- take a strong opioid for pain – participants needing this for clinical care will be withdrawn from IMP and nIMP, but may continue providing data if they wish. However, where this commenced **before** the primary endpoint, their data will be omitted from the final analysis dataset for the primary outcome. Where this is commenced **after** the primary endpoint they will be included in the intention-to-treat analysis.

In the event that the clinician deemed that there is no equally appropriate alternative to prohibited medications, then the participant may need to be withdrawn from the trial and the clinician should seek the advice of the Chief Investigator or deputy.

8.9.3 Medications permitted with caution

Consistent with current clinical practice and as stated in the RSI, concomitant use of medicines such as benzodiazepines or related drugs is permitted with caution. Concomitant use of morphine and sedative may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are considered not possible by their clinician with responsibility. The two studies which investigated the safety (hospital admission and mortality) of benzodiazepines in people with advanced COPD and in ILD, showed an association with increased mortality and admission in people taking higher doses (>0.3 benzodiazepine daily dose equivalents).[26;27] Thus any doses over 20mg/day diazepam equivalent will not be permitted in this study.

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If a decision is made to prescribe concomitant sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible. Appropriate clinical review for signs and symptoms of respiratory depression and sedation, and information given to patient and caregivers of these symptoms, by their clinician is recommended.

8.10 Trial restrictions

- Women of childbearing potential are required to use adequate contraception for the duration of the trial. Details are given in Sections 2 and 6.2.
- Morphine may cause drowsiness. If affected the participant should not drive or operate machinery in accordance with the SmPC. It is recommended that additional caution is taken during the first 7 days of IMP and nIMP, and the first 7 days of dose titration (if relevant) until the participant is able to see whether they are affected. At the doses used in this study, it is very unlikely that participants will have serum levels near or over the UK legal limit for driving.[64]

8.11 Assessment of compliance

Participants will not be observed taking IMP and nIMP.

Opened bottles will be returned by the participants or carer to the study team at follow up visits. The study team will count the number of returned unused capsules of Morphine Sulfate modified release/placebo and Docusate Sodium/placebo and will complete the drug accountability form in the e-CRF. The study team will return the unused capsules to the dispensing pharmacist who will re-count and document unused medication following Controlled Drug requirements.

If the participant or carer returns the bottles directly to the dispensing pharmacist, the trial pharmacy team will count the number of returned unused capsules and inform the study team so that the drug accountability form can be completed in the e-CRF

Any unused remaining medication will be destroyed in accordance with legal requirements and following authorisation by the Sponsor.
In this pragmatic trial, levels of adherence will not influence the decision to continue or stop the trial but will be included in trial reports to Sponsor.

The aim of the trial's clinical training for site clinicians with regard to early detection and management of morphine-related side-effects will improve tolerance and thus compliance. Also it is hoped that clinicians who are more confident about their prescribing and monitoring of morphine will result in more confident participants.
Non-compliant subjects who continue to provide trial data will be followed up according to the protocol.

8.12 Name and description of Non-Investigational Medicinal Product (nIMP)

As constipation is a common side-effect of morphine, corresponding laxative (100mg twice daily oral Docusate Sodium) or placebo laxative will be given as a non-investigational medicinal product (nIMP) to prevent unblinding. Again, these will be prepared as identical capsules by SMPU to ensure blinding is maintained. The colour of the nIMP will be different to the IMP (see Pharmacy Manual).

Docusate Sodium 100mg capsules will be supplied by Cardiff and Vale University Local Health Board, St Mary's Pharmaceutical Unit (SMPU), 20 Field Way, Cardiff CF14 4HY (manufacturing authorisation number MIA (IMP) 35929). Capsules will be over-encapsulated into a gelatin size 00 capsule with added lactose monohydrate.

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The same process will be used for evaluation of compliance as for IMP. As the nIMP is not a controlled drug, there are no measures, in addition to those required by the trial, for storage, dispensing and destruction.

9.0 PHARMACOVIGILANCE

9.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other ‘important medical events’ may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out: • in the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product

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	• in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above and relates to the consequence of the event.

Monitoring and reporting of pharmacovigilance aspects of the trial will be in accordance with the trial Standard Operating Procedures and detailed in the Trial Monitoring Plan.

9.2 Operational definitions for (S)AEs

In this blinded CTIMP, participants are expected to have a high morbidity or mortality, and there is no intention (or plausible biological reason) that the intervention will affect the course of the participants' underlying disease.

Morphine has a well-known safety profile and is in regular common usage as part of its license for pain. However, although Kapanol® (a sustained release morphine preparation) has a license for chronic breathlessness in Australia, MST® Continus® (or any other preparation available in the UK) does not have a licence for chronic breathlessness. Further, longer-term (longer than 7 days) data are few, therefore, all AEs and ARs will be reported as they will improve the knowledge regarding the safety profile of the drug for this purpose in this patient population, and will be required for the trial analysis.

(S)AEs and (S)ARs of special interest – that is, known common morphine-related side-effects, will be evaluated for duration and intensity according to the National Cancer Institute Common Terminology Criteria for Adverse Events V5.0 (NCI-CTCAE).

9.2.1 Expected Serious Adverse Events

Due to the seriousness of the disease(s) in this study, the following expected SAEs will not require reporting on the trial's SAE report form. The events will need to be recorded in the clinical record and a monthly return of number of expected events will be reported to HHTU. The number of expected SAEs exempt from SAE notification will still require reporting to the DMEC and annually on the Development Safety Update Report.
Expected SAEs exempt from SAE notification are listed in Table 3.

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Table 3. Expected SAEs due to causative medical condition exempt from SAE reporting

• Admission to hospital or prolongation of existing hospitalisation for acute exacerbation/complication of causative medical condition or known co-morbidities (e.g. decompensation of heart failure, infective exacerbation of COPD, angina, arrhythmia)
• Death due to causative medical condition or known co-morbidities
• Life-threatening complication of causative medical condition or known co-morbidities not resulting in hospital admission
• Exacerbation/complication of causative medical condition or known co-morbidities resulting in persistent disability
• Worsening of symptoms of causative medical condition or known co-morbidities resulting in persistent disability
• Elective surgery, or admission to hospital, or prolongation of existing hospitalisation for pre-existing conditions
• Worsening of laboratory values due to causative medical condition or known co-morbidities resulting in persistent disability, hospital admission or death
• It is expected that patients with advanced cardio-respiratory disease, especially those with heart failure, are at risk of variation in renal function, and morphine is excreted through the kidneys. Therefore a patient who has tolerated IMP may develop signs of toxicity in the event of renal dysfunction. Renal function should be reviewed in response to clinical indicators according to routine practice.
• Any admission to hospital or other institution for general care where there was no deterioration in condition, e.g. planned pacemaker battery change.
• Treatment on an emergency, outpatient basis for an event due to causative medical condition **not** fulfilling any of the definitions of serious as given above and not resulting in hospital admission.

Note: The reference safety information (RSI) will be Section 4.8 of the MHRA approved SmPC. This will be updated during the trial as relevant. Site training will emphasise that site clinicians describing the event should use the relevant term in this document.

9.2.1.1 Expected morphine-related side-effects with consequences meeting criteria for seriousness (SARs)

Unlike the expected SAEs in Table 3, these **will** be reported as SAEs (SARs) but will only require reporting within 14 days and not the expedited report within 24 hours.

These will be recorded as part of the eCRF and rated according to CTCAE severity grading (e.g. nausea, vomiting, constipation etc.). If they meet MABEL protocol criteria for “seriousness”, a SAE form will be completed. If AE or SAE forms are completed for such events, these are categorised as expected AE/SAEs.

Expected morphine-related side-effects with consequences meeting MABEL protocol criteria for seriousness (SARs), unlike the expected SAEs in Table 2, these will be reported as SAEs (SARs) but will only require reporting within 14 days and not the expedited report within 24 hours.

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However please note that a SAR whose nature and severity is not consistent with the applicable product information (the MHRA approved SmPC) and where a report could add significant information on the specificity, increase of occurrence or severity of a known and already documented SAR, is considered a SUSAR and will require completion of an SAE form within 24 hours of becoming aware of the event.

9.2.2 Expected (non-serious) Adverse Events due to disease and comorbidities

A pre-existing condition (i.e. a disorder present at the baseline study visit and noted on the baseline medical history/physical examination form/medical notes), is not to be reported as an AE unless the condition worsens or episodes increase in frequency during the AE-reporting period. Expected (non-serious) AEs will not be required to be reported or entered into the eCRF but **will** need to be recorded in the patient's clinical record.

9.3 Recording and reporting of SAEs AND SUSARs

The Sponsor's pharmacovigilance SOP and study specific instructions about the process for reporting must be followed. Sites will receive training on pharmacovigilance reporting during site set-up, and copies of SOPs/Instructions will be available in the study site file.

9.3.1 Reporting Period

The AE reporting period for this trial begins as soon as participants are consented to the trial and ends one month after the patient's final study treatment duration assessment (Day 56). The AEs and SAE reporting starts from consent, and SUSAR/SAR reporting starts from the first IMP dose and is the same for all participants irrespective of allocation. However, if a patient provides informed consent but is subsequently found to be ineligible, then the reporting period will end at the point that the decision was made that the patient was ineligible. Participants' health status will be checked at each study assessment and the local investigator will record all directly observed AEs and all AEs reported by the trial participant (as per defined).

Where a participant withdraws consent for further processing of data, this does not preclude the reporting of SARs and SUSARs which are required to continue being reported according to the protocol for regulatory purposes. The PIS will include a section explaining this to the participant.

9.3.2 Reporting process

All reportable adverse events as defined in section 9.2 (serious and non-serious) will be recorded on an Adverse Event Form within the electronic data capture system provided by HHTU for this study, as well as in patients' medical records/notes. All AEs will be followed-up by site staff until the event has resolved or a decision has been taken for no further follow-up. If a clinically significant abnormal laboratory value occurs, this abnormality will be recorded as an adverse event/reaction.

In all cases unexpected SAEs, SARS and SUSARs will be reported to the Sponsor, **within 24 hours** of the research staff becoming aware of the event. Expected SARs (Section 9.2.1.1) will be exempt expedited 24 hour reporting but must be reported **within 14 days** of research staff becoming aware of the event.

Expected SAEs related to the underlying condition (Table 3) will be exempt from SAE reporting (Section 9.2.1). The **number** only of these expected SAEs will be monitored by HHTU and reported to sponsor.

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They will not be further categorised unless further information is requested by the DMEC in the event of unequal numbers between the arms.

For each **reported** SAE the following information will be collected:

- full details in medical terms and case description
- event duration (start and end dates, if applicable, and if admitted, admission and discharge dates, with specialty noted)
- action taken
- outcome
- seriousness criteria
- causality (i.e. relatedness to trial drug / investigation), in the opinion of the investigator
- whether the event would be considered expected or unexpected.

Each SAE will be identified by a local site SAE sequential number (e.g. SAE-001). The SAE should be documented on a SAE log kept in the site trial file. The SAE forms will consist of an 'initial' SAE report form and a 'follow up' SAE form. The 'initial' SAE form will capture the early data about the event but may not be able to report a SAE outcome. In this event, the 'follow up' SAE form should be used to provide ongoing data about the event. Several 'follow up' SAE forms may be required to provide ongoing data about the event until an outcome is determined by the site PI. A final 'follow up' SAE form should be used to report an SAE outcome when this is known.

All AE and SAE reporting forms will be available on paper and in the HHTU RCC EDC system used for this study. Paper forms will be provided in the Investigator site file. Paper SAE reporting forms should be scanned and emailed to HHTU (hhtusafetyreporting@hyms.ac.uk) within 24 hours of becoming aware of an event. The SAE event will also be recorded in the RCC EDC and an automatic alert will notify the HHTU team when a SAE form has been created.

Assessment of severity, seriousness and causality will be made by the PI or authorised Study Doctor on the delegation log. The PI/Study Doctor will decide whether the serious event is an SAE or SAR by assessing whether the event is either unrelated or possibly related to the IMP (causality). If the event is possibly related then it is a SAR and an assessment needs to be made by the Chief Investigator (on behalf of the Sponsor) as to whether the event is expected or not for the IMP. If the SAR is listed in the MHRA approved Summary of Product Characteristics then it is expected.

In addition to the PI, the CI will also assess causality and document their assessment on the SAE form. The CI must assess causality after the PI and must confirm that they have not influenced the PI. The PI's assessment of causality must not be downgraded by the CI.

If the PI/Study Doctor from the reporting site is unavailable, initial reports without a causality and seriousness assessment will be submitted to HHTU and sponsor by the site study team within 24 hours of becoming aware of the SAE, but will be followed-up by a medical assessment as soon as possible thereafter. The PI/Study Doctor must always review the SAE form and sign to confirm the contents of the report are accurate and complete and that he/she has also assessed the severity, seriousness and causality of the SAE.

Any change of condition or other follow-up information should be reported to the Sponsor as soon as it becomes available. Events will be followed up until the event has resolved or a final outcome has been reached. The PI is required to assess causality again on the follow-up form. If the PI has a change of opinion on causality after considering the additional follow-up information, the CI will be required to reassess causality and, if a SAR, then to assess expectedness.

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All SAEs / SARs assigned by the PI/Study Doctor as possibly related to IMP treatment and those the CI has assessed as unexpected will be classified as SUSARs and will be subject to expedited reporting to the MHRA. The Sponsor will inform the MHRA and the REC of SUSARs within the required expedited reporting timescales.

9.4 Responsibilities

The responsibilities regarding AE and AR reporting are as follows:

9.4.1 Principal Investigator (PI):

Checking for AEs and ARs when participants attend for treatment / follow-up.

1. Using medical judgement in assigning severity, seriousness and causality
2. Ensuring that all SAEs and SARs are recorded and reported in line with the requirements of the protocol, and SUSARs are recorded and reported to the Sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs and SARs (including SUSARs) are chased with Sponsor if a record of receipt is not received within 2 working days of initial reporting
3. Ensuring that AEs and ARs are recorded and reported in line with the requirements of the protocol

9.4.2 Chief Investigator (CI) / delegate or independent clinical reviewer:

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit
2. Using medical judgement in assessing causality of SAEs
3. Using medical judgement in assessing expectedness
4. Immediate (within 24 hours) review of all SUSARs
5. Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol as detailed in the Study Monitoring Plan
6. Assigning Medical Dictionary for Regulatory Activities (MedDRA) or Body System coding to all SAEs and SARs
7. Preparing the clinical sections and final sign off of the Development Safety Update Report (DSUR)

9.4.3 Sponsor or CTU on behalf of the Sponsor:

1. Central data collection and verification of AEs, ARs, SAEs, SARs, unexpected SARs and SUSARs according to the trial protocol
2. Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit according to the Study Monitoring Plan
3. Reporting safety information to the independent oversight committees identified for the trial: Data Monitoring and Ethics Committee (DMEC) and / or Trial Steering Committee (TSC) according to the Trial Monitoring Plan
4. Expedited reporting of SUSARs to the Competent Authority (MHRA in UK) and REC within required timelines
5. Notifying Investigators of SUSARs that occur within the trial
6. The unblinding of a participant for the purpose of expedited SUSAR reporting
7. Checking for (annually) and notifying PIs of updates to the Reference Safety Information for the trial

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8. Preparing standard tables and other relevant information for the DSUR in collaboration with the CI and ensuring timely submission to the MHRA and REC

9.4.4 Trial Steering Committee (TSC):

In accordance with the Trial Terms of Reference for the TSC, periodically reviewing safety data and liaising with the DMEC regarding safety issues.

9.4.5 Data Monitoring Committee (DMEC):

In accordance with the Trial Terms of Reference for the DMEC, periodically reviewing unblinded overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

9.5 Notification of deaths

Only deaths that are assessed to be caused by the IMP will be reported to the Sponsor. This report will be immediate.

9.6 Pregnancy reporting

If a study patient becomes pregnant whilst participating in the trial, the patient will be withdrawn from study treatment but will continue to be followed-up for study outcomes. The pregnancy will not be considered an AE. The patient will be followed up by one to two monthly visits/telephone contacts during pregnancy, and at birth and at 3 months after the birth of the baby. Should there be a congenital anomaly or birth defect, then this will be reported as an SAE/SAR/SUSAR.

9.7 Overdose

The most likely cause is inadvertent repetition of a single dose, although given the size of the capsules this is most unlikely; or a participant taking two doses of IMP rather than one dose of IMP and one dose of nIMP by mistake. Again, as the colours will be different this is unlikely.

In the event of an overdose, a history will be taken and the IMP package examined to estimate how many and over what period of time the overdose was taken. A clinical review, including a clinical cognitive assessment, will be undertaken by a clinician with responsibility for the participant and appropriate measures according with their clinical judgement taken to ensure participant safety.

If the participant does not require clinical intervention (that is, no or mild self-limiting effects only), then the participant will be advised to omit the next dose and continue as prescribed thereafter.

Serious effects are unlikely but possible, and in the event of respiratory depression the participant should be managed according to the schedule described in Section 8.8. If an SAE is associated with the overdose, ensure the overdose if fully described in the SAE report form. Overdoses will be noted, but the participant will remain included for analysis.

9.8 Reporting urgent safety measures

If any urgent safety measures are taken the CI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the MHRA and the relevant REC of the measures taken and the circumstances giving rise to those measures.

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Safety reporting will comply with MHRA guidance:
http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Safetyreporting-SUSARSandASRs/index.htm

9.9 Development safety update reports

The CI will provide (in addition to the expedited reporting above) DSURs once a year throughout the clinical trial, or on request, to the Competent Authority (MHRA in the UK), Ethics Committee, Host NHS Trust and Sponsor. The MHRA approved SmPC will need to be reviewed for up-dates annually at the time the DSUR is completed. If the SmPC has been updated, the CI and Sponsor will risk assess the changes and decide if they have an impact on patient safety. If the decision is that the updated SmPC needs to be used as the new Reference Safety Information (RSI) then this must be submitted to the MHRA as a substantial amendment. The updated SmPC/IB can be used once approved by the MHRA.

9.10 Safety Notifications

The Chief Investigator must inform all sites rapidly of emerging safety issues, such as the occurrence of potential SUSARs. For double-blind trials, a potential SUSAR will be notified to all sites regardless of whether the subject was on placebo or IMP to minimise the risk of unblinding staff. A basic description of the event should be provided, but the sites will remain blind. The Sponsor must be copied into the correspondence to all sites.

10.0 STATISTICS AND DATA ANALYSIS

10.1 Sample size calculation

For 90% power and a 5% level of significance to detect an effect size of 0.4[14] in the primary outcome of NRS-worst breathlessness/past 24 hours at Day 28, a sample size of 264 participants (132 per group) is required. This effect size denotes a moderate effect and equates to a 1 point change in NRS[16], assuming a standard deviation of around 2.5[18;65;66]. NRS-worst breathlessness will be measured weekly at baseline, Day 7, 14, 20 and 28. It is assumed that there will be correlation of approximately 0.5 between these post-randomisation measures which then reduces the estimated sample size to 168. Further adjustment for baseline covariates (again assuming a correlation with outcome of 0.5) reduces the sample size to 126. Allowing for 20% attrition, would require an increase in the sample size to a total of 158 participants (79 per group).

These assumptions are reasonable given a post-randomisation correlation of 0.67 from participants in the BreatheMOR-HF trial. However, assumptions will be checked after 50 participants have been randomised and have reached the Day 28 outcome point.

10.2 Planned recruitment rate

Recruitment rates have been estimated based on prior experience of recruiting to previous opioid and other drug placebo-controlled palliative care trials for breathlessness.

The recruitment target is 158 participants, randomised in 14 centres over 18 calendar months. This will give a total of around 187 recruiting months across all centres over the 18 month recruitment period, equating to a recruitment rate of approximately 1 participant per centre per month.

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10.3 Proposed analyses

A detailed statistical analysis plan (SAP) will be developed and finalised prior to the locking of the trial database in consultation with the trial steering committee (TSC).

Throughout, a 5% two-sided significance level will be used. The intention to treat principle will be followed in the primary analysis.

The primary outcome is NRS worst breathlessness over the previous 24 hours at Day 28.

The primary analysis will be a repeated measures analysis of covariance, including terms for treatment and breathlessness measurements at Days 2, 4, 7, 14, (Days 16 and 18 where appropriate), 20 and 28. The variables on which the randomisation was stratified (site and causal disease) will be included and the model will be adjusted for baseline NRS worst breathlessness. The model will also include a treatment by time interaction. The repeated measures analysis will not only enable the estimation of a treatment effect at Day 28, but will also allow for an overall assessment of the treatment effect during the 28 day outcome period, taking into consideration NRS worst breathlessness measured across all pre-specified time points.

Where possible, secondary outcomes (as documented in Section 3.3.2) will be analysed as per the primary outcome, utilising the repeated measures nature of the data where appropriate.

Where outcomes are not measured at multiple time points, analyses will be undertaken using the appropriate version of the generalised linear model suitable for the distribution of that specific secondary outcome (e.g. linear, logistic or count). Outcome definitions will align in the statistical and health economic analyses.

Missing data will be assessed for any differential ‘missingness’ between randomised groups and investigated using appropriate missing data mechanisms. Details will be provided in the Statistical Analysis Plan.

An exploratory sub-group analysis will be conducted, to assess differences in those with causal disease compared to those without causal disease. In addition, any participant recruited through pulmonary rehabilitation clinics will form a subgroup for exploratory analysis. However, the study will not be formally powered to assess either of these subgroup analyses.

10.4 Interim analysis and criteria for the premature termination of the trial

There will be no formal planned interim analysis for early stopping due to efficacy or futility or safety. Details of the DMEC responsibilities and processes will appear in the DMEC Charter. The DMEC may request an interim analysis for safety reasons to indicate whether the study should be continued, modified or stopped. Such an analysis would be conducted by suitably qualified personnel. The Trial Steering Committee (TSC) would be advised by the DMEC whether the study should continue, be modified or stopped but would remain blind to the interim analysis results. A substantial amendment will be submitted if the study is modified.

10.5 Economic evaluation

The main health economic analysis will comprise a cost consequences analysis over the follow-up period of the trial. Service utilisation frequencies and mean costs adjusted to a common base-year will be described alongside consequences comprising the primary and secondary endpoints. Stratification, adjustment and subgroup analysis will mirror the statistical analysis and will likely rely on a generalised linear model for costs. Confidence intervals will be assigned by bootstrapping. Missing data will be

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handled in line with the statistical analysis plan and will likely rely on multiple imputation for missing cost and utility data. Data will be scrutinised for compliance and feasibility of cost assignment, blind to randomisation arm, at the end of the internal pilot and again in advance of the final analysis.

10.5.1 Analytical perspective and scope

The cost analysis will be conducted from an NHS and Personal Social Services perspective, in line with the NICE reference case,[67] including secondary care, primary care and community NHS activity. An additional analysis will take a societal perspective and will include charitable costs, patient out-of-pocket expenses, lost productivity, welfare support and informal care, provided feasibility of data collection is confirmed in the internal pilot. An important objective will be to assess any potential re-distribution of resource consumption between provider organisations between trial arms.

10.5.2 Cost-utility analysis

A cost-effectiveness analysis will present the ICER in terms of cost per QALY. Health utility (preference based quality of life) will be measured using the EuroQoL EQ-5D-5L questionnaire. The EQ-5D tariff score will rely on the 3L crosswalk function recommended by NICE [68]and will define a utility function which, by weighting the Kaplan-Meier estimated survival function will generate a QALY estimate for each cohort over the follow-up period expressed as the Incremental Net Benefit.[53] In light of the evolving discussion in the scientific literature about the interpretation of the QALY in end of life settings, the SF-6D and the ICECAP-SCM will be used in sensitivity analysis. Uncertainty will be presented using the Scatterplot on the Cost-effectiveness Plane and the Cost-effectiveness Acceptability Curve.

11.0 DATA HANDLING

A trial specific data management plan agreed by the Chief Investigator, Sponsor, HHTU and ECTU statistician will be drafted to provide detailed instructions and guidance relevant to database set up, data entry, validation, review, query generation and resolution, quality control processes involving data access and transfer of data to the sponsor at the end of the study and archiving.

A statement of permission to access source data by study staff and for regulatory and audit purposes will be included within the participant consent form with explicit explanation as part of the consent process and Participant Information Sheet. In principle, anonymised data will be made available for meta-analysis and where requested by other authorised researchers and journals for publication purposes. Requests for access to data will be reviewed by the Chief Investigator and Study Sponsor.

The Investigator(s)/Institution will permit monitoring, audits, REC and MHRA review (as applicable) and provide direct access to source data and documents.

11.1 Data collection and source document identification

11.1.1 Record of study contact in clinical notes

As a minimum, the following information will be recorded in patients' clinical file for study visits or telephone contacts:

- Clearly written date of visit or contact, brief study title/acronym and visit number.
- Date patient given Patient Information Sheet and which version was given.
- Date and version of Consent Form signed.
- Date of screening.
- Medical history, concomitant diseases and medication including study medication, and any changes in concomitant diseases and medication at subsequent visits.

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- Anything which is relevant to the ongoing care of the patient;
  - Relevant results and study doctor's assessment of these results.
  - Brief description of any AEs with start and stop times/dates and any significant test results or a medical summary of events if more appropriate.
- Any other relevant information.

11.1.2 Source Data

Source data are defined as "all information in original records and certified copies of original records or clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies)."

Source documents are defined as "original documents, data and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries of evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial)."

In this trial, data will be sourced from the following as seen in Table 3:

Data will be collected using questionnaires by Study Nurses or Site Investigators as required (patient NRS scores, health service access, etc.). Demographic data will be collected from the patient case notes and further demographics will be collected through the Baseline Patient Questionnaire. Please refer to the schedule detailed on Page 12, regarding timing and types of assessment.

Table 4 - Data sources

Measure	**Source**	**Completed by:**
Eligibility	Case notes	Study doctor
Consent	Clinical file and study consent form	Study doctor or registered independent prescriber
General demographic details	Case notes file and Baseline patient questionnaire	Study nurse and participant
General Medical information, clinical examination	Case notes	Study doctor/
Concomitant medications	Case notes	Study doctor/ study nurse
Dose titration decision	Case notes	Study Doctor
Pathology results	Pathology report in Case notes	Pathology service
Vital signs, BMI,	Clinical file	Study nurse
AKPS, Co-morbidity Checklist, mMRC-BS, NRS breathlessness severity, distress, cough, pain, ESS, KSS, SLUMS, SF-12, ESS, EQ-5D-5L/EQVAS, ICECAP, SOWS, ZBI-12 (carers) , VOICES (carers)	Patient questionnaires	Participant / carer

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ActiGraphy	CRF	Study nurse
Side effects, safety	Case notes	Study nurse
Drug accountability	Prescriptions, pharmacy records/logs	Study doctor, study pharmacist, study nurse
Healthcare Resource Utilisation questionnaire	Patient questionnaires	Participant

11.1.3 Case report forms

Individual patient data required by the trial protocol will be recorded on the study case report form (CRF). Site research staff will enter collected data from the paper CRF onto the online electronic CRF (e-CRF) provided by the HHTU. The design of the e-CRF will:

- enable adequate collection of data
- provide an audit trail to demonstrate the validity of the trial (both during and after the trial)
- ensure that only the data required by the protocol are captured

The trial site will retain a copy of the paper CRFs and a copy of the data entered on the e-CRF to ensure that the PI can provide access to the source documents to a monitor, auditor, or regulatory agency to check for any transcription errors.

11.2 Minimisation of missing data

Efforts to minimise missing data will be made as follows:

- Use of minimal and short-form questionnaires (where possible)
- Maintaining regular contact with patients and assistance from study nurse (phone and face–to-face) to help complete questionnaires
- Minimum requirement for patient to attend hospital for study assessments

Furthermore the reasons for missing data and trial withdrawal will be actively monitored throughout the trial process, in keeping with ICH Good Clinical Practice guidance section 4.3.4.[69] In palliative and supportive care trials rates of withdrawal are higher than other clinical disciplines yet almost nothing is known about the reasons for withdrawal from trials although factors may include: intercurrent disease progression; toxicities or lack of effect; or burdens from trial participation. Delineating each of these becomes imperative if trial design is to be optimised, and standard ways of analysing such trials in palliative care are to be developed and agreed.

11.3 Data handling and record keeping

Full details are given in the trial specific data management plan.

Study data will be recorded in a number of files for both the administration of the study and collection of participant data.

All data will be completely anonymised for purposes of analysis and any subsequent reports or publications. For the purposes of ongoing data management, once created as a subject on the RCC database, individual patients will only be identified by their unique Subject ID Number. Paper and electronic Case Report Forms (e-CRFs) will be created by HHTU.

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11.3.1 Data entry

The data collected by sites using paper questionnaires will be entered by the site into the RCC EDC specifically developed for this study. Confirmation of the data received by HHTU will be given to the site. If a site used a paper CRF, the data will be entered into RCC EDC and the paper CRF will remain at the recruiting site as source data.

Data will be checked according to procedures detailed in the trial specific data management plan.

11.3.2 Data storage

Each site will hold data according to the General Data Protection Regulation Act (2018) and data will be collated in CRFs identified by a unique identification number. For example, eligibility forms will contain a number (Screening ID Number) to identify the site and a screening number unique to each patient at that site. This number will be manually created in chronological order by site team members. Once created as a Subject on RCC, the automatically RCC generated Subject ID Number unique to each participant will be used on all subsequent forms . A screening log at each site will list Screening ID numbers against allocated Subject ID numbers for those randomised.

All study files will be stored in accordance with GCP guidelines. Electronic data will be password protected and stored on a secure server by HHTU. Only participants' unique Subject ID Numbers will be used to identify patients on the online electronic Case Report Forms (e-CRFs).

Study documents (paper and electronic) will be retained in a secure (locked when not in use) location during and after the trial has finished. All essential documents, including source documents, will be retained for a minimum period of 15 years after study completion as the data might be used to support further marketing authorisation applications. Where the local Trust's procedures allow, a sticker stating the date after which the documents can be destroyed will be placed on the inside front cover of the case-notes of trial participants.

Both HHTU (based within University of Hull) and ECTU (based within the University of Edinburgh), have backup procedures approved by auditors for disaster recovery. There will be a separate archival of electronic data performed at the end of the trial to safeguard the data, and in accordance with regulatory requirements.

RCC EDC data will be transferred to ECTU for analysis at the end of the study or for interim data analysis reporting. Sites will receive a copy of their locked dataset before the final analysis takes place. RCC EDC data transfer will comply with the General Data Protection Regulation Act (2018). Further details regarding data storage and transfer will be given in the Trial Data Management Plan.

11.4 Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

Trial documents (paper and electronic) will be retained in a secure location during and after the trial has finished.

11.5 Access to the final trial dataset

The database will be 'locked' to obtain the final dataset after:

- trial completion (last patient, last visit)
- completion of coding and data entry

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- all data queries resolved and the database updated, any serious adverse event queries have been resolved and the database updated
- trial team notified of date of lock

A copy of the final trial dataset and end of trial notification will be sent to HUTH R&D as Sponsor before the randomisation list will be released by the organisation in charge of randomisation prior to the statistical analysis. A copy of individual site's data will be sent to that site.

A copy of the final trial dataset will also be archived by the HHTU and sent to the Chief Investigator(s) . Other authorised, researchers requesting access to the dataset for further research may apply through the Chief Investigator(s). Applications will be considered in keeping with the publications policy which will be agreed by the Trial Steering Committee.

11.6 Archiving

Archiving will be authorised by the Sponsor following submission of the end of study report. All essential trial documents including source documents will be archived in accordance with the HHTU Trial Data Handling Plan for a minimum period of 25 years after study completion. Destruction of essential documents will require authorisation from the Sponsor.

Where permitted in local Trusts, a sticker stating the date after which the documents can be destroyed will be placed on the inside front cover of paper medical records of trial participants.

12.0 SUB-STUDY IMPLEMENTATION

This mixed-methods study will use Normalisation Process Theory[70] (NPT) to structure data collection and analysis of clinicians', patients', and carers' perspectives on the experience, practice of and attitudes about morphine use for chronic breathlessness. To maximise insights and ensure efficient study design, results at each stage of data collection (surveys, interviews) will be used to focus subsequent data collection about key issues.

This sub-study will run in parallel to the main RCT and will be led by Dr Mark Pearson at the University of Hull. Co-ordination and oversight of the study, data collection, data management and analysis will be the responsibility of Dr Pearson in collaboration with the HHTU. Processes will be *separate* to the CTIMP aspects of the hybrid trial conducted and managed by HHTU. The findings from the CTIMP and implementation study will be synthesised after database lock and jointly reported as part of the main study analysis.

12.1 Clinician pre and post clinical training surveys

Aim: To provide an early indication of experiences and attitudes that impact on morphine prescribing, establish a clinician and service user population for later purposive sampling, identify practice issues, and inform the focus of interview and observation data collection and analysis.

12.1.1 Survey 1 - exploratory

The site research team will invite relevant clinicians from their site (n~2-5 at each of 14 sites) to provide their email address to access the clinical training and participate in the implementation study. The invitation will explain the rationale for the implementation study, provide a summary of the data collection methods and the time required of clinicians to participate in the surveys and interviews and for what

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purpose and for how long their email address will be kept. Clinicians providing their email address (implied consent) will then be sent the URL link by the implementation study researcher for a short online survey of their knowledge, understanding, skills, attitudes, and behaviour in relation to their practice around using opioids for breathlessness. On completion, they have a choice to submit the data from the survey, or go directly to the online narrated training slides. On completion of the training, they will have option to complete survey 2 (see below). They will be sent a CPD certificate for their appraisal folders and invited to an optional question-answer webinar run by one of the MABEL clinical training team to address any remaining concerns or questions.

Survey completion will be taken as implied consent and will be completely anonymous. Only simple demographics are collected (age bracket, gender, prescriber/non-prescriber, doctor/nurse) to minimise identification of individuals. Participants have the right to decline participation and are not required to complete the online survey.

A rapid high-level thematic analysis of free-text responses will be conducted by the implementation study researcher to enable rapid feedback to inform subsequent training and feedback webinars. Once all surveys are completed, all free text responses will be subjected to thematic analysis and quantitative findings presented with simple descriptive statistics (numbers and proportions).

12.1.2 Survey 2 - perceptions of implementation enablers and barriers (two time points)

On completion of the clinical training slides, all clinicians will be invited to complete (online) a modified Normalisation Measurement Instrument (NoMad). Likert scale responses will measure the extent to which morphine prescribing fits with current practice in relation to each component of NPT - coherence with existing practices; cognitive participation of clinicians, patients and carers; and collective action and reflexive monitoring by clinicians, patients and carers. Face validity of adapted questions in NoMad (the instrument is designed to be adapted for use in different settings) will be piloted with a clinician outside of the trial to ensure relevance, acceptability, and comprehensibility.

Survey completion online will be taken as implied consent and will be completely anonymous. Only simple demographics of age bracket, gender, prescriber/non-prescriber, doctor/nurse will be collected to minimise identification of individuals.

At the end of survey 2, clinicians will be invited to complete a tick box providing consent i) to being contacted after 4 months for a repeat NoMad survey (online version) and ii) to be contacted to take part in an audio-interview (either phone or other technology e.g. Skype audio).

The modified NoMad survey (survey 2) will be repeated (online) for those willing to be contacted around 4 months after the training so that changes in perceptions over time are detected.

12.1.3 Survey data management

Data collection and management will be delivered by the HHTU according to an agreed Data Management Plan. All survey data will be anonymous. Online surveys will be administered through the secure HHTU online data capture system. Access to the system is managed by HHTU staff who will create role-based user access on behalf of the MABEL trial team. Data are encrypted at rest and in transit.

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12.1.4 Survey analysis

Survey 1. A rapid high-level thematic analysis of free-text responses will be conducted by the implementation study researcher to enable rapid feedback to inform subsequent training at other sites. Once all surveys are completed, all free text responses will be subjected to thematic analysis and quantitative findings presented with simple descriptive statistics (numbers and proportions).

Survey 2.Descriptive statistics will be used to analyse Likert scale responses about 1) the extent to which the intervention fits with current practice in relation to the components of NPT; and 2) how this fit has changed (or not) since the training. Free-text responses will be deductively thematically-analysed using NPT constructs (coherence, cognitive participation, collective action, reflexive monitoring) as a framework, whilst also allowing for inductive thematic analysis if responses do not fit within the framework. Thematic patterns and outliers will be identified. The analysis will also identify further barriers and enablers to implementation - these will inform the structure, content, and focus of the clinician, patient, and carer interviews.

12.2 Clinician, patients and carers interviews

Aim: To explore in more depth clinicians', patients', and carers' perspectives about safe morphine use, and to identify potential ways to facilitate safe prescribing and monitoring.

12.2.1 Sample and recruitment

Inclusion criteria:

Clinicians:

- Prescribers (or those supporting prescribers) at trial sites whether or not they have attended a site clinical training session, and willing to provide verbal recorded consent

Patients and carers:

- CTIMP participants and their carers where the participant has completed at least 14 days of the trial
- Those willing to participate in a face-to-face or telephone interview and able to provide informed written or verbal recorded consent

Exclusion criteria:

Clinicians:

- Clinicians not working at a trial site

Patients and carers:

- Participants with insufficient written or conversational English to be able to provide informed consent or take part in an interview and adequate translation facilities are unavailable

Sampling:

Maximum variation purposive sampling strategy to optimise exploration of a range of clinicians', patients', and carers' perspectives about safe morphine use, with the aim of collecting rich data that will provide insight into people's behaviour.[71] An initial purposive sampling grid for clinicians (profession, years of clinical practice) will be expanded with further purposeful sampling criteria identified through

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the free-text implementation study survey responses (12.1.1 and 12.1.2) - for example, if NPT component 'collective action' in the form of senior strategic support is identified as a barrier, the sample would ensure sufficient inclusion of senior clinicians. Or, if NPT component 'cognitive participation' and the role played by knowledge and professional cultures is identified as a barrier, the sample would ensure sufficient inclusion of particular professional groups or clinical specialties. The purposive sampling grid for patients and carers will initially be structured by diagnosis (lung cancer; lung fibrosis; COPD; heart failure, and amount of breathlessness) and will be developed further in consultation with our PPI representative. Both of the sampling grids will clearly identify the characteristics of participants needed for the sample to maximise variation in relation to key characteristics.

Sample size: We do not state sample size *a priori* as a qualitative approach to sampling and data analysis means that sampling will stop once theoretical saturation has been reached. Consistent with good practice in qualitative research where conceptual categories are pre-established by existing theory[72] we pre-specify *minimum* sample size (n=5 clinicians; n=5 patients; n=5 carers, although if preferred by participants, some patients and carers will be interviewed together) and stopping criterion once the minimal sample size is attained, namely: for each group (clinicians, patients/carers), after each successive interview (i.e. 6, 7, etc.) we will assess whether any new analytic themes are emerging, and if no new themes emerge in three successive interviews then data saturation will be considered to have been reached.

Recruitment and consent

Clinicians:

The implementation study will be introduced to all clinicians invited to the clinical training in their invitation letter. They will be provided with an information sheet about the interview study in the clinical training packs. Study information will include aims of the implementation study, how they could participate, how anonymity will be maintained, data management, and their right to decline participation or withdraw from the implementation study at any time. Those willing to be contacted by email to participate in an interview will be provided with an information sheet by an implementation researcher.

An implementation researcher will email an invite to participate in the interview sub-study to clinicians chosen using the sampling strategy. For those that respond and express interest, the researcher will arrange an audio-call (either phone or other suitable means e.g. Skype audio) at a time convenient to the clinician. Given the low risk nature of this aspect of the study, and the pressures on clinicians' time, verbal recorded consent will be obtained prior to the call but participants will have the opportunity to discuss with the researcher at the start and withdraw if they wish.

Patients and/or carers:

Study nurses will ask CTIMP participants who have completed at least 14 days of the trial if they would be willing to take part in an interview to explore their views of morphine treatment for chronic breathlessness and their experience of the trial so far including their views about the support provided for side effects which might be related to study drug. The study nurse will explain that the researchers will not need to interview everybody and only a sample representing people of all ages, both sexes and amounts of breathlessness is needed. The participant will be given a patient information sheet which explains the aims of the implementation study, how they could participate, how anonymity will be maintained, data management, and their right to decline participation or withdraw from the

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implementation study at any time without the need to give an explanation and without detriment to their overall treatment or participation in the trial.

Those who express interest will be given a PIS and asked to provide verbal consent for their age, sex and last measured level of breathlessness to be shared with the Hull implementation study research team. If an interviewee with their characteristics is still needed (the implementation study researcher will refer to their sampling grid), potential interview participants will be contacted by the Hull implementation study researcher and offered the opportunity to ask any questions they may have about the research. If they are not needed for an interview, the study nurse will be informed, who will thank the participant for their willingness but inform them that they are not required. They will have at least 24 hours between receiving the PIS and providing consent. For remote interviews, verbal recorded Informed consent will be taken prior to an interview and checked by the Hull team. For face to face interviews, the implementation study interviewer will take written informed consent.

12.2.2 Data collection

The implementation study team will develop semi-structured interview guides, informed by NPT constructs, to ensure that critical topics are covered consistently throughout all interviews whilst maintaining the flexibility that will allow participants to identify and explore other relevant issues. All interviews will take place remotely, or in hospital, hospice, or community settings, according to participant preference and current circumstances (e.g. COVID-19 distancing requirements) and researcher resource. Interviews will recorded on encrypted files and transcribed verbatim.

12.2.3 Data storage

Electronic survey data will be collected and stored in an online electronic data capture system managed by the Hull Health Trials Unit. The EDC system is RedCap Cloud (RCC). This is a cloud based EDC system provided by nPhase. Data is stored on dedicated RCC hardware in EU with data encrypted at rest and in transit.

Access to the EDC system is managed by HHTU staff who will create role-based user access on behalf of the MABEL trial team.

Identifiable data will be stored within the HHTU managed Box file storage system, the HHTU managed REDCap Cloud Instance, HHTU managed DocuSign instance and the HHTU Data Safe Haven. Data will be held in accordance with the General Data Protection Regulation (GDPR 2018). The HHTU holds an NHS IG toolkit (replaced by the Data Security and Protection toolkit from March 2019) covering all systems within the HHTU. The study will be conducted in compliance with the current approved protocol, with Good Clinical Practice (GCP), and with applicable regulatory requirements.

12.2.4 Data analysis

The maximal variation sample will enable analysis that maximises use of critical comparison to produce insights from the data. A matrix-based approach to qualitative data analysis (Framework analysis)[73] using NPT's constructs as the starting point, will be used to classify, order, and synthesise themes from the interview data, and to identify promising strategies for safe clinical practice from the perspectives of clinicians, patients, and carers.

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12.3 Development of a safe prescribing and monitoring process

Aim: To produce a coherent and practical process to ensure optimal prescription and monitoring of study drug that could be used clinically rapidly and at-scale if the trial is positive.

First, using a pragmatic intervention development process,[74] we shall map the implementation study findings (section 12.2) and the strength of evidence for each, to the framework of NPT (coherence, cognitive participation, collective action, and reflexive monitoring).

Second, the findings will be presented using the framework of NPT at a half-day co-design workshop with clinicians, patients and carers, managers, and commissioners. We shall use Powell *et al*.'s classification of implementation strategies (Expert Recommendations for Implementing Change (ERIC))[75] to link the evidence about implementation to practical actions. The development of a process to ensure optimal prescription and monitoring will be further informed by tightly-focused bibliographic database searches to identify evidence about the effectiveness of potential components.

Third, using step five of the 6 Steps in Quality in Development process,[76] components of the prescribing and monitoring process will be formatively tested and refined as indicated. For example, in response to alternative components, clinicians may collect quantitative data on opioid adherence, or commissioners could feedback qualitative data about how evidence is used in commissioning decisions.

12.4 Synthesis of implementation study findings with RCT results

This will occur once all CTIMP and implementation study data collection has completed and the dataset locked.
We will use the data to improve our understanding about clinicians' optimal prescription and monitoring of morphine and patient adherence. We will use Critical Interpretative Synthesis (CIS) [77] to synthesise the CTIMP data and qualitative data. Whilst CIS was originally developed as a systematic review method, the principle of using data of one form (e.g. quantitative) to structure interpretation of another form (e.g. qualitative) is the same for primary data. This process of 'reciprocal translation analysis' has been demonstrated by Fleming[78] who used effectiveness data as a framework for synthesising with quantitative and qualitative data on morphine for pain.[78;79]

As our aim is to delineate clinically translatable process, we shall use the NPT model as a framework for integrating the implementation study and CTIMP findings. By populating this grid with the evidence from the trial, and making additions to the framework where indicated by the trial results, we shall produce a long-list of codes (thematic descriptors integrating quantitative and qualitative data). From these codes we shall generate new, synthesised, constructs (explanatory themes) that can then be used to re-interpret the findings within the context of the evidence as a whole. This will enable us to produce 'synthesised arguments' that integrate the quantitative and qualitative data and provide a transparent audit record back to the underpinning data. These synthesised arguments will be presented in Plain English so that a diverse group of stakeholders will be able to comprehend and engage with the evidence presented in them.

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13.0 Infographic Study Within A Trial (SWAT)

Tailoring or shortening the Patient Information Sheet (PIS) is reported to make little or no difference to recruitment (80). However, the evidence around the potential effectiveness of including information graphics in a health context is persuasive, if limited. Infographics have been shown to improve patient knowledge; both in relation to personally relevant information such as discharge instructions, and statistical information such as the association of age with cancer risk (80) (81). A further study with patients, students and doctors found that infographics did not increase knowledge when compared to plain language summaries the infographics, but did improve reader experience and user-friendliness (82)
These findings suggest that there may be the potential for infographics to improve participant experience and understanding of health research leading to increased recruitment.

In this SWAT, we will evaluate the effect of using an Infographic Sheet (visual document explaining the study) on participant recruitment. Participants will be randomised (on a site by site basis) to receive an Infographic Sheet plus standard PIS versus a standard PIS only.

As is usual with embedded trials, the sample size is constrained by the number of potential participants approached, hence a formal power calculation to determine sample size has not been conducted.

13.1 SWAT study design

The embedded SWAT study design will be a cluster trial; randomisation will be carried out at the site level to reduce cross contamination. The allocation ratio will be 1 to 1. Generation of the allocation sequence will be undertaken independently by a researcher not involved with the recruitment of participants. Randomisation will not utilise a minimisation strategy as the sites selected for the main study are largely uniform in terms of size, source of participant identification and recruitment, and recruitment target as documented in site feasibility assessments.

The primary outcome of this embedded SWAT study will be the recruitment rate, i.e. the proportion of participants in each group who are randomised into the main study. Secondary outcomes will include the proportion of participants in each group who are screened but do not go on to consent and the cost effectiveness of the intervention.

13.2 SWAT Data Analysis

Primary analysis: the difference in recruitment rate between those receiving the Infographic Sheet plus standard PIS versus standard PIS only will be analysed via logistic regression with site as a random effect.

Secondary analyses: the difference in proportion of participants who are approached but do not consent to the main study who received the Infographic Sheet plus standard PIS versus those receiving the standard PIS only will be analysed via logistic regression with site as a random effect.

The difference in cost per recruited participant who received the Infographic Sheet plus standard PIS versus the standard PIS only will be calculated.

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13.3 SWAT study output

The sample size of this embedded SWAT study will be too small to be a robust standalone a piece of research but combined with other similar studies and viewed as part of a meta-analysis, the results of this SWAT embedded study will add to the growing library of evidence about the value of using Infographics in clinical research.

14.0 OVERARCHING RESEARCH GOVERNANCE AND QUALITY CONTROL

The study will be performed subject to Research Ethics Committee favourable opinion, MHRA Clinical Trial Authorisation, and HUTH and local site NHS permissions.

This study will be conducted in accordance with The Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments; the International Conference for Harmonisation of Good Clinical Practice (ICH GCP) guidelines; and the UK Policy Framework for Health and Social Care Research.

14.1 Study Organisation Structures and Responsibilities

The Sponsor of the trial will be Hull University Teaching Hospitals NHS Trust (HUTHT) who will have overall responsibility for the trial. The trial will be managed by the HHTU, on behalf of Professor Marie Fallon (Chief Investigator). The study will be monitored by HHTU in accordance with HHTU's Standard Operating Procedures to ensure compliance with UK Clinical Trial Regulations. All trial related documents will be made available upon request for monitoring by HHTU monitors and for inspection by the MHRA.

14.1.1 Chief Investigator **-** The Chief Investigator will have responsibility for the design, coordination and management of the study. These include:

- Trial authorisation including responsibility for the protocol, and obtaining approvals from the MHRA, Research Ethics Committee (REC) and R&D.
- Ensuring that the trial is conducted according to the UK Clinical Trial regulations and Good Clinical Practice (GCP).
- Assessment of SAEs and expedited reporting of any SUSARs.

14.1.2 Clinical Trials Unit **-**The Sponsor, Chief Investigator, ECTU (statistics and health economics) and HHTU duties will be stipulated clearly in the Sponsor-collaboration agreement

14.1.3 Statistical Analysis – Dr Catriona Keerie employed by the University of Edinburgh, will oversee the statistical aspects of this study including the drafting of the analysis plan, the conduct of analyses and reporting of results.

14.1.4 The Principal Investigator at each participating centre will be responsible for local site-specific assessment approval, and for the local conduct of the study. All correspondence relating to the study at site should be filed in the Investigator Site File and maintained by the Principal Investigator.

14.1.5 Local Project Teams – These will consist of Physicians or registered independent prescribers

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(nurses who are registered with the Nursing and Midwifery Council (NMC) as an Independent Prescriber and are permitted to prescribe controlled drugs) (responsible for introducing the patient to the trial and ensuring eligibility and consent) and Study Nurses (responsible for patient recruitment, supporting the consent process and co-ordination of all aspects of data collection). Sites are specifically responsible for conducting the trial in accordance with the protocol, SOPs, trial agreement, the UK Clinical Trial Regulations and GCP. Where independent prescribers are to take consent, the Sponsor will review registration and the level of competence prior to “green light” approval for a site.

14.1.6 Implementation study – Dr Mark Pearson employed by the University of Hull will oversee the implementation study aspects of the study including responsibility for the relevant aspects in the protocol, management and data management, analysis and reporting of results.

14.2 Trial Management, Monitoring and Oversight

14.2.1 Independent Data Monitoring and Ethics Committee (DMEC)
The DMEC will review the safety and ethics of the trial by reviewing interim data approximately every 6 months from the start of recruitment and membership to this group will include an independent statistician. The terms of reference of the DMEC are to:

- Ensure that patient considerations are of prime importance
- To review any safety issues arising during the trial (including any SAEs, SARs and SUSARs)
- To report (following each DMEC meeting) its recommendations regarding trial continuation to the Trial Steering Committee
- To consider any requests for release of interim trial data and to make recommendations to the Trial Steering Committee on the advisability of this
- Should data summaries be required during the study, to provide to the Trial Steering Committee appropriate information and advice on the data gathered to date that will not jeopardise the integrity of the study
- The DMEC will not consider matters in relation to the implementation study aspects of the study

The DMEC will consist of:

- An experienced palliative care physician
- An experienced physician with relevant experience
- A clinical trials statistician

14.2.2 Trial Steering Committee (TSC)

The TSC will provide overall supervision of the trial, in particular trial progress, adherence to protocol, patient safety and consideration of new information. An independent chair will be appointed, two other independent members and three PPI attendees. The Committee will meet approximately every 6 months. The terms of reference of the Trial Steering Committee are as follows:

- To provide overall supervision of the trial, ensuring adherence to protocol
- To review developments during the trial and recommend appropriate action
- To ensure that the rights, safety and well-being of trial participants is safeguarded and prioritised
- To review at regular intervals relevant information from other sources (e.g. other related trials),

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and recommend appropriate action (e.g. changes to trial protocol, stopping or extending the trial)
- To keep any issues discussed in the meetings or written in the minutes confidential, unless otherwise agreed
- The TSC will also consider matters pertaining to the implementation study aspects of the trial

14.2.3 Trial Management Group (TMG)

The TMG will comprise of the Chief Investigator, other lead investigators (clinical and non-clinical), members with a specific interest (e.g. nurses; patient representatives [two]), and members of HHTU and a Sponsor representative. The TMG will also consider matters pertaining to the implementation study aspects of the trial.

14.3 Quality control

14.3.1 Training
The following training procedures will be conducted to ensure quality control.

Person trained	**Description**
Study nurse, Site Principal Investigator/nominated clinicians	• Blood sampling (if required) • Consent procedure (and ICH GCP if consenting patients) • Data collection and management • Safety and efficacy assessments • Randomisation
Site Principal Investigator / nominated clinicians	• Eligibility assessment • Prescription
Clinical trials pharmacist	Randomisation, medication preparation procedures

14.3.2 Blood sampling
Venous blood samples will be drawn for eligibility screening if necessary. Study nurse competency in blood sampling will be recorded at the study site, with a copy filed in each Investigator site file if available. In some instances blood samples, checked in the preceding period (renal function within 21 days), will be used for eligibility if the clinical situation is otherwise unchanged. The results will be held in the patient's medical notes as source data. Each study site must print off the appropriate results, with the date of printing, have the results reviewed by the PI/Study Doctor, and have the results signed and dated. The site will keep a copy of the pathology service guidelines for obtaining, transporting and storing blood samples. Blood samples will be destroyed after analysis.

14.3.3 Site Approval, Start-up Procedures and Ongoing Support
The following documentation must be received by HHTU in order for an institution to be eligible to participate in the Trial. This list is not exhaustive and will follow the Sponsor's Working Instruction:

- A copy of HRA approval and site R&D Capability and Capacity assessment
- A copy of signed Clinical Trial Agreement including Principal Investigator agreement
- Completed Investigator Statement, signed by the institution Principal Investigator on behalf of all staff at the site who will be working on the study
- Completed Delegation Log and Contact Details
- ISF Checklist signed by a member of the research team

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- CVs, including evidence of GCP training for named persons
- Copies of honorary contracts
- Pharmacy Final Greenlight Confirmation Ready to Dispense Checklist

Once this documentation has been received, confirmation that the study may commence at that site will be sent to the site Principal Investigator by the sponsor (Sponsor green light).

Prior to commencing the study, each study site will be visited either face-to-face or via tele/video conference by HHTU or Chief Investigator.

Clinical (including pharmacy) and research teams at the site will be trained in the data collection, data entry, and filing and other trial procedures in order to comply with GCP. At this time the pharmacy procedures will be clarified, the protocol reviewed in detail and a pharmacy manual provided. A Site Initiation Report will be created and a copy sent to the study site.

Phone support, and visit support, will be provided to sites as per their requirements during the course of the study, mainly by the Trial Coordinators, with the support of HHTU as appropriate.

By including the implementation sub-study in the protocol submitted to the necessary governances, permissions will be synchronous.

14.4 Monitoring, audit and inspection

CTIMP monitoring, audit and inspection

The trial will be monitored in accordance with HHTU Standard Operating Procedures and Trial Monitoring Plan to ensure compliance with UK Clinical Trial Regulations and ICH GCP. All trial related documents will be made available upon request for monitoring by HHTU monitors and for inspection by the MHRA.

Full details are given in the Trial Monitoring Plan which will be developed and agreed by the Trial Management Group (TMG) and TSC based on the trial risk assessment. Monitoring will be a combination of central and site monitoring, with appropriate risk adaptations considered during the risk assessment. HHTU will co-ordinate and perform monitoring and submit reports to the sites and Sponsor, and escalate findings as required.

Monitors will visit each site after 3 participants have been recruited, at the study midpoint and at the end of the study.

15.0 ETHICAL AND REGULATORY CONSIDERATIONS

15.1 Research Ethics Committee (REC) review and reports

The following will be observed:

- Before the start of the trial, approval will be sought from a REC for the trial protocol, informed consent forms and other relevant documents e.g. advertisements and GP information letters
- Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the study (note that amendments may also need to be reviewed and accepted by the MHRA and/or NHS R&D departments before they can be implemented in practice at sites)

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- All correspondence with the REC will be retained in the Trial Master File/Investigator Site File
- An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended
- The Chief Investigator will be responsible for the annual and end of study reports as required.

15.2 Regulatory Compliance

The study will comply with the following regulations:

- The trial will not commence until a Clinical Trial Authorisation (CTA) is obtained from the MHRA
- The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments
- Before any site can enrol patients into the trial, the Chief Investigator/Principal Investigator or designee will apply for NHS HRA permission and complete a Capacity and Capability assessment with the site's Research & Development (R&D) department
- For any amendment that will potentially affect a site's NHS permission, the Chief Investigator/ Principal Investigator or designee will confirm with that site's R&D department that NHS permission is ongoing (note that both substantial amendments, and amendments considered to be non-substantial for the purposes of REC and/or MHRA may still need to be notified to NHS R&D)

15.3 Protocol compliance

Protocol deviations, non-compliances, or breaches are departures from the approved protocol.

- Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and will not be used e.g. patients will not be enrolled if they do not meet the eligibility criteria or restrictions specified in the trial protocol.
- Accidental protocol deviations can happen at any time. They will be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately.
- Deviations from the protocol which are found to frequently recur will require immediate action and may be classified as a serious breach.

15.4 Notification of Serious Breaches to GCP and/or the protocol

A "serious breach" is a breach which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the subjects of the trial; or
(b) the scientific value of the trial

In the event of a serious breach:

- the Sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase
- the Sponsor will notify the licensing authority in writing of any serious breach of

(a) the conditions and principles of GCP in connection with that trial; or

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(b) the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach

15.5 Data protection and patient confidentiality

Full details will be available in the Trial Data Management Plan.

All investigators and trial site staff must comply with the requirements of the General Data Protection Regulation 2016/679, with regards to the collection, storage, processing and disclosure of personal information and will uphold the Regulation's core principles.

HHTU, ECTU and HUTH will maintain the confidentiality of all patients' data in accordance with General Data Protection Regulation Act (2018) and will not reproduce or disclose any information by which patients could be identified. Representatives of HHTU and HUTH will be required to have access to patients' medical records for the purposes of monitoring and source data verification. In addition, representatives of HUTHT, as Sponsor, in keeping with MHRA requirements, may be required to have access to patients' medical records. Confidentiality will be maintained at all times. Representatives of regulatory authorities may require access to patients' medical records for regulatory purposes only. These points will be made clear in the Patient Information Sheet and trial Consent Form.

The patient's full name, date of birth, hospital number and NHS number (Community Health Index and/or hospital number in Scotland) will be collected to enable tracing through national records. The Principal Investigator (or delegated person) at each site will keep a patient identification list of patients' trial numbers, names, addresses and hospital and NHS numbers. The Principal Investigator must ensure that patient confidentiality is maintained and that all trial documents (e.g. consent forms) are maintained in strict confidence.

15.6 Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall trial management

Any competing interests that might influence trial design, conduct, or reporting will be identified, disclosed and documented in the Trial Master File. The oversight groups will determine what it is appropriate to report; details will be in the Dissemination and Publication Plan.

Disclosure should reflect:

- ownership interests that may be related to products, services, or interventions considered for use in the trial or that may be significantly affected by the trial
- commercial ties requiring disclosure include, but are not restricted to, any pharmaceutical, behaviour modification, and/or technology company
- any non-commercial potential conflicts e.g. professional collaborations that may impact on academic promotion

15.7 Indemnity

15.7.1 Potential legal liability of the sponsor or employer.
This is an NHS-sponsored research trial and NHS indemnity covers Sponsor potential legal liability for harm to participants arising from the design of the research. Protocol authors with a substantive university contract will also have indemnity cover from their employing university.

15.7.2 Potential legal liability of investigators/collaborators

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If there is negligent harm during the clinical trial, the NHS body owes a duty of care to the person harmed. NHS indemnity covers NHS staff and medical academic staff with honorary contracts only when the trial has received confirmation of capability and capacity from the Trust R&D department.

14.7.3 Arrangements in the absence of legal liability

NHS indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Protocol authors with a substantive university contract will also have indemnity cover from their employing university. The universities do not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm.

15.8 Amendments

The process for making and communicating amendments will be as described in the relevant Standard Operating Procedure.

Under the Medicines for Human Use (Clinical Trials) Regulations 2004, the Sponsor may make a non-substantial amendment at any time during a trial. There is no requirement for investigators to notify the MHRA or REC of non-substantial amendments, however the HRA must be notified. If the Sponsor wishes to make a substantial amendment to the CTA or the documents that supported the original application for the CTA, the Sponsor must submit a valid notice of amendment to the licencing authority (MHRA) for consideration. If the Sponsor wishes to make a substantial amendment to the REC application or the supporting documents, the Sponsor must submit a valid notice of amendment to the REC for consideration. The MHRA and/or the REC will provide a response regarding the amendment within 35 days of receipt of the notice. It is the Sponsor's responsibility to decide whether an amendment is substantial or non-substantial for the purposes of submission to the MHRA and/or REC.

If applicable, other specialist review bodies (e.g. CAG) need to be notified about substantial amendments in case the amendment affects their opinion of the study.

Amendments also need to be notified to NHS R&D departments of participating sites to assess whether the amendment affects the NHS permission for that site. Note that some amendments that may be considered to be non-substantial for the purposes of REC and/or MHRA may still need to be notified to NHS R&D (e.g. a change to the funding arrangements). For studies with English sites processed in NIHR CSP the amendment should be submitted in IRAS to the lead CRN, which will determine whether the amendment requires notification to English sites or may be implemented immediately (subject to REC/MHRA approval were necessary).

15.9 General ethical considerations

The patient population under study is a group living with advanced disease and care should be taken not to introduce further physical, psychological or financial burden with entry into studies. However, this must be balanced with the need to test practices. In order to try to address some of these concerns, this study:

- Includes a research team with a broad base of clinical experience including palliative care and psychology
- Minimises the need for hospital visits, by employing sufficient study nurses to allow home visits for follow- up
- Uses assessments kept to short form and non-invasive techniques
- Will reimburse reasonable travel costs
- Provides support for participants as part of study nurse role

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- Has an emergency unblinding procedure which will apply in the event of necessary clinical concern.
- Allows open label provision of the study intervention at the end of the trial if participants wish. As study blinding will not be broken until the end of the trial, usual clinical care will be provided by the participant's usual doctor assuming the patient is opioid naïve.
- It is recognised that some participants will be in a position of clinical dependence with some of the research team as patients under their care. GCP procedures with regard to consent will be observed.

15.10 Post trial care

After the 56-day placebo-controlled trial period, as morphine is available for management of chronic breathlessness, participants will have the opportunity to take open label morphine after the end of the study if their usual clinician agrees. They will remain blinded to previous study allocation. Prescribing and monitoring responsibility for open label morphine will lie with their usual clinician. Participants also have the option of providing longer-term minimum data, whether or not they are receiving open label morphine, until the past participant has completed the 56-day trial period. All participants stopping IMP will receive a phone call from the study nurse after a few days and those completing the Day 56 assessment will also complete a questionnaire to assess for opioid withdrawal at a few days after the Day 56 assessment.

Details are given in sections 7.7 Long term follow up assessment and 3.5 Timetabling of assessments.

15.11 Peer review

This study has undergone extensive peer review as part of the grant submission process to the funder. Firstly, internal peer review (two reviewers independent from the project) as part of the university submission process, and secondly, extensive external peer review at both the outline submission and full application (6 independent, expert reviewers with expertise across methodology and clinical experience, including lay review) stages of the grant application.

16.0 PUBLIC AND PATIENT INVOLVEMENT

The Edinburgh Clinical Research Facility Patient Advisory Group (PAG) and the Hull Respiratory Support Group (RSG) informed this study and support the value to patients of quantifying the net effects (benefits and side-effects) of morphine in chronic breathlessness. The lay summary was rewritten by the PAG. The Hull RSG and patients known to the Edinburgh community respiratory team felt that the intervention and assessments were acceptable. The timing of the ActiGraph monitors was altered after consultation and we will address concerns about morphine in study patient information sheets.

Patients will be involved in all aspects of study monitoring. Three PAG members will provide advice as Trial Steering Committee members. They will be mentored and trained by the PPI facilitator, and supported by the Lothian Palliative and Supportive Care PPI group. A trial team PPI lead (MF) will coordinate and facilitate this activity. Two Hull Palliative and Supportive Care PPI group members will be on the Trial Management Group, mentored by a member of the Hull team . We are committed to active patient involvement at all stages of the study to ensure the research is grounded and relevant to the experiences of patients, family members and the wider public. As members of the Trial Management Committee, patients will be involved in all practical and strategic decisions about study conduct and management. These patient members will communicate with the wider Lothian and Hull PPI groups

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where wider discussion with patients is needed. Lay members will also be involved in the interpretation of analysed findings, and dissemination.

17.0 DISSEMINATION POLICY

17.1 Dissemination policy

Details will be found in the Trial Dissemination and Publications Plan which will be approved by the Trial Steering Group.

Publications for the trial will meet the standards required for submission to high quality peer reviewed journals and will be reported in accordance with the CONSORT guidance. http://www.consort-statement.org/.

On completion of the trial, the data will be analysed and tabulated and a Final Study Report prepared. As an HTA funded trial, the Final Study Report will be available as a peer-reviewed published manuscript for the HTA Journal. The HTA journal allows that publication can be delayed until the primary paper is published in a relevant journal.

The results will be disseminated in peer reviewed journals, through the local cardiology, respiratory, palliative care and other relevant clinical networks and at national and international meetings. Patients participating in the trial will be sent a summary of the findings, if requested, co-ordinated at site level. Participants may request the summary results from their PI after the Final Study Report, and a copy of the final accepted manuscript of the primary paper after the results have been published.

The funding source will be acknowledged within all publications, and a copy sent for their prior information according to their requirements. The Funder does not have publication rights of the data from the trial.

The trial protocol manuscript will be prepared and published. The protocol will be available on the CI's website, and the trial design synopsis available on the ISRCTN and EudraCT website. The participant level dataset will be available to authorised researchers through application to the CI.

17.2 Authorship eligibility guidelines and any intended use of professional writers

All publications and presentations relating to the trial are required to be authorised by the Trial Management Group (TMG), who will prepare the Trial Dissemination and Publications Plan.

. The agreement will include:

- guidelines on authorship on the final trial report consistent with the Vancouver Recommendations from The International Committee of Medical Journal Editors
- whether participating investigators have rights to publish any of the trial data
- any time limits or review requirements on the publications

Professional medical writers will not be hired.

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