Low-dose KETamine as an adjunct to MOrphine for acute pain in the ED: a randomized, double-blinded, trial

Acronym: KeTMo

TRIAL PROTOCOL

Version 3.2

Date: 26/05-2023

EudraCT number: 2021-005116-64

Sponsor

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Contents

Preface

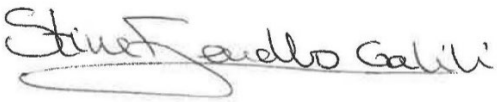
Low-dose-ketamine for acute pain in the ED, a randomized, double-blinded, trial will be conducted according to this protocol. The trial will be conducted in accordance with all applicable national and international laws, regulations, and guidelines including the revised version of the Declaration of Helsinki[1], European regulations[2], and the international Good Clinical Practice guidelines[3]. The trial and this protocol is developed in accordance with the International Conference on Harmonization (ICH) guidelines[4] and the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement[5]. The principal investigator wrote the protocol with input from the project group. Any substantial changes or amendments to the protocol will be clearly documented and communicated to all relevant parties.

Aarhus 4/10-2021

Lone Nikolajsen, Clinical Professor and Chair

Aarhus 4/10-2021

Stine Fjendbo Galili, M.D, PhD student



LIST OF ABBREVIATIONS

AE:	Adverse event
AR:	Adverse reaction
AUH:	Aarhus University Hospital
ED:	Emergency Department
eCRF:	Electronic case report form
GCP:	Good Clinical Practice
IV:	Intravenous
LDK:	Low-dose-ketamine
NRS:	Numeric Rating Scale
RCT:	Randomized Controlled Trial
SAE:	Serious adverse event
SAR:	Serious adverse reaction
SPIRIT:	Standard Protocol Items: Recommendations for Interventional Trials
SUSAR:	Suspected unexpected serious adverse reaction

Overview

Registry and trial number	EudraCT number: 2021-005116-64
Date of registration	EudraCT: 16/09-2021
Sources of monetary or material support	Health Research Foundation of Central Denmark Region
Sponsor	Lone Nikolajsen, Aarhus University Hospital
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Primary investigator	Stine Fjendbo Galili, Aarhus University Hospital
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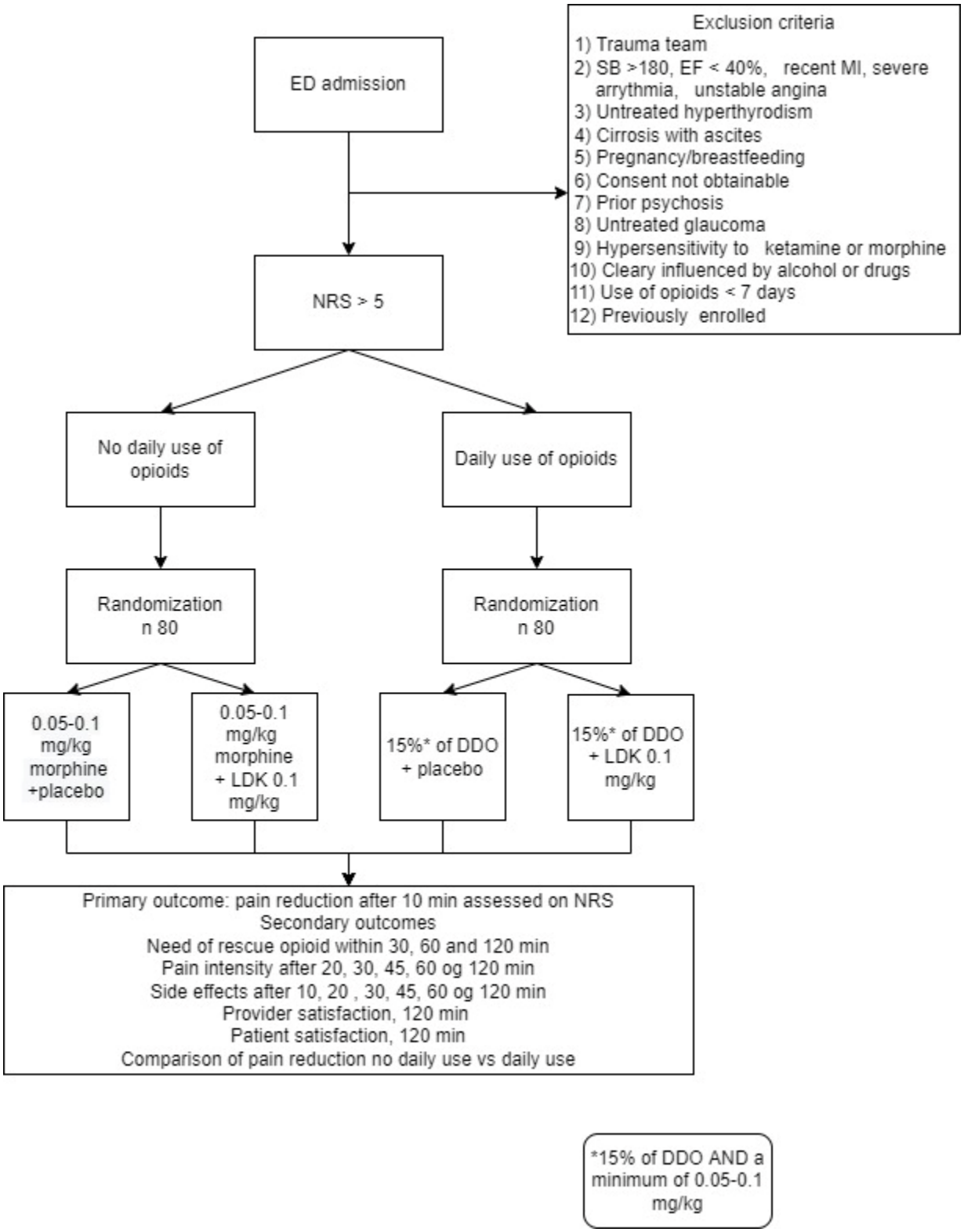
Title	Low-dose-ketamine for acute pain in the ED, a randomized, controlled, double-blinded, trial
Country of recruitment	Denmark
Condition studied	Acute pain in the ED
Intervention	LDK 0.1 mg/kg as an adjunct to morphine
Comparator	Morphine and placebo
Inclusion criteria	1) Emergency Department admission 2) Age ≥ 18 years 3) NRS ≥ 5 4) Stable vital signs defined as systolic blood pressure ≥ 90 mmHg, heart rate between 50 and 160 per minute, respiratory rate between 8 and 30 per minute, oxygen saturation greater than or equal to 92%
Exclusion criteria	1) Initial management by trauma-team 2) Systolic blood pressure ≥ 180mmHg, severe untreated arrhythmia, unstable angina, recent myocardial infarction (< 30 days), severe heart-failure (Ejection fraction < 40 %)

	3) Symptoms of untreated hyperthyroidism 4) Cirrhosis with ascites 5) Known/suspected pregnancy or breastfeeding 6) Patients for whom consent is not obtainable or psychiatric forced treatment. 7) Previously enrolled in the trial 8) Psychiatric illness prior to admission defined as prior psychosis/schizophrenia 9) Untreated diagnosed glaucoma 10) Known hypersensitivity to ketamine or to any excipient or prior use of ketamine with a negative experience (i.e. hallucinations) 11) Patient clearly influenced by drugs or alcohol	
Study type	Interventional Intervention model: Parallel group	Allocation Randomized (1:1) Masking: Double blinded
Date of first screening	15-05-2022	
Target sample size	160	
Recruitment status	Recruiting	
Primary outcomes	The primary outcome measurement is pain reduction after 10 min assessed on NRS.	

Trial flowchart



Project group

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Conflicts of interest

The members of the project group have no conflicts of interest related to the current trial. A list of all conflict of interests is provided in Appendix 1. Trial site

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Amendments

Version 3.2

Version 3.1 (Apr. 19, 2023) to 3.2 (May 26, 2023)

- Clarifications in the screening process p 35

Version 3.0 (Apr. 19, 2022) to 3.1 Apr. 19, 2023)

- Corrections of minor typos and grammatical issues as well as minor clarifications and updated flowchart

- Precision on timepoint for registration of vital parameters (p 24)
- Precision of doses for patients with a daily use of opioids (last version 10% of daily dose, this version 15% of daily dose, AND a minimum of 0.05-0.1
- Precision of opioid doses for patients without a daily use of opioids (last version 0.1 mg/kg, this version 0.05-0.1 mg/kg)
- Stable pulse changed from 60-150 to 50-160
- Respiratory frequency changed from 8-24 to 8-30

Version 2.0 (Nov. 22, 2021) to 3.0 (Apr. 19, 2022)

- Corrections of minor typos and grammatical issues as well as minor clarifications
- Addition of EudraCT
- Addition of Study Kits
- Addition on blinding details
- Addition of Hospital Pharmacy
- Clarification that that the unblinded pharmacy staff and nurse will not be involved in outcome evaluation, section 2.4
- Change in timepoints (not primary outcome time point)

Version 1.0 (Oct. 4, 2021) to 2.0 (Nov. 22, 2021)

- IDMC is deleted from the protocol
- Criteria for patient withdrawel is described
- Exlusion criteria add
- Corrections in section 4.3.1 , Safety and Harm, general considerations
- Corrections conserving Sponsors evaluation of SAR/SUSAR
- Labels added

BACKGROUND

1.1 Pain in the ED – the participant population

1.1.1 Incidence and mortality

The Danish ED's have 1.8 million contacts each year[6] and several studies find that 70-80% of these arrives from patients in pain[7,8,9,10].

This makes pain management an essential component of emergency medicine, but also a challenge in many cases and ineffective and/or delayed analgesia for patients attending the ED is a common feature[11,12,13].

Many variables contribute to this finding, including limited resources, lack of diligence for assessing and treating pain, side effect barriers, inadequate education of providers, and misconceptions on behalf of both patients and staff [14].

This is very unfortunate since the insufficient treatment of acute pain can lead to a number of complications, extended hospital stays, chronic pain, and prolonged course of illness[15,16].

A frequent and increasing challenge in the ED is the opioid-tolerant patients requiring acute pain management[17]. They are a group of patients who seek medical help much more often than their opioid naïve counterparts[18,19], i.e. in the EDs. Since Denmark has one of the highest rates of opioid consumption in the world with 3-5% of the population using opioids daily or regularly [20], these patients have a strong presence in the ED.

Besides the above mentioned risks of complications, these patients are in risk of withdrawal symptoms and stigmatization because of the need for much larger doses of opioids to achieve pain relief than others. The staff in the ED can be reluctant to deviate from standard treatment and the patient can be perceived as pleading for opioids. These barriers may be the reason that opioid-tolerant patients often do not receive the doses of opioids required to relief their pain[21].

1.1.2 Treatment of pain

The primary basis for acute pain relief is the administration of systemic analgesic agents such as paracetamol (1 g x 4/24h)[22], nonsteroidal anti-inflammatory drugs (NSAIDs) (400 mg x 3/24h)[23] (if no contraindications), and opioids i.e. morphine 0.05- 0.1 mg/kg or fentanyl 0.5-1 µg/kg[24,25].

Single opioid doses less than 0.1 mg/kg of intravenous morphine or 1 µg/kg of intravenous fentanyl are likely to be inadequate for severe, acute pain and the need for additional doses should be anticipated[13].

1.2 Low-dose ketamine – the trial intervention

1.2.1 The NMDA receptor

Ketamine functions primarily as an antagonist of the N-methyl-D-aspartate receptor (NMDA), thus counteracting signals and impulses, which lead to hyperalgesia, central sensitization and opioid tolerance, besides reducing the wind-up phenomenon, and activating descending inhibitory monoaminergic pain pathways via interaction with opioid receptors[26 27 28].

1.2.2 Use in pain treatment

Low-dose ketamine (LDK) has been used for decades and has been shown to be safe and effective in the reduction of acute postoperative pain and to reduce analgesic consumption in a variety of surgical interventions[28,29,30,31,32,33,34]. Furthermore, LDK has been shown to prevent hyperalgesia and acute opioid tolerance due to the use of morphine and/or fentanyl[10,28].

LDK has been studied as analgesic in a variety of contexts, including as a stand-alone treatment, as an adjunct to opioids, and, to a lesser extent, as an intranasal formulation [26,35,30,36].

1.2.3 Use in the ED

Regarding management of acute pain in the ED, finding alternatives to opioids has become increasingly interesting and LDK is studied both as a single agent [37,38,39,40,41,42] and as an adjunct to morphine[43,44,45,46,47]. These studies overall found that both LDK and LDK + morphine had analgesic effects within the 60 minutes of administration, was opioid sparing, and had comparable safety profiles with placebo.

These studies conducted in the ED did not mention/or excluded patients with chronic pain and patients with prior opioid consumption. Therefore, these above mentioned RCTs provide no information regarding the management of patients with chronic pain and/or opioid tolerance.

Studies evaluating the benefits of LDK in the opioid tolerant patients have exclusively been conducted in the peri- and postoperative setting, and have been found to reduce postoperative pain[48] and opioid requirements[29,31]. Other (smaller) studies in the opioid tolerant population have found less or no benefit[49,50,51]. Taken together, these studies suggest at least a mild benefit for ketamine in the opioid-tolerant population in the postoperative period.

We believe that patients with chronic pain and/or opioid tolerance would in particular benefit from LDK [52,53] when presenting in the ED with acute pain. As a NMDA receptor antagonist it presents analgesic effects independent of opioid tolerance[54].

To our knowledge, there are no prospective randomized trials that evaluate the role of LDK in managing a variety of acute, painful conditions in the opioid tolerant patients in the ED. Furthermore, additional data describing its safety and efficacy in the general ED setting is warranted[55].

1.2.4 Ketamine

Ketamine's analgesic properties in sub-anesthetic doses (0.1-0.5 mg/kg) have been recognized for decades (average anesthetic induction dose is 2 mg/kg)[35] and S-ketamine produces analgesia at plasma concentrations of 100 to 200 ng/mL, which represent a very small fraction of plasma concentrations after general anesthesia doses (9000–25,000 ng/mL)[35].

The recommended sub-anesthetic dose of ketamine used in pain treatment or in the prehospital emergency setting is 0.125-0.25 mg/kg bolus given IV over at least one minute[56]. In these doses LDK show analgesic effects without sedative or hypnotic effect[57]. When used as per- and postoperative pain treatment at AUH doses are (perioperative) 0.3 mg/kg/h and (postoperatively) 0,02 mg/kg/h[58].

Studies from the ED [46,59,60,61,62] finds little to no psychoperceptual effects at the dose of 0.1 mg/kg as will be used in this study.

1.2.5 Side effects reported following anesthetic doses

The side effects reported below are all related to doses and administration pace. They are reported after ketamine is used in anesthetic doses, and thus much larger doses than in this study.

Frequency:

Very common: >10 %

Common: >1 % and <10 %

Not common: >0.1 % and <1 %

Rare: >0.01 % and <0.1 %

Very rare: <0.01 %

Not known (can't be estimated from available data)

Immune system disorders Rare	Anaphylaxis.
Neuropsychological manifestations Common Frequency unknown	 Emergence reactions (post-operative delirium)[1,] vivid dream, nightmares, dizziness and restlessness, hallucnations[2]. Dysphoria, anxiety, disorientation
Nervous system Not common	 Enhanced muscle tone and spasms (resembling a partial motor or generalized motor seizure).
Eyes Common Not common	 Blurred vision Diplopia, increased intraocular pressure, nystagmus
Heart Common Rare	 Transient tachycardia, elevated blood pressure and heart frequency Arrhythmia, bradycardia
Vascular system Rare	 Hypotension (when used in circulatory collapse)
Airways, thorax and mediastinum Common	 Increased vascular resistance in the lung circulation, increased mucus secretion, increased

	need of oxygen, laryngospasm, transient respiratory depression*
Abdominal Common	Nausea, vomiting, hypersalivation
Hepatobiliary dysfunction Frequency unknown	Abnormal test of liver function Drug induced liver injury**
Skin and subcutaneous tissue disorders Not common	Transient erythema and/or morbilliform rash, reactions at the injection site (pain and reddening)

1. When S-ketamine is used as single agent for anesthesia, up to 30 % of the patients are observed to have side effect in the recovery phase.

2. Frequency of these side effects can be reduced significantly by using a benzodiazepine.

*Large doses and rapid rate of administration

** After longer use (> 3 days).

2. TRIAL DESIGN, OBJECTIVES AND HYPOTHESES

2.1 Overview

2.1.1 Design

This is an investigator-initiated, randomized, parallel-grouped, double-blinded, superiority trial, investigating the combination of IV LDK and IV morphine versus IV morphine and placebo as regards to analgesic effect.

2.1.2 Hypotheses

- The combination of IV LDK and IV morphine will be superior to IV morphine alone as regards analgesic effect measured as reduction on the NRS scale.
- The combination of IV LDK and IV morphine will provide a larger reduction on the NRS scale for patients with a prior use of opioids than for patients with no prior use of opioids.
- The combination of IV LDK and IV morphine will reduce the opioid consumption within the first hour.
- The frequency of side effects will be similar in the two treatment groups (ketamine vs. placebo)

2.1.3 Location

The study will be conducted at Aarhus University Hospital

2.1.4 Participants

160 patients presenting in the ED with NRS ≥ 5 will be enrolled.

2.1.5 Objective

To determine efficacy and safety of IV LDK as an adjunct to IV morphine for the treatment of severe acute pain in the ED and compare the effect in patients with a prior use of opioid and patients without.

2.2 ALLOCATION

Patients fulfilling all inclusion criteria and no exclusion criteria will be randomized as follows:

Group 1 = patients with a prior use of opioids.

Group 2 = patients without a prior use of opioids.

Patients in group 1 are allocated randomization numbers 101-190

Patients in group 2 are allocated randomization numbers 201-290

There are 10 additional numbers in each group to be used if a patient is excluded after the administration of study medicine.

If a patient is excluded after randomization, but before study medicine is administered, the randomization number can be re-used by adding and registering a, b, c and so on.

Patients (n=160) will be randomized in a 1:1 ratio to either s-ketamine or placebo (NaCl) in blocks of 2, 4 and 6 patients

The randomization process will be performed by the hospital pharmacy using www.sealedenvelope.com.

The randomization list is kept at the hospital pharmacy during the study and only delivered to the PI when the inclusion and the data analysis are completed.

PI will be provided with numbered blinded kits including either S-ketamine or placebo ensuring allocation concealment.

The kit consist of:

Active:

- Esketamin “Orifarm” 5 mg/ml 1x 5 ml
- NatriumChloride Fresenius Kabi 20 x 10 ml 1 x 10 ml
- Emballage, 1 ml, neutral syringes 2 pieces
- Emballage, cardboard (with label) 1 karton
- Labels, 2 pieces, for the syringes 2 pieces
- Envelope for emergency unblinding

Placebo:

- NatriumChloride Fresenius Kabi 20 x 10 ml 1 x 10 ml
- Emballage, 1 ml, neutral syringes 2 pieces
- Emballage, cardboard (with label) 1 karton
- Labels, 2 pieces, for the syringes 2 pieces
- Envelope for emergency unblinding

2.3 INTERVENTIONS

2.3.1 Intervention groups

	Morphine + LDK	Morphine + Placebo
Prior opioid use	N 40 IV morphine (15 % of the total 24-hour opioid consumption) + Ketamine 0,1 mg/kg	N 40 IV morphine (15 % of the total 24-hour opioid consumption) + Placebo (saline)
No prior opioid use	N 40 IV morphine, 0.05- 0.1 mg/kg + Ketamine 0,1 mg/kg	N 40 IV morphine, 0.05- 0.1 mg/kg + placebo (saline)

2.3.2 Concomitant interventions

All procedures, except for the administration of study medicine and data collection for the study purpose, will be conducted according to the standard at Aarhus University Hospital.

During the observational period, 120 min, relevant procedures will be registered in eCRF:

- Nerve block
- Repositioning of joints/fractures or casting
- Paracetamol and NSAID

2.3.3 Criteria for modification of interventions for a given trial participant and protocol violations

The clinical team may at any time violate the protocol if they find it to be in the interest of the participating patient.

2.3.4 Assessment of participant compliance

The trial site is monitored through the electronic case report form (eCRF). In addition, the trial will be monitored according to the Good Clinical Practice (GCP) directive and the monitoring plan.

2.4 BLINDING

The trial intervention (morphine + LDK vs. morphine + placebo) will be blinded for investigators, clinical staff, and participants.

Only the pharmacy providing the numbered kits and the nurse who draw the medication will be aware of the allocation.

Patients will be randomized according to the allocation list.

The randomization number will be entered directly in the eCRF.

Study medicine is delivered by the pharmacy in blinded kits, the PI provides a study nurse (who is not otherwise involved in the study) with the kit and he or she will draw the study medicine in the two, 1 ml, syringes contained in the kit, mark them with the labels in the kit and hand them over to the PI.

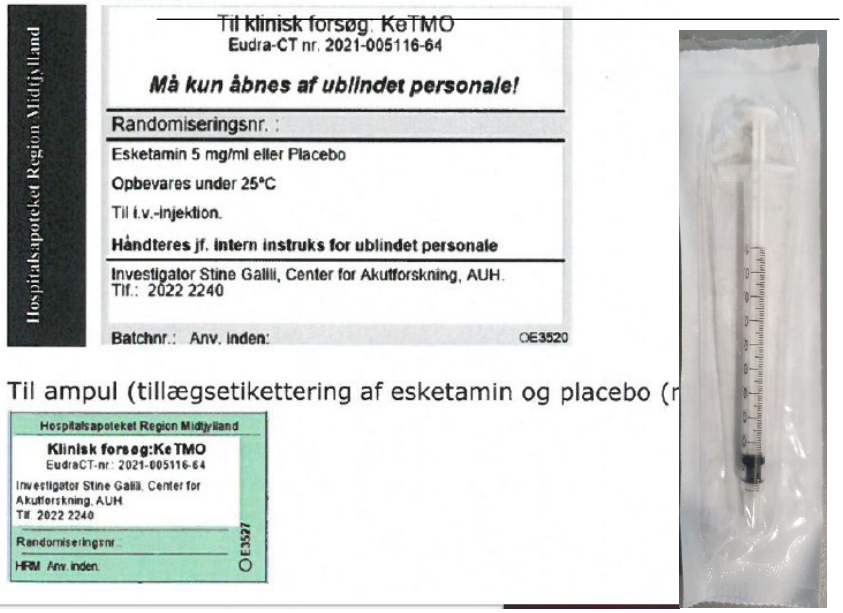
Both ketamine and NaCl is colorless and without any identifying features.

The PI has entered the sex and weigth in the eCPR and a calculated field gives the ideal weigth. The PI administers the correct doses according to ideal weigth.

Doses are marked in table 1, (ideal weight, 0.1 mg/kg).

Labels (Danish):

Til karton (kit):



Til ampul (tillægsetikettering af esketamin og placebo (r

In the blinded intervention kit, a sealed opaque envelope will contain the allocation assignment which will allow for emergency unblinding. The decision to unblind will be at the complete discretion of the treating physician and clinical team. However, we do not expect scenarios where emergency unblinding will be necessary. In case unblinding occurs, the reason(s) will be clearly documented in the case report form. The patient will remain in the trial.

Table 1

Ideal weight*, kg	40	45	50	55	60	65	70	75	80	85	90	95	100	105	110
Ketamine, mg	4	4,5	5	5,5	6	6,5	7	7,5	8	8,5	9	9,5	10	10,5	11
Study medication, ml (S-ketamine 5 mg/ml or placebo)	0,8	0,9	1	1,1	1,2	1,3	1,4	1,5	1,6	1,7	1,8	1,9	2	2,1	2,2

*ideal weight: height (in cm) - 100

If cancellation/postponement of treatment or withdrawal of consent occurs before the study medication is given, but after randomization has taken place, the randomization number will not be reused. Besides study medication, emergency department staff provides usual pain treatment (0.05-0.1 mg/kg morphine or if the patient has a prior use of opioids 15% of 24 hour dose in morphine equivalent – in both cases titration until NRS ≤ 3.)

The unblinded pharmaceutical staff and nurse who draws study medicine will not be involved in outcome evaluation or patient treatment.

2.5 TRIAL PROCEDURES

2.5.1 Patients

The trial procedures will be limited to the interventions given with the first dose of morphine (see section 2.3)
Data will be obtained from the study specific eCRF and from the electronic medical records.

T_0 defined as when the ED physician/nurse evaluates NRS and the PI gives the study medication.

The trial and observation period is T_0 - 120 min.

	T_0	10 min	20 min	30 min	45 min	60 min	120 min
NRS	x	x	x	x	x	x	x

Patient rated pain relief*		x					x
Vital parameters	X	X	X	X	X	X	X
Patient reported side effects**		x		x			x
Physician reported side effects***							x
Provider satisfaction score****							x
Patient satisfaction score							x
RASS*****		x	x	x	x	x	x

*Patients will be asked to rate their pain relief on a 6-point scale ("worse pain," "no," "little," "moderate," "good," or "complete pain relief").

**Patient-Reported Side effects: nausea, lightheadedness or dizziness, disorientation, euphoria, itching, tinnitus, double vision, abnormal dreaming or hallucinations.

In addition, patients are encouraged to spontaneously report any other side effects/adverse advent. The timing of onset and resolution of all adverse effects during the observation period will be recorded.

***Physician-reported side effects: nystagmus, hypertension, respiratory depression, bradycardia, hallucinations.

****Provider satisfaction with pain control will be recorded on the 4-point Likert scale with 0 being "completely unsatisfied" and 3 being "very satisfied.

*****Richmond Agitation-Sedation Scale (RASS) will be used to evaluate agitation or sedation. (appendix 2)

TRIAGE[63] and TOKS[63] (tidlig opsporing af kritisk sygdom) according to the standard at AUH will be used to evaluate differences in vital parameters.

There will be no questionnaires for the participants to answer, they will be asked verbally and their answers will be entered in RedCap.

2.5.2 Clinical personnel

Prior to the beginning of patient enrollment and continuously throughout the enrollment period, the clinical teams involved in the treatment of patients at the participating hospital will be informed about the background and objectives of the trial, the inclusion/exclusion criteria, the interventions, and the trial procedures they are involved in. We anticipate, in-person didactics monthly with informal sessions.

Provider Satisfaction Score will be used after the observation period is over (120 min after study medication is injected) to evaluate provider's clinical satisfaction with the treatment. Provider satisfaction with pain control will be recorded on the 4-point Likert scale with 0 being “completely unsatisfied” and 3 being “very satisfied. There will be no questionnaires for the provider, they will be asked verbally and their answers entered in RedCap.

3. SETTING AND PATIENT POPULATION

3.1 Setting

The trial will be conducted at the ED at Aarhus University Hospital, and may be expanded to the ED at Regional Hospital West Jutland at a later stage. (an amendment will be added in this case)

3.2 Inclusion criteria

PI will screen ED patients at ED admission for the following inclusion criteria:

1. Emergency Department admission
2. Age ≥ 18 years and
3. A painful condition (NRS $\geq$ 5)
4. Stable vital signs defined as systolic blood pressure ≥ 90 mmHg, heart rate between 50 and 150 per minute, respiratory rate between 8 and 30 per minute, oxygen saturation greater than or equal to 92%.

Further subcategorized into

1. Prior use of opioids (daily for one week before admission)

2. No prior use of opioids (daily for one week before admission)

These broad inclusion criteria are chosen to investigate the effect of LDK in the entire, broad population with pain in the ED and the subcategorization to investigate whether LDK leads to a larger reduction on NRS in the group of patients with a prior use of opioids than those without a prior use of opioids.

We will strive to enroll participants as soon as they fulfill the criteria in the ED.

3.3 Exclusion criteria

1) Initial management by trauma-team
2) Systolic blood pressure ≥ 180 mmHg, severe untreated arrhythmia, unstable angina pectoris, recent myocardial infarction (< 30 days), severe heart failure (Ejection fraction < 40 %)
3) Symptoms of untreated hyperthyroidism
4) Cirrhosis with ascites
5) Known/suspected pregnancy, or breastfeeding
6) Patients, for whom consent is not obtainable or psychiatric forced treatment.
7) Previously enrolled in the trial
8) Psychiatric illness prior to admission defined as prior psychosis/schizophrenia
9) Diagnosed untreated glaucoma
10) Known hypersensitivity to ketamine or to any excipient or prior use of ketamine with a negative experience (i.e. hallucinations)
11) Patient clearly influenced by drugs or alcohol

3.4 Withdrawal

Each participant has the right to withdraw from the trial at any time. In addition, the Investigator may discontinue a participant from the trial at any time if the Investigator considers it necessary for any reason including:

- Ineligibility (either arising during the trial or retrospectively having been overlooked at screening)

- Significant protocol deviation
- Withdrawal of consent
- Loss to follow up

3.5 Co-enrollment

There will be no general restrictions on entry into other clinical trials, although this will be evaluated on a case-by-case basis. However, patients enrolled in this study will not be able to be enrolled in other acute-pain treatment projects at the time of admission in the ED and the first 120 minutes after study medicine is given.

4. OUTCOMES

4.1 Primary outcome

4.1.1 Definition

The primary outcome measurement is pain reduction assessed on NRS 10 minutes after study medication is given, T_0 .

(T_0 = when the physician/nurse evaluates pain at administration of study medication)

4.1.2 Rationale

This study is powered to detect a difference in pain reduction of at least 1.5 on the NRS scale between the groups. (LDK vs placebo)

4.2 Secondary outcomes

4.2.1 Definitions

Secondary outcomes:

- Need of morphine within the 30, 60 and 120 min after administration of study medication
- Pain intensity after 20, 30, 45, 60 and 120 min
- Side effects
- Patients satisfaction Score
- Provider Satisfaction Score

- Comparison of pain reduction in the two parallel groups (prior opioid, no prior opioid) on all time intervals.

4.2.2 Rationale

Very few prospective studies have examined the effect of LDK as an adjunct to opioid for acute pain treatment in the ED setting. Almost none in the general patient population with pain and no one have evaluated the effect in patients having a prior use of opioids.

Increasing the efficacy of pain treatment and reducing the incidence of adverse side effects is always a desirable clinical improvement, as is the reduction of resources necessary to effectively treat pain in the ED.

Adding LDK to morphine may result in a better pain treatment for the patient and reduced need for opioids.

4.3 Safety and harm

4.3.1 General consideration

The personal in the ED are highly trained in acute pain therapy. The PI is Specialty trainee in anesthesiology, Department of Anesthesiology AUH and she will be at trial site whenever study medicine is given. The doses used in this study are very low (0,1 mg/kg), and we do not expect any serious adverse reactions with this dose[46,59,60,61]. We therefore believe it is safe for both individual patients and at the group level to be enrolled into this study after relevant inclusion and exclusion criteria.

The overall benefit and potential harm will be captured in our secondary outcomes, and the clinical team/PI will document any specific adverse reactions suspected to be related to the intervention - if there are AE or AR´s after the observation period (T_0-T_{120}), the patients are observed as standard on AUH.

All participants are expected to receive opioids, but the amount is hypothesized to differ.

AE as natural consequences of the reason for hospitalization will not be registered in the eCRF. (i.e. blood transfusion).

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an AE is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance will be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (where applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
  Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

4.3.2 Definitions for adverse events and reactions

The following definitions will be used[2]:

Adverse event (AE): any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

Adverse reaction (AR): all untoward and unintended responses to an investigational medicinal product related to any dose administered.

Serious adverse event (SAE): any untoward medical occurrence that at any dose requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death.

Serious adverse Reaction (SAR): an adverse drug reaction that is serious (see above) and at least possibly related to an investigational medicinal product related to any dose administered.

Suspected unexpected serious adverse reaction (SUSAR): a serious adverse reaction, the nature, severity or outcome of which is not consistent with the reference safety information.

4.3.3 Reporting

Serious adverse reactions and events (SAE and SARs) and suspected unexpected adverse reactions (SUSARs) will be recorded daily in the eCRF during the intervention period. PI is to report potential SARs and SUSARs without undue delay to the sponsor, which in turn will evaluate the event according to the Danish summaries of product characteristics and report any SAR's and/or SUSARs , which in turn will report these to the Danish Health and Medicine Authorities 7 days at the latest after the report has been received. The sponsor will yearly submit a list of all registered AEs that have occurred during the trial period as well as a report on safety (SAR) of the trial subjects to the Danish Medicines Agency and Scientific Ethics Committee.

The sponsor will notify the Danish Medicines Agency when the trial has been completed (no later than 90 days thereafter). The results from the clinical trial including important adverse events will be recorded on EudraCT.

5. SAMPLE SIZE CALCULATION AND STATISTICAL ANALYSIS PLAN

5.1 Sample size calculation

We consider a mean reduction in pain intensity of 1 (SD ±2) on the NRS scale to be realistic in the control group and that the reduction should be 2.5 (SD ± 2) in the intervention group for the addition of LDK to be meaningful. Based on these estimates, an alpha of 5%, a power of 90% and a two-sample t-test (assuming that the pain reduction is normally distributed), a sample size of 78 patients is required; 39 in each treatment arm (two independent samples =156 patients).

The primary (continuous) and secondary outcomes (binary and continuous variables) will be presented as follows: Categorical variables will be compared using Fisher's exact test and continuous variables

using t-tests or Wilcoxon rank-sum test as appropriate. P < 0.05 will be considered statistically significant.

To investigate the hypothesis of heterogeneity in effect of LDK addition depending on prior morphine use, we will compare treatment effect between the two groups (no prior morphine use vs prior morphine use). If we assume the two groups to have equal size (78 patients) then the expected SE of the difference between treatment effects of the two groups (no prior morphine vs prior) will be 0.64, i.e. the corresponding 95% confidence interval will have a width of approximately 2.6.

To handle potential differences in baseline pain intensity between the standard and the LDK treatment group, we will assess the relative (%) change in NRS from baseline (T0) to 10 min after administration of study medicine in a supplemental post-hoc analysis. The relative change in pain scores will be assessed by multilevel mixed effect ordinal logistic regression model[64].

5.2 General considerations

The statistical analyses and reporting will adhere to the CONSORT guidelines.[65]. All tests will be two-sided, a p-value < 0.05 will be considered significant, and all confidence intervals will have 95% coverage.

Patient inclusion and exclusion will be illustrated in a CONSORT flow diagram (see Appendix 3).

We will include measures related to feasibility including the enrolled to screened ratio, time to randomization, and protocol adherence/major protocol violations. All analyses will be conducted in the modified intention-to-treat (MITT) population defined as all randomized participants for whom consent was obtained.

6. DATA COLLECTION AND DATAMANAGEMENT

6.1 Data collection process

The site investigator (PI) is responsible for data collection and entry. This will include the patient identifier (i.e. Danish Central Personal Register number), study ID, and timing of enrollment. Data will be obtained in eCRFs especially regarding pain therapy as well as from medical journals; all data will be based on measurements and assessments made by the clinical team. Data are continuously entered

into RedCap (Institute for Clinical Medicine, Aarhus University), which is considered as the Case Report Form. RedCap is a secure web application geared to support data capture for research studies[66]

6.2. Variables

6.2.1 Overview

All patients admitted to the ED during study days with a painfull condition AUH, will be entered into a screening log. For those screened but not randomized, a specific reason for non-inclusion/exclusion will be documented. All randomized patients will be entered into the main database.

A detailed data dictionary that clearly defines all included variables will be created prior to patient enrollment. The data dictionary will provide the name of the variable (including the code used in the database), a detailed definition of the variable, categories for categorical variables, and units and ranges for continuous variables.

The number of collected variables will be kept relatively small to limit resource use and data entry mistakes. Below is provided a brief overview of the included variables, but details are reserved for the data dictionary.

6.2.2 Baseline characteristics

Trial related variables

- Study ID
- Inclusion criteria
- Exclusion criteria
- Opioids given before study medication (i.e. in ambulance)
- Date and time consent for data collection is obtained

Patient demographics and characteristics

- Unique patient identifier (CPR number)
- Age
- Sex
- Height

Weight

Medications prior to enrollment

Prior opioid use, dose, duration

Reason for prior opioid use (cancer/non-cancer pain, postoperative, addiction)

Cancer/non-cancer

Site of pain/injury:

Fracture/orthopedic

Abdominal/flank

Groin pain

Postoperative pain

Other/unknown

Prior to randomization:

Vital parameters

NRS

At 10, 20, 30, 45 60 and 120 min after randomization:

NRS

RASS

Need for rescue morphine and total use of morphine

Physician reported side effects: nystagmus, hypertension, respiratory depression, bradycardia, arrhythmia.

TOKS and triage values as standard procedures

Patient-reported side effects: nausea, lightheadedness or dizziness, dry mouth, disorientation, euphoria, itching, tinnitus, double vision, abnormal dreaming or hallucinations.

Patient satisfaction. To be able to compare with other and future studies “no pain” and “worst pain imaginable” are chosen as anchors[67].

Provider satisfaction with pain control will be recorded on the 4-point Likert scale with 0 being "completely unsatisfied" and 3 being "very satisfied.

Protocol violation.

6.3 Data quality and validity

Data quality and validity will be optimized by having trained PI entering all data according to a detailed data dictionary. Research Electronic Data Capture (REDCap) (see section 7.4) is designed such that data forms contain field-specific validation checks ensuring that mandatory fields are filled out and that continuous variables are within predefined ranges. Given its limited utility, double-data entry will not be performed[68,69].

6.4 Data storage and security

REDCap[66] is a professional database that provides a user-friendly interface. The REDCap data management system is secure, fully compliant with all regulatory guidelines, and includes a complete audit-trail for data entry validation. Through these mechanisms, as well as relevant training for all involved parties, patient confidentiality will be safeguarded. REDCap is available for free at participating sites.

The consent form for each patient will be stored in a secure, locked place at Research Center for Emergency Medicine in Aarhus. Here they will be securely stored in locked cabinets, where only the principal investigator will have access. The files will be stored for 5 years after the end of the trial, whereupon they will be destroyed.

Data will be handled according to all relevant Danish laws including the General Data Protection Regulation ("Databeskyttelsesforordningen") and the Data Protection Act ("Databeskyttelsesloven"). The project will be registered with the Central Denmark Region's internal list of research projects.

6.5 Data access

Each patient will receive a unique trial identification number. During the trial, the principal investigator will have access to the entire database.

Once the database is locked and data is analyzed as group A and B, two conclusions will be written before unblinding, one where LDK is A and one where LDK is not A.

A de-identified version of the database will be made available to the members of the project group. The Good Clinical Practice unit, regulatory agencies, and other relevant entities will have direct access to patients' records and to all relevant trial data including the case report form as applicable.

6.6 Data obtained from patient records

6.6.1 Data that will be obtained before informed consent and inclusion

The electronic patient record will only be screened for in- and exclusion criteria(see page 22-23), pain intensity and opioids given before the informed consent, i.e in ambulance. If a patient is excluded the reason for exclusion will be entered in the screening log.

No other data will be obtained.

6.6.2 Data that will be obtained after informed consent and inclusion

Reason for contact to the ED (ie abdominal pain, broken ankle)

Use of opioids prior to the admission (yes or no, drug and dose)

Use of other analgesic except NSAIDs and paracetamol

Access to patient journals:

The written informed consent gives PI, Sponsor, sponsors representatives and monitor direct access to all relevant data in the electronic patient record concerning the patients health, relevant for the execution of the trial. Furthermore for the legal monitoring and purpose of controlling the study including own-check, quality control and monitoring of the study that these obliged to perform.

7. CLINICAL TREATMENT

7.1 Screening, information and enrollment

Patients will be screened and recruited according to the following process:

Information on all patients "on their way" to the ED is being passed on to the PI in "Klinisk Logistic" and whenever a patients is referred with a pain full condition (i.e. abdominal pain, backpain or suspicion of broken hip) the PI markes the patient "Candidate for KetMO, Please call PI at arrival". The visitation nurse is the gatekeeper at the ED, AUH and she/he is contacted by every doctor or paramedic who refers patients to the ED. If patients are presenting to the ED unannounced it is also the visitations nurse that registers the patient. The visition nurse will call the PI when a relevant patient arrives at the ED or is already admitted in the ED.

The PI screens the medical record for exclusion criteria. If the patient fulfills no exclusion criteria the patient will be approached and asked for inclusion criteria and risk/chance of pregnancy – if yes to inclusion criteria an certain no to risk of pregnancy the patient can be included in the study and the formal information procedure will begin.

In as calm surroundings as possible and, if feasible, with companion, the patient will be informed, verbally and in writing, about the background and significance of the study, inclusion criteria, potential risks and benefits, as well as a brief description of the study intervention. The patient may ask questions and provide written informed consent utilizing the informed consent form approved by the Ethical Review Committee. If a patient denies participation in the trial, no data besides the screening log will be collected[71].

It is exclusively the PI who informs and enrolls the patients. and The information and enrolment is as soon as possible at admission in the ED.

The study protocol will begin as soon as the patient have given verbal and written consent.

The clinical management of included patients, other than pain treatment according to randomization, will be at the complete discretion of the treating clinical team in order to test the interventions in a real-life clinical scenario.

8. ETHICAL CONSIDERATIONS

8.1 General considerations

For ethical reasons, treatment of acute must be initiated as soon as possible. This is also stated in international guidelines[70] and in a local guideline at our institution.

We therefore often need patients to provide consent within a timeframe less than one hour (from information about the study until consent). If this is not possible for the patient (he or she needs longer time to consider), the patient will not be included

The current trial will adhere to the revised Declaration of Helsinki as well as all applicable laws and regulatory guidelines.

8.2 Procedures

8.2.1 Ethical review committee

The trial is approved by the Regional Ethics Committee.

8.3.1 Insurance

The patients in the study are covered by the Danish patient insurance[72].

9. MONITORING

9.1 Good Clinical Practice monitoring

The site will be monitored by the regional Good Clinical Practice monitoring unit affiliated with Aarhus University Hospital and Central Denmark Region. A detailed monitoring plan will be developed prior to trial commencement.

10. TIMELINE AND ENROLLMENT

10.1 Timeline

	Spring/Summer 2021	Autum 2021	Autumn/Winter 2021	2022	2023
Funding	X				
Protocol development and modifications	x				

Ethical approval		x			
Registration with the Danish Medicine Agency		x			
Creation of data dictionary		x			
Trial registration		x			
Creation of randomization list			x		
Education of site personnel			x	x	
Good Clinical Practice monitoring				x	x
Enrollment and assessment of outcomes				x	
Writing and publication of methodology article			x		
Cleaning and closing of the database					x
Data analysis					x
Main manuscript writing					x
Unblinding					x
Publication and presentation of results					x

10.2 Feasibility

We expect to enroll 1 patient 3 days a week during the study period. 160 patients must be included – 160 days → 53 weeks for inclusion of participants.

10.3 Enrollment

Enrollment will be continuously performed and monitored by the PI. Formal reports outlining the number of pain patients and the proportion of those enrolled will be shared with the project group every second week during enrollment.

12. PUBLICATION PLAN

Two manuscripts are planned from the current trial. Prior to the clinical study, a methodology article will be published including a detailed description of the trial and the statistical analysis plan. The second and primary manuscript will include the main results including pre-defined primary and secondary outcomes. The manuscript will adhere to the CONSORT guidelines[73,74]. The principal investigator will be the first and corresponding author. Additional authorship will follow authorship guidelines from the International Committee of Medical Journal Editors[75] and will include members of the project group. The main results will be presented at international conferences. The trial results will not be shared directly with the participating patients. Study findings will be published if the results are positive, negative or inconclusive.

13. DATA SHARING

Six months after the publication of the last results, all de-identified individual patient data will be made available for data sharing[76]. Procedures, including re-coding of key variables, will be put in place to allow for complete de-identification of the data. Data will be completely anonymized according to Danish law.

All relevant trial-related documents, including the protocol, data dictionary, and the main statistical code, will be shared along with the data. There will be no predetermined end date for the data sharing. Data will be available for any research purpose to all interested parties who have approval from an independent review committee and who have a methodological sound proposal as determined by the project group of the current trial. Only the methodological qualities and not the purpose or objective of the proposal will be considered. Interested parties will be able to request the data by contacting the principal investigator. Authorship of publications emerging from the shared data will follow standard authorship guidelines from the International Committee of Medical Journal Editors[75] and may or may not include authors from the project group depending on the nature of their involvement.

14. FUNDING

Funding for the trial is provided by Dansk Selskab for Anæstesi og Intensiv medicin (DKK 40,000), Health Research Foundation of Central Denmark Region, “Akutpuljen” (DKK 220,000), Central Denmark Region 1,5 mio (salary for PI, PhD student). Funding is administered at the Research Center for Emergency Medicine, Central Denmark Region and is used for salary support, monitoring, and additional operational expenses. Additional funding will be applied for at various private and public foundations. The funding agencies or any pharmaceutical companies will have no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

15. TASKS AND RESPONSIBILITIES

PI and sponsor: Overall responsibility for protocol development, funding, budget overview, data dictionary development, ethical approval, trial registration, daily management, trial oversight, contact to the pharmacy, contact to Good Clinical Practice monitoring unit and the data and safety monitoring board, assessment of overall recruitments and education, potential recruitment of additional sites, data analysis, and dissemination and presentation of results.

PI: Responsible for site-specific enrollment and participant consent for data collection, evaluation of eligible patients not included, education of personnel at participating sites, reporting of site-specific issues or challenges to the principal investigator, participant consent for data collection.

Daily management, education of personnel at participating sites, contact to Good Clinical Practice monitoring unit, data dictionary development, data entry and management, patient follow-up, budget overview

Project group: Protocol development, funding, budget overview, data dictionary development, trial oversight, dissemination of results, responsibilities as principal investigator for short time periods.

Appendix 1, Conflict of interest disclosures for project group

	Industry	Other

Stine Fjendbo Galili	None	None
Lone Nikolajsen	None	None
Hans Kirkegaard	None	Chairman of the steering committee for DANARREST
Jette Ahrensberg	None	None
Bodil Hammer Bech	None	None

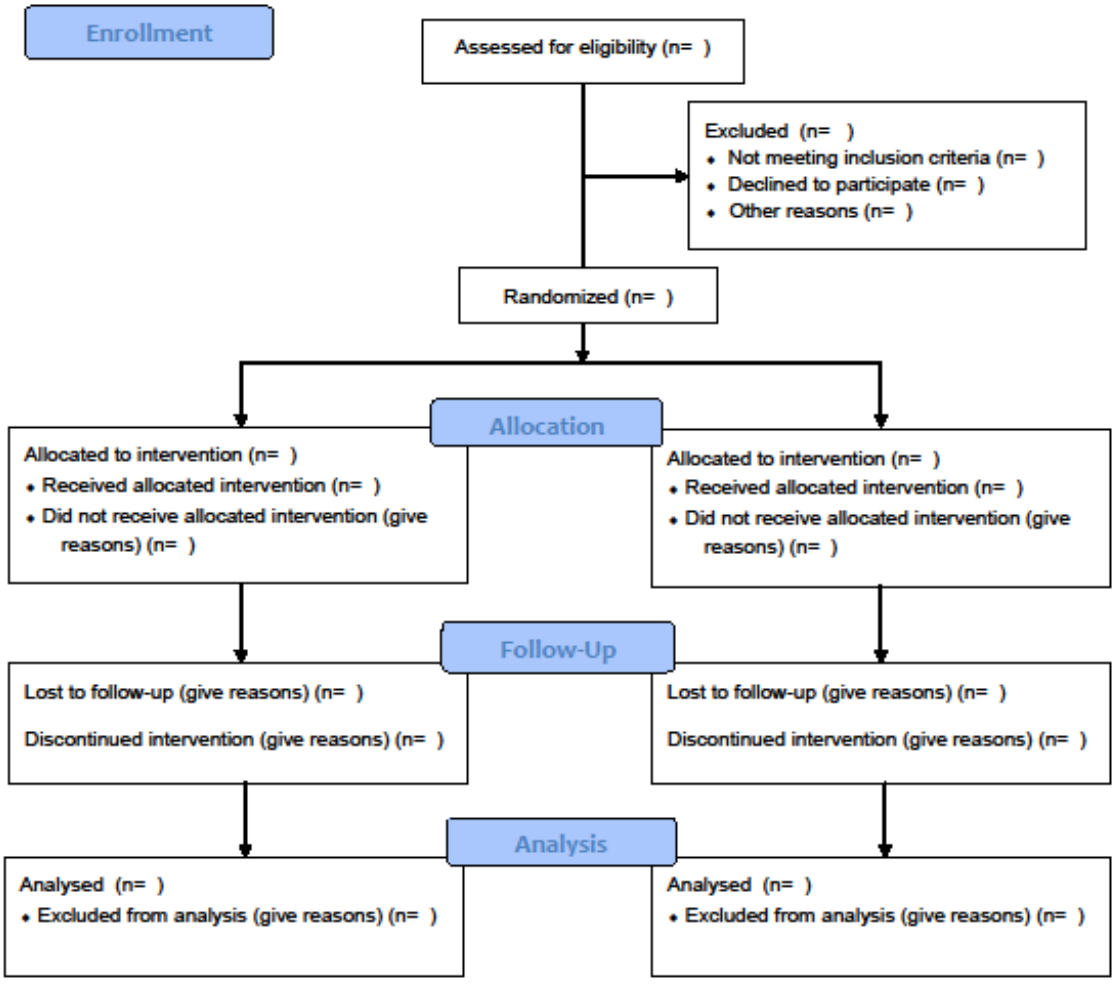
Appendix 2, Richmond Agitation and Sedation Scale

Richmond Agitation and Sedation Scale (Rass)		
+4	Combative	Violent, immediate danger to staff
+3	Very Agitated	Pulls or removes tube (s) or catheters; aggressive
+2	Agitated	Frequent non-purposeful movement, fights ventilator
+1	Restless	Anxious, apprehensive but movements not aggressive or vigorous
0	Alert and Calm	
-1	Drowsy	Not fully alert, but has sustained awakening to voice (eye opening and contact > 10 sec)
-2	Light sedation	Briefly awakens to voice (eye opening & contact < 10 sec)
-3	Moderate sedation	Movement or eye opening to voice (but no eye contact)
-4	Deep sedation	No response to voice, but movement or eye opening to physical stimulation
-5	Unarousable	No response to voice or physical stimulation

Appendix 3, CONSORT flow diagram

CONSORT
TRANSPARENT REPORTING of TRIALS

CONSORT 2010 Flow Diagram



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