Early initiated vasopressor therapy vs. standard care of primarily fluid therapy in hypotensive patients in the emergency department – A pragmatic, multi-center, superiority, randomized controlled trial

Acronym: VASOSHOCK

TRIAL PROTOCOL

Version 1.1

25-08-2023

EU CT identification: 2023-504584-16-00

Clinicaltrials.gov identification:

Coordinating Investigator

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Preface

We hereby declare, as Sponsor-Investigator and Coordinating Investigator, that the trial "Early initiated vasopressor therapy vs. standard care of primarily fluid therapy in hypotensive patients in the emergency department – A pragmatic, multi-center, superiority, randomized controlled trial (VASOSHOCK)" will be conducted in accordance with the written protocol. The trial will follow the applicable national and international laws, guidelines including the European Regulations,[1] ICH-GCP [2] and the revised version of the Declaration of Helsinki on ethical principles for medical research involving human subjects.[3]

This protocol is developed in accordance with the Standard Protocol Items: Recommendations for International Trials (SPIRIT) statement.[4]

This protocol was written by the Coordinating Investigator with input and revision suggestions by the Steering Committee. The Sponsor-Investigator and Coordinating Investigator takes responsibility that any substantial changes or modifications will be documented and reported to all relevant parties when applicable.

Coordinating Investigator – Department of Emergency Medicine – Odense University Hospital

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Lasse Paludan Bentsen, M.D. **Date**

Sponsor and Principal Investigator – Department of Emergency Medicine – Odense University Hospital

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Mikkel Brabrand, M.D., Ph.d. **Date**

We hereby declare as principal investigators to conduct the trial at the sites we are responsible for, in accordance with the written protocol. Our departments have agreed to the conduction of the trial at each site, including treating of patients in accordance with the written protocol and collection and use of data for participants included in the trial.

Principal investigator – Department of Emergency Medicine - University Hospital of Southern Denmark Esbjerg

_____

Peter Biesenbach, M.D. **Date**

Principal Investigator – Emergency Department – Zealand University Hospital Køge

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Gerhard Tiwald, M.D. **Date**

Principal Investigator – The Emergency Department – Regional Hospital Gødstrup

_____

Larshan Perinpam, M.D. **Date**

Sponsor Statement

As Sponsor, I hereby confirm that all investigators, their related trial institutions, and departments have agreed to be involved in the clinical trial and agree to allow trial related monitoring, audit and inspection from the relevant authorities, including direct access to source data and documents.

Sponsor and Principal Investigator – Department of Emergency Medicine – Odense University Hospital

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Mikkel Brabrand, M.D., Ph.d. **Date**

Overview

PROTOCOL VERSION	**VERSION 1.1**
REGISTRY AND TRIAL NUMBER	EU CT: 2023-504584-16-00 Clinicaltrials.gov: Not registered yet
DATE OF REGISTRATION	13-06-2023
PLANNED START OF TRIAL	01-10-2023
PLANNED END OF TRIAL	31-08-2026
SOURCES OF MONETARY OR MATERIAL SUPPORT	The PhD Fund of the Region of Southern Denmark, The Medicine Fund of the Danish Regions and The Region of Southern Denmark and Region Zealand Research Fund.
SPONSOR AND PRINCIPAL INVESTIGATOR	Mikkel Brabrand Department of Emergency Medicine and Research Unit for Emergency Medicine Odense University Hospital Kløvervænget 25c DK-5000 Odense C, Denmark
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COORDINATING INVESTIGATOR	Lasse Paludan Bentsen Department of Emergency Medicine and Research Unit for Emergency Medicine Odense University Hospital Kløvervænget 25c DK-5000 Odense C, Denmark
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COUNTRY OF RECRUITMENT	Denmark
STUDIED SUBJECT	Hypotension and shock not related to anaphylaxis, cardiogenic, neurogenic, or haemorrhagic cause.
INTERVENTION	Early initiated peripherally infused noradrenaline during ED admittance
COMPARATOR	Standard treatment according to local guidelines without ED initiation of vasopressor therapy
INCLUSION CRITERIA	1. At least 18 years of age with a Danish social security number. 2. Signs or suspicion of hypotension or shock (Defined as SBP < 100 mmHg or MAP < 65 mmHg combined with lactate > 2.0 mmol/L or by physician defined blood pressure for the individual patient combined with a lactate > 2.0 mmol/L). Shock can be any type of shock such as septic, vasodilatory or hypovolaemic not listed in the exclusion criteria. 3. Received at least 500ml of intravenous fluid before study entry (Including prehospital administration) within the first 4 hours of ED arrival. 4. Clinical Frailty Score (CFS) of ≤4. If CFS is ≥5 and the treating physician find the patient suitable for ICU admittance, the participant can be enrolled, if the on-call ICU doctor would accept the patient for ICU admittance. If the treating physician is unsure of ICU eligibility, regardless of CFS score, the patient should be consulted with the ICU consultant before study inclusion.

EXCLUSION CRITERIA	1. Cardiogenic, anaphylactic, haemorrhagic or neurogenic shock as adjudicated by the treating physician. 2. Fertile women (<60 years of age) with positive urine human gonadotropin (hCG) or plasma-hCG or women breastfeeding. 3. Patient deemed terminally ill or with a severe co-morbid status resulting in non-eligibility for ICU admittance decided by either the treating physician or ICU consultant. 4. Known allergy to noradrenaline.
STUDY TYPE	Interventional study Allocation: Block Randomized (1:1) Intervention model: Parallel group Blinding: None
TARGET SAMPLE SIZE	320
RECRUITMENT STATUS	Planning
PRIMARY OUTCOME	Proportion of patients achieving either SBP > 100 mmHg or MAP > 65 mmHg or a target blood pressure set by the treating physician at 90 minutes after inclusion.
KEY SECONDARY OUTCOMES	Number of ICU free days alive within 30 days Hours without shock within 24 hours 30-day all-cause mortality. In-hospital mortality

Steering Committee

Lasse Paludan Bentsen, M.D. **Coordinating Investigator** **Emergency Medicine Registrar and Ph.D. fellow** Research Unit for Emergency Medicine Department of Emergency Medicine Odense University Hospital Department of Emergency Medicine Lillebaelt University Hospital, Kolding	**Mikkel Brabrand, M.D., Ph.D.** **Sponsor and Principal Investigator** **Professor and Senior Consultant** Research Unit for Emergency Medicine Department of Emergency Medicine Odense University Hospital
Thomas Strøm, M.D., Ph.D. **Professor and Senior Consultant** Department of Anesthesiology and Intensive Care Medicine Hospital of Southern Jutland Department of Anesthesiology and Intensive Care Medicine Odense University Hospital	**Peter Biesenbach, M.D.** **Consultant and Site Principal Investigator** Department of Emergency Medicine University Hospital of Southern Denmark Esbjerg
Larshan Perinpam, M.D. **Senior Consultant and Site Principal Investigator** The Emergency Department Regional Hospital Gødstrup	

Trial sites and investigators

All trial sites and principal investigators is listed in the Clinical Trials Information System (CTIS) listing.

List of abbreviations

AE: Adverse Event

AR: Adverse Reaction

CFS: Clinical Frailty Score

CI: Cardiac Index

CRF: Case Report Form

CTIS: Clinical Trial Information System

CVC: Central Venous Catheter

DBP: Diastolic Blood Pressure

ECG: Electrocardiogram

ED: Emergency Department

EoT: End of Trial

GCP: Good Clinical Practice

GDPR: General Data Protection Regulation

ICH-GCP: International Conference on Harmonisation of Good Clinical Practice

ICMJE: International Committee of Medical Journal Editors

ICU: Intensive Care Unit

IMP: Investigational Medicinal Product

MAP: Mean Arterial Pressure

NIBP: Non-invasive Blood Pressure

OUH: Odense University Hospital

PVC: Peripheral Venous Catheter

RSI: Reference Safety Information

SAE: Serious Adverse Event

SAR: Serious Adverse Reaction

SBP: Systolic Blood Pressure

SCC: Surviving Sepsis Campaign

SD: Standard Deviation

SOP: Standard Operating Procedure

SUSAR: Suspected Unexpected Serious Adverse Reaction

SpO_2: Peripheral Saturation of O_2

Modifications to the protocol

13-06-2023: Version 1.0

25-08-2023: Version 1.1:

- Removed the list of trial sites and principal investigators and added information where to locate these.
- Product summary changed to summary of product characteristics to follow correct nomenclature.
- Changed LPB to Coordinating Investigator and MB to Sponsor and Principal Investigator at OUH.
- Updated the inclusion criteria point 2 regarding types of shock included in the trial.
- Updated section 3.7 to not include data from national registers. Subsequently to this, section 9.4 and appendix 6 has also been updated.
- Added section 3.9 criteria for early trial termination and moved trial flow-chart to section 3.10.
- Updated the rationale of the dosing regimen for the IMP, section 6.2.
- Updated section 6.4 regarding mixing of the IMP including tables for dosages mixed with either isotonic saline or glucose and specified documentation of the IMP.
- Updated section 7.0 and subsections for evaluating AE and SAE including reporting procedures. Subsequently, appendix 4 including the attached flow-chart has also been updated.
- Update to section 9.2.1 regarding data from deceased participants.
- Updated section 9.3 on data protection regulations.
- Added section 9.5 on reporting of the summary of results.
- Updated section 10.0 and subsections regarding screening procedures, ethical requirements, identification of the next of kin/legal representative, legal guardian, how consent obtained in case of the deceased participant and data protection rules.

1.0 Background and rationale

1.1 Shock and hypotension in Danish emergency departments

Early recognition and treatment of shock is vital. Shock is widely defined as inadequate tissue perfusion, cellular damage and metabolic changes, which can lead to death.[5] Shock is a common occurrence in Danish Emergency Departments (ED).[6] Over the course of 3 years, Odense University Hospital (OUH) had 175,278 patient contacts and 2,137 (1.2%) presented with hypotension[7] and data suggests that the number is increasing.[8] At the same time, hypotension in the ED is associated with in-hospital mortality of 12% and even higher (33-52%) if identified in the pre-hospital setting.[9] Fluid resuscitation in the ED and ICU for treatment of hypotension and improvement of organ perfusion is widespread.[10,11] In Danish settings, the amount of fluid infusion can vary greatly among patients.[12].

1.2 Evaluation of fluid therapy responsiveness in shock

Evaluation of fluid responsiveness in a clinical setting can be complicated.[13,14] This usually leads to bed-side clinical judgement, that can be difficult to interpret, as patients can present with a range of symptoms and parameters. Bed-side evaluation can include clinical presentation with skin turgor, assessment of cognitive status, measurement of blood pressure, pulse, capillary refill time and ultrasound (e.g. measurement of the inferior vena cava diameter and collapsibility).[15] When evaluating fluid responsiveness in patients through invasive or non-invasive measurements, the therapeutic effects are best seen as change in Cardiac Index (CI), even though targets, such as increase in MAP, are frequently used due of the availability of this parameter.[16-18] Other than MAP, these measurements are not universally available in the Danish ED setting. However, the hemodynamic effect of fluid infusion can be short-lived. Previous studies have shown that any increase in blood pressure from fluid administration has vanished within one hour.[19].

1.3 Excessive fluid therapy and current practice in Danish EDs

Liberal fluid resuscitation, such as more than 5 litres over a short period of time, may cause harm[20-23] and hypotension that is not responsive to fluid therapy require earlier infusion of vasopressors such as noradrenaline[24]. Previous studies evaluating a restrictive approach of a for fluid therapy, such as less than 2-3 litres, seems feasible in both the ED for septic patients and the ICU for septic shock[25,26] Most studies on fluid resuscitation have been on patients admitted to intensive care (ICU), and thus only a subgroup of patients seen in the ED.[27] The most recent study in restrictive use of fluid in septic shock, CLOVERS, did not

show a benefit in this subgroup in regard to a more restrictive fluid approach compared to a more liberal approach.[28] Canadian and international Surviving Sepsis guidelines recommend routine use of noradrenaline in hypotensive septic patients not responding to early fluid boluses, though the data for early treatment has previously been sparse[24,29], at least until the CLOVERS study was published.[28]

Current treatment of hypotensive patients in the ED varies by department, which could be due to the different organizational models in Denmark.[11,12,30,31] Emergency Medicine as a specialty was founded in 2017, though the current organization of ED's was begun in 2007. Therefore, till now and for the most part, EDs in Denmark are still staffed mostly by registrars, senior registrars and consultants from other specialties than emergency medicine. Few Danish EDs are staffed 24/7/365 by at least one specialist in Emergency Medicine.[30]

There are currently no national guidelines in Denmark for treatment of undifferentiated shock. Current guidelines are usually focused on specific conditions, such as sepsis and septic shock, or adhere to the SSC recommendation.[24] Others are written as local guidelines directed at a specific subgroups, such as patients already admitted to the ICU.

In Denmark, the use of vasopressor treatment is not standard care in the ED, and they are primarily used in the perioperative or intensive care setting and administered by anaesthesiologists.[6] If vasopressor support is needed, the ED staff will contact the ICU consultant for admittance to the ICU and most vasopressor initiations are initiated after the patient have been transferred to the ICU. Only a few patients, to our knowledge, receive vasopressor therapy in the ED.[32,33] Admittance to the ICU in Denmark is decided by the ICU consultant and most patients with medical conditions admitted to the ICU, are without severe restrictions in daily activities. Patients with moderate to severe restrictions might be deemed ineligible for admittance.[34]

For many Danish patients with hypotension from a non-bleeding cause, this results in use of fluid therapy to treat dehydration, intravascular depletion, hypotension or initial stages of shock.[11,12,26] This approach might not stabilize the patient, due to only temporarily blood pressure increase, even though that's the goal of the treatment, with risk of excessive fluid therapy and by that, possible complications. [11,12,22,26,27,35-39] Choice of fluid can differ by department, though normal saline and balanced crystalloids such as Ringers Acetate or Lactate, are the most commonly used.[12,40] Previous international studies have shown that low-dose vasopressor therapy safely can be administered in the ED, and that this probably is sufficient care for most patients with circulatory mono-organ failure.[24,36,41,42]

1.4 Early vasopressor therapy for hypotension and shock

Vasopressors are commonly used for treatment of hypotension and shock. One of these, noradrenaline, is a catecholamine, a natural hormone and neurotransmitter in the human body. Noradrenaline has several acting sites in the human physiology, some of them consisting of blood pressure regulation, and subsequently organ and tissue perfusion, with primary action on α-receptors in the blood vessels and partly β-receptors in the heart muscle.[43] Noradrenaline, as well as other vasopressor and inopressors, have historically been indicated, when fluid therapy or other treatments, are not sufficient to reach perfusion goals and stabilization of the critically ill[24,28,29,35,36,38,39,44-47].

A single-center study of peripherally administered noradrenaline in sepsis from Thailand, the CENSER trial from 2019, reported that early initiation of noradrenaline lead to faster shock control than usual care, defined as following the Survival Sepsis Campaign recommendations[24,48]. Likewise, delayed initiation of vasopressor therapy in septic shock is associated with increased mortality.[35] But even though the use of central venous catheter (CVC) has historically been deemed the safest option for infusion of noradrenaline, due to risk of extravasation and skin necrosis, placement takes time, and are sometimes not possible in the critically ill when compared to peripheral catheter placement.[29,35,36,38,42,44-47,49-52] Initiation of vasopressor therapy through peripheral catheters, when compared to central venous access, lead to reduced time for initiation of therapy, and, importantly, with no increase in mortality risk.[24,36,38] At the same time, complications and adverse events from use of vasopressor infusion through peripheral catheters is miniscule.[28,41,42,46,53]

The CLOVERS trial[28], was a multi-center randomized trial but failed to show lower mortality in the restrictive fluid therapy arm. This, however, was conducted in the United States of America, where treatment protocols and guidelines differ substantially from Denmark.

CLOVERS reported 750 patients receiving vasopressor at any point during the trial, of which 500 received the treatment through peripheral catheter at some point. Only 3 (0.6%) of these had complications, documented as extravasation, though no subsequent skin necrosis were observed. In contrast, 14 (3.9%) had a CVC placement with complications, including serious adverse events such as deep vein thrombosis (3), ventricular arrhythmia (1), atrial arrhythmia (7) and pneumothorax (1). CENSER have not specified adverse events related to peripheral lines for each group, and both groups had CVC inserted during the trial (43.8% vs. 46.1%). The early intervention group had significantly less events of reported cardiogenic pulmonary oedema (14.4% vs. 27.7% p=0.004), but all other adverse events were with non-significant difference between groups.

This may suggest that the early use of vasopressors through peripheral venous access may lead to improved outcomes for patients presenting in the ED with septic shock.

1.5 Rationale for studying early initiated peripheral noradrenaline in the Danish setting

This study will provide evidence if early initiated vasopressor therapy can decrease to time for achieving shock control and subsequentially improve outcomes, such as avoiding ICU admission or reduce length of stay, for some of the most critically ill patients in the Danish ED setting. Current studies shows that there exists a clinical equipoise in treatment of the patient group, but it's tested in different organizational models and settings, which challenges the consideration and implementation of treatment recommendations in Denmark. Hypotension is a time-critical condition and improving the treatment of hypotensive patients might decrease mortality, morbidity, and ability to return to usual live and work.

1.6 Systematic review of existing literature

We performed a structured search of PubMed, EMBASE, CINAHL and the Cochrane Library for any relevant studies for treatment of shock with vasopressors in the ED through peripheral catheters in non-traumatic hypotension. The setting of the ICU or operation theatre is widely different from the average ED and are therefore not considered in our review.

We also searched registers in clinical trial databases (Clinicaltrials.gov, EU-CTR and ANZCTR). We identified two currently completed studies, CENSER and CLOVERS[28,48] and two studies currently recruiting patients, EVIS and ARISE.[54,55]

1.7 Choice of comparators with prior and on-going studies on early vasopressor therapy

The CENSER[48] study was a single-center study comparing early vasopressor therapy through peripheral catheters in patients with suspected sepsis with hypotension. Patients were randomized 1:1 to either early noradrenaline (n=155) or standard treatment (n=155). The early vasopressor arm had a significantly higher proportion of patients achieving shock control within 6 hours after diagnosis (76.1% vs. 48.4%, odds ratio 3.4 (95%CI 2.09-5.53)) and the control arm presented with a higher quantity of adverse events such as cardiogenic pulmonary oedema, probably due to more excessive use of fluid therapy. There was no significant difference between the groups when comparing mortality or admittance to the ICU, but the

study was not powered for these endpoints.

The CLOVERS trial was a multi-center randomized clinical trial including patients in both ED, ward and ICU settings, assessing whether fluid therapy or early vasopressor therapy for septic shock, could improve patient outcomes, with a primary endpoint of mortality before discharge home by day 90.[28] They found no difference between the intervention and control group with a mortality of 14.0 (11.6-16.4) in the restrictive fluid group with early vasopressor compared to 14.9 (12.4-17.4) in the liberal fluid group.

The CLOVERS study had several issues regarding generalizability. More than 12,000 patients were screened with only 1,563 randomized and 7,408 patients excluded due to fulfilling one or more exclusion criteria such as 1) more than 4 hours elapsed since inclusion criteria met (2,874 patients) or 2) having received more than 3 litres of fluid before screening (1,786 patients). Also, a total of 3,303 patients met the eligible criteria, but were not enrolled due to issues such as 1) Unable to obtain informed consent (900 patients), 2) Patient or surrogate declined consent (887 patients), 3) physician refused patient participation (873), 4) surrogate not available (565 patients), and 5) not excluded but not enrolled (346 patients).

These issues could cause a risk of selection bias, as alone more than 2/3 of patients were not enrolled due to time, fluid therapy received before inclusion (including pre-hospital fluid) or the lack of consent for any cause. One could theorise that the substantial number of exclusions before enrolment could have influenced the results.

The ARISE[55] and EVIS[54] trials are actively recruiting and evaluate early vasopressor therapy in the emergency departments. Both studies investigate mortality where CLOVERS failed to show benefit in the restrictive fluid group. Our study will differentiate from these studies, as shown in Table 1, due to not only including septic patients, but other patients with hypotension as well. Also, the participants will primarily receive vasopressor therapy in the ED through a peripheral venous catheter (PVC), as in the EVIS trial, but will not be compared to a group receiving delayed vasopressor therapy in the ED. Our target goals for treatment and primary outcomes differ.

We therefore argue to randomize patients to either standard care compared to standard care and early vasopressor initiation through a peripheral venous catheter, using a pragmatic study design in a setting as close to current daily treatment algorithms in the Danish ED. Current treatment options in the control group, are far more restricted than presented in other trials on vasopressor therapy. We can subsequently evaluate if patients can avoid ICU admittance if treated up to 24 hours in the ED.

Table 1: Overview of VASOSHOCK, ARISE and EVIS

	VASOSHOCK	ARISE	EVIS
Inclusion criteria	Signs or suspicion of hypotension or shock (Defined as SBP <100mmHg or MAP <65mmHg combined with lactate >2.0mmol/L or by physician defined blood pressure for the individual patient combined with a lactate >2.0mmol/L). Shock can be any type of shock such as septic, vasodilatory or hypovolaemic not listed in the exclusion criteria.	SBP < 90 mmHg and lactate > 2.0 mmol/L	Either SBP < 90 mmHg or MAP < 65 mmHg AND lactate > 2.0 mmol/L
Patient group	Hypotension not related to cardiogenic, anaphylactic, neurogenic or haemorrhagic cause	Septic shock	Sepsis and hypotension
Number of patients planned	320	1000	3286
Time to enrolment	Within 4 hours of presentation	Within 6 hours of presentation	Within 12 hours of presentation
Pre-randomisation fluid	> 0.5L	1 to 2L	Up to 1.5L
Intervention	Peripheral vasopressor or local standard of care	Fluids or vasopressor according to study protocol	Early peripheral vasopressor or standard of care in accordance with SSC or local guidelines
Duration of intervention	Up to 24 hours	6-24 hours	Up to 48 hours
Target treatment goal	SBP > 100 mmHg or MAP > 65 mmHg or defined by physician	Determined by physician	MAP > 65 mmHg
Vasopressor use before trial in the ED	No	Yes	Yes
Primary outcome	Proportion of patients fulfilling treatment goal within 90 minutes	Days alive out of hospital at 90 days	30-day all-cause mortality

2.0 Objectives

2.1 Aim

The aim is to investigate whether the use of early initiated vasopressor therapy (i.e., noradrenaline) compared to fluid therapy alone in non-bleeding hypotensive patients presenting in the ED can improve time to shock control and by that, reduce the need for ICU admittance.

2.2 Primary outcome

The primary outcome is proportion of patients achieving either SBP > 100 mmHg or MAP > 65 mmHg or a target blood pressure set by the treating physician at 90 minutes after inclusion.

2.3 Key secondary outcomes

Key secondary outcomes are:

- Number of ICU free days alive within 30 days
- Hours without shock within 24 hours
- 30-day all-cause mortality.
- In-hospital mortality

All outcomes are listed in section 5.0 Outcomes.

3.0 Trial design

3.1 Overview

This study will be a pragmatic,[56,57] multi-center, superiority, randomized controlled trial, randomizing patients 1:1 to either the intervention group (early vasopressors in the ED) or control group (standard care in the ED). Hypotensive patients who received at least 500 ml fluid bolus prior to screening will be assessed for eligibility.

3.2 Allocation and randomization

Patients fulfilling all inclusion criteria and no exclusions criteria (see below) will be randomized in a 1:1 ratio using block randomization by random size of 2, 4, 6 or 8, stratified by trial site. Randomization will be conducted using the web-based randomization system provided in REDCap to ensure allocation concealment.[58]

The investigators will access the randomization page using a unique QR code allocated for each trial site, directing to an online registry form. Each investigator will be registered for their specific trial site, and if applicable, for any other trial sites they are employed at (either full or part-time). Basic data will be entered from eligible patients prior to randomization, as described in section 9.0 Data collection and management.

The randomization allocation sequence is generated by the OPEN data manager and stored securely in relation to the REDCap database. Only the data manager, or REDCap administrator, for the project have access to the allocation sequence if necessary. Individuals screening and commencing inclusion of patients in the trial, will not have access to the allocation sequence.

3.3 Blinding

Blinding of vasopressor therapy with noradrenaline is deemed impossible due to expected quick response in blood pressure levels with infusion of the medication, compared to fluid therapy at these rates. Therefore, blinding is not considered possible for this study.

3.4 Intervention

Eligible patients will be randomized to receive noradrenaline at 0.05microg/kg/min through a peripheral

venous catheter and titrated to either SBP >100mmHg or MAP >65mmHg or a physician predefined blood pressure goal, up to a maximum dose of 0.15microg/kg/min. Decision for dosing regimen can be seen in section 6.2 Dosing regime and rationale for dosing levels. For patient monitoring, blood pressure is recommended with measurements using Non-invasive Blood Pressure (NIBP) every 15 minutes combined with continuous 3-lead ECG and peripheral oxygen saturation (SpO_2) if they receive noradrenaline infusion. Using a paper-CRF, the clinical personnel is recommended to note blood pressure and pulse on the form every 2 hours, if possible, in the clinical setting. Other measures during monitoring of the intervention group are not systematically registered during the trial period.

When possible, down titration will be conducted if the goal SBP or MAP is still achieved. During the 24-hour intervention period, infusion of noradrenaline can be temporarily stopped and resumed within this timeframe. If temporarily stopped, the clinical staff should note time for this event, as well as reason on the CRF, and when the infusion is resumed, if pragmatically possible regarding external factors in the ED. Noradrenaline infusion will be terminated fully if the patient stabilizes to the target values without the need for vasopressor therapy during the intervention period. Patients that require more than 0.15microg/kg/min or have signs of multi-organ failure will be consulted with the ICU team for admission to the ICU.

There will be no restrictions on concurrent care and the infusion of noradrenaline can be supported by further fluid infusion, if the treating physician decides it is necessary for the patient in accordance with local guidelines.

To ensure generalizability of the results, and due to the pragmatic nature of the study, the ordering and administration of vasopressors, including monitoring and registration of bedside clinical data, will be handled by the regular ED staff. Each trial site will have at least one research nurse part time, that will assist in ensuring trial progression, inclusion, and answer questions from the ED staff regarding the trial in collaboration with the local trial investigator.

A trial flow chart to support the clinical staff are presented in section 3.10: Trial Flow Chart.

3.5.1 Termination of intervention

Patients included in the intervention arm will be treated in the ED for up to 24 hours with administration of noradrenaline. If the patients are still requiring noradrenaline at 24 hours, the ICU consultant will be contacted for patient transfer to the ICU. The intervention is fully terminated when the patient is either

discharged from the hospital, admitted to another department or ICU, is dead during the intervention period, consent withdrawn by physician, patient is sufficiently mentally well to withdraw consent by their own choice or their next of kin.

3.5.2 Weaning of noradrenaline infusion during ED admittance

During the 24-hour intervention period, patients can stabilize and therefore not require further noradrenaline infusion in the ED. If the treatment goals are reached, either set by usual blood pressure targets as protocolized or determined by the treating physician, the clinical staff can begin to lower and wean the vasopressor dose. This can be done by reducing the dose slowly by 0.01-0.03microg/kg/min and closely evaluate the patient afterwards within the next 15 minutes. After 15 minutes, the dose can be lowered further if criteria are met. If it is possible to completely wean the patient of the infusion, the intervention can be stopped, but it is allowed to resume the intervention within the first 24 hours of study entry if the patient is still present in the ED.

Time of termination or recommencing should be clearly noted in the paper-CRF.

3.5.3 Early termination of treatment

Participants in the trial can have the intervention terminated before full conclusion of the treatment period. This can include fully termination of participation in the clinical trial including data collection and usage as defined in section 9.0 and 10.3.4. This is considered in the following situations:

1. The patient, or next of kin if the patient is unable to, withdraws their consent to participate prior to completing the necessary intervention.
2. The investigator for safety reasons finds it of best interest of the patient.

In case of early termination of the trial participation and therefore treatment, the clinical staff and investigators must take appropriate steps to ensure the patients treatment and stability of their disease process during early weaning of noradrenaline. This can include quick transfer to the ICU for further treatment of their condition.

Early termination of treatment should be clearly noted, including reason for early termination, in the paper CRF for the patient.

3.6 Control group

The control group will be receiving standard care as ordered by the treating physician according to local guidelines at the ED and fluid therapy will be noted on the paper-CRF by the clinical staff until the patients are discharged from the ED due to any cause. Current Danish practice are mentioned in section 1.0: Background and rationale.

3.7 Long-term follow-up

A pre-planned long-term follow-up of patients will be completed after inclusion in the trial. This long-term follow-up will partly be from direct contact to the participants (e.g. by phone) and patient electronic medical records. The study will assess areas such as patient ability to live without caregiving from others, such as municipality home-care. See more in Appendix 6.

3.8 End of Trial

The End of Trial (EoT) is defined as the Last Patients Last Visit. Due to the planned long-term follow-up study, the EoT will be after all patients have been contacted by, expected to be 1 year after their inclusion. If the last patients cannot be contacted within 30 days after the 1-year inclusion mark, the trial will be considered to have reached EoT, even though some data might not be available.

The expected EoT will be 31st August 2026.

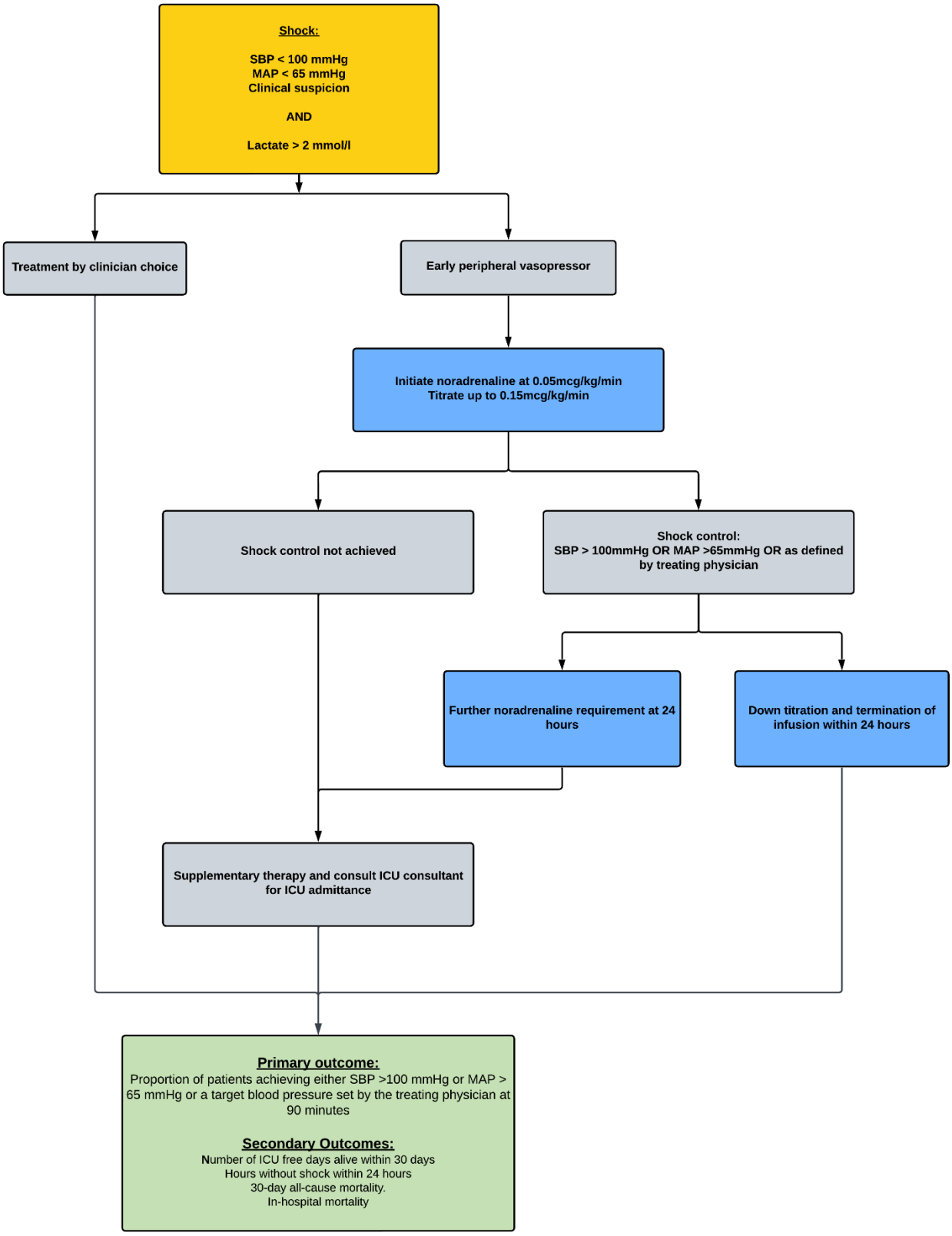
3.9 Early termination of the trial

The trial can be terminated early in the following circumstances:

1. The Sponsor receives a substantial number of SAE or SAR leading to a concerning level of risk for the patients.
2. The trial is no longer feasible at any of the trial sites due to local organisational or clinical implications, such as unavailability of noradrenaline.
3. Slow inclusion rate at trial sites leading to a problematic timeframe to complete the study, such as double required time to complete the study.

In any of these circumstances, the Sponsor will contact members of the steering committee and the steering committee will decide whether the trial can continue in a safe and reasonable manner.

3.10 Trial flow chart



4.0 Study setting and patient population

4.1 Study setting

Danish EDs admit a group of undifferentiated patients arriving either by prior evaluation from a general practitioner, by ambulance through the national emergency number or by self-referral, though the latter is very uncommon. The physician staffing varies from each department, with most having a mixture of both consultants with specialization in Emergency Medicine and other specialties (Internal medicine, general surgery etc.).[30,31,59]

The patients will be included under the regulation for "Acute drug trial" – See section 10.3.2 for specification.

4.2 Eligibility criteria

Patients admitted to the ED with signs or suspicion of hypotension or shock will be screened.

4.3 Inclusion criteria

1. At least 18 years of age
2. Signs or suspicion of hypotension or shock (Defined as SBP < 100mmHg or MAP < 65 mmHg combined with lactate > 2.0 mmol/L or by physician defined blood pressure for the individual patient combined with a lactate > 2.0 mmol/L). Shock can be any type of shock such as septic, vasodilatory or hypovolaemic not listed in the exclusion criteria.
3. Received at least 500ml of intravenous fluid before study inclusion (Including prehospital administration) within the first 4 hours of ED arrival.
4. Clinical Frailty Score (CFS), see appendix 2, of ≤4. If CFS is ≥5 and the treating physician find the patient suitable for ICU admittance, the participant can be enrolled, if the on-call ICU doctor would accept the patient for ICU admittance. If the treating physician is unsure of ICU eligibility, regardless of CFS score, the patient should be consulted with the ICU consultant before study inclusion.

4.4 Exclusion criteria

1. Cardiogenic, anaphylactic, haemorrhagic, or neurogenic shock suspected by the treating physician.
2. Fertile women (<60 years of age) with positive urine human gonadotropin (hCG) or plasma-hCG or

women breastfeeding.

3. Patient deemed terminally ill or with a severe co-morbid status resulting in non-eligibility for ICU admittance decided by either the treating physician or ICU consultant.
4. Known allergy to noradrenaline.

5.0 Outcomes

5.1 Primary outcome

The primary outcome is the proportion of patients achieving either SBP >100 mmHg or MAP > 65 mmHg or a target blood pressure set by the treating physician at 90 minutes after inclusion.

5.2 Secondary outcomes

- Number of ICU free days alive within 30 days
- Hours without shock within 24 hours
- 30-day all-cause mortality
- In-hospital mortality

5.3 Tertiary outcomes

- Proportion of patients receiving vasopressor at any point within 24 hours.
- Time to vasopressor initiation
- Hours of vasopressor infusion
- Proportion of patients developing pulmonary oedema within 72 hours (Diagnosed by physician in accordance with local guidelines, e.g., clinical decision including evaluation with paraclinical imaging such as x-ray or lung ultrasound).
- Proportion of patients developing acute kidney injury within 72 hours (Defined as an absolute increase of creatinine ≥26.5µmol/L or ≥1.5 fold from baseline)
- Lactate level at study entry
- Adverse events to peripheral vasopressor infusion, as specified in section 7.0 Safety and harm.
- Re-admission within 30 days
- ED length of stay
- Proportion of patients admitted to the ICU
- Hospital length of stay
- ICU length of stay
- Need for mechanical ventilation (either invasive or non-invasive ventilation)
- Need for renal replacement therapy (continuous renal replacement therapy or dialysis)
- Amount of fluid therapy received within the first 24 hours

6.0 Pharmacovigilance

6.1 Choice of drug

The investigational medicinal product (IMP) for this trial will be noradrenaline (ATC-code C01CA03). An example summary of product characteristic can be found in Appendix 5. Current international guidelines suggest the use for noradrenaline as first choice in patients with shock not due to trauma. The IMP is already approved for clinical use and is used in the trial in accordance with this approval.

6.2 Dosing regime and rationale for dosing levels

Current guidelines in Denmark only sparsely recommend use of peripheral noradrenaline infusion and usually at low concentrations. As such, a clinical guideline at Odense University Hospital (Guideline 971736 updated 03-03-2023) describes the use of peripheral noradrenaline. This guideline does not describe the use of weight-based noradrenaline infusion, but a fixed dose infusion of 2mg/ml noradrenaline in 98ml isotonic NaCl unless the patient weighs 50kg or less. The suggested infusion rate are 15-30ml/hour with no statement of maximum recommended infusion rate.

For a 70kg patient this would yield the following infusion rate.

First dosage of mg/hr is derived from the following formula:

$$\frac{R\ x\ A}{V}$$

R being rate of infusion, A being dose of the medication and V being total volume of the dose when mixed. This can be calculated based on the guideline:

$$\frac{30\frac{ml}{hr} x\ 2\ mg}{100 m\ l} = 0.06\ mg/hr$$

Afterwards the dosage can be converted from mg/hr to mcg/kg/min to compare to the used dosing regimens in this trial:

$$\frac{D\ x\ 1000\ mg}{60\ \text{min}\ x\ W}$$

D being dose in mg and W being patient weight in kg.

We can therefore calculate the infusion rate mandated in this guideline for a 70kg patient receiving

peripheral noradrenaline infusion:

$$\frac{0.06\ mg\ x\ 1000\ mg}{60\ \text{min}\ x\ 70} = 0.14\frac{mcg}{kg}/min$$

The presented guideline is based on recommendations from the manufacturer and a Danish publication on peripheral infusion of noradrenaline published in 2017.[60] However, this publication is before further knowledge on the safety of peripheral noradrenaline were published.

Recent studies[28,46,51] suggest that dosing of noradrenaline through PVC show adverse event in extravasation, that might be unrelated to the dose given. E.g., Lewis et al.[51] reported that extravasation was unrelated to dose level, but more related to length of peripheral infusion. The included trials reported a median max dose of noradrenaline of 0.13 mcg/kg/min and found no events of skin necrosis, even considering 8 events of extravasation. CENSER[48] conducted an intervention of noradrenaline infusion up to 0.05mcg/kg/min in the trial protocol, though they did report higher vasopressor doses received, including open label use. CLOVERS[28] protocolized up to 0.25mcg/kg/min for patients in the restrictive fluid group before providing further fluid therapy. Five hundred patients received peripheral vasopressors at some point during this trial. None of these trials reported any serious adverse events in relation to peripheral administration of noradrenaline. This is in relation to a higher and more severe observation of SAE for patients receiving central lines and noradrenaline infusion through these, including pneumothorax and arrhythmias requiring subsequent DC-conversion. Details on previous publications on the safety in peripheral vasopressor therapy is described in section 1.4. The trial details for the intervention are specified in section 3.4.

Choice of dosing regime, considering the above data, will range from 0.05-0.15 mcg/kg/min, to maximize effectiveness of the intervention while still ensuring high patient safety for trial participants. This dose is close to the current recommendation at Odense University Hospital as described earlier, even when taking newer data and safety assessments into consideration.

The dosing regimen will prevent possible increased risk of extravasation complications with high dosing or the need for higher level of observation, such as the ICU, including supplementary treatment requirements when higher doses are necessary to stabilise the patient.

6.3 Storage and handling of study medication

Most Danish ED's already store noradrenaline but are currently only accessed by the staff from the

anaesthesiology department or ICU. Also, as the medication is fully approved by the Danish Medicines Agency, storage of noradrenaline for the study does not require special permissions.

As the medication is standard assortment in the hospital and department, no additional labelling is required, and the medication is delivered by the hospital pharmacies ready for mixing.

To ease the access and use for the clinical personnel during the trial period, we will implement the following considerations as necessary for each department:

1. The medication will be stored in accordance with local department or hospital guidelines.
2. A box will be placed with visible distinction from other medications. The box will be in easy identifiable colours regulated so it does not resemble already used boxes in each department, with a clear marking of the trial name and drug on the box.
3. Necessary utensils (such as syringes, infusion pumps etc.) will be placed in the box.

The handling of the medication will be completed in accordance with usual guidelines, including mixing of dosage in relation to patient weight as required, including handling of discontinuation of used medications and utensils.

The infusion pumps used in the trial will be cleaned in accordance with usual guidelines before use for another patient or before it's repacked by the clinical personnel in the storage box.

6.4 Preparation of study medication

The study medication will be prepared by the clinical staff in accordance with a trial specific standard operating procedure (SOP). The SOP will describe how the drug is mixed before being used for infusion, including type of fluid used for the solution and dose of noradrenaline in accordance with the individual patient weight.

Mixing of the IMP will follow table 2 for mixing with 100ml of either isotonic saline or isotonic glucose prior to administration. The mixing doses follow local guidelines for mixing of noradrenaline used in the intensive care unit and operating theatres at Odense University Hospital.

Study medication dose, batch, preparation and administration time will be registered in the paper-CRF.

Table 2: Noradrenaline mixing dose

IV infusion			
Infusion concentrates		Noradrenaline 1mg/ml, vial or ampoule of 10ml	
Medication shelf life		Infusion has a shelf life after mixing of 24 hours at room temperature.	
Administration		Dosing through infusion pump.	
Mixing dose for infusion through infusion pump		0.03mg x patient weight in kg mixed with isotonic NaCl or Glucose to a total volume of 100ml. 1ml/time = 0.01 mcg/kg/min	
Weight (kg)	**Noradrenaline (mg)**	**Noradrenaline (ml)**	**Isotonic NaCl or Glucose (ml)**
30	1.8	1.8	98.2
35	2.1	2.1	97.9
40	2.4	2.4	97.6
45	2.7	2.7	97.3
50	3.0	3.0	97.0
55	3.3	3.3	96.7
60	3.6	3.6	96.4
65	3.9	3.9	96.1
70	4.2	4.2	95.8
75	4.5	4.5	95.5
80	4.5	4.5	95.5
85	5.1	5.1	94.9
90	5.4	5.4	94.6
95	5.7	5.7	94.3
100	6.0	6.0	94.0
105	6.3	6.3	93.7
110	6.6	6.6	93.4
115	6.9	6.9	93.1
120	7.2	7.2	92.8
125	7.5	7.5	92.5
130	7.8	7.8	92.2

6.5 Termination and destruction of study medication

When the intervention is terminated, either due to stabilization of the patient or admittance to the ICU, the total dose should be noted on the paper-CRF by the clinical staff. These data will be transferred to REDCap with the rest of the paper-CRF data as detailed in section 9.0 Data collection methods.

When the drug is terminated (including necessity to change utensils with new filled syringes), any remaining drug will be stashed in the departments yellow boxes used for storage of used drugs and utensils. Boxes are handled according to local guidelines including collection for future destruction.

6.6 Insertion of peripheral catheters

Insertion of PVC should be with a high assurance of correct in-vessel placement, therefore, the following considerations should be considered during placement before and during noradrenaline infusion:

1) The placement should be done in a preferable large, more central vein in the arm (e.g. close to the fossa cubiti) and not in a small superficial vein (e.g. on a small vein at the dorsum of the hand).
2) If there is any sign of venous puncture with outflow of blood or fluid when flushing, this vein should not be used for the infusion site.
3) US guided placement of PVC for infusion should be done in a more superficial, rather than deep vein, due to easier evaluation extravasation.
4) Flushing should be able to be completed with ease after placement before infusion start.
5) If the PVC shows signs of extravasation after infusion start, the PVC should be terminated and another one placed sufficiently, before resuming the infusion in the new PVC.

6.7 Suspected extravasation

There is a risk of extravasation of noradrenaline, which is a leakage of a drug into the tissue surrounding the catheter. This is, however, a rare complication, but one that potentially can cause subsequent skin necrosis of the affected area or limb. The current evidence suggest that report of patient harm is minimal.[36,42,46,49,52,53,61]. This risk has not previously been studied in the Danish ED setting, and this study will be the first one to address the issue in this population. Therefore, it is necessary to evaluate catheter placement and quality throughout the intervention period, and handle any signs or suspicion of extravasation.

Clinical personnel should suspect extravasation if the patient reports pain or itching or if there is sign of pallor, oedema, or erythema at the infusion site. When suspicion of extravasation is maintained, the following actions are recommended:

- Stop the infusion.
- Disconnect the line from the PVC
- If possible, attempt to aspirate up to 5 mL from the PVC
- Remove the PVC and apply dressing.
- Mark the site of suspected extravasation
- Inform treating physician.

Supplementary therapy can be:

- Elevation of arm to reduce swelling
- Involve surgeon if there is a concern of skin vitality
- Analgesia if necessary and applicable

The suspected extravasation should be noted on the paper-CRF, uploaded to the eCRF as well as reported to the Sponsor as a serious adverse event.

6.8 Unintended overdose of noradrenaline

Several of the serious adverse reactions, as mentioned in section 7.0 Safety and harm, can be caused by noradrenaline overdose, most importantly severe hypertension, and reflex bradycardia. Patients can experience extreme headaches, photophobia, retrosternal pain, pallor, intense sweating, and vomiting, while clinical related issues are increased peripheral resistance or reduced cardiac output. If there is sign and suspicion of a serious adverse reaction, the following actions are recommended:

- Stop in the infusion.
- Disconnect the line from the PVC
- Attempt aspiration of 5ml from the PVC.
- Remove cannula and apply dressing.

Handling of patient symptoms is done in relation to usual supportive care in accordance with local guidelines (E.g., analgesia for pain).

In the event of the listed serious adverse reactions, severe hypertension, or bradycardia, these should be noted on the paper-CRF, uploaded to the eCRF and reported to the Sponsor as required by the trial protocol.

7.0 Safety and harm

7.1 Definitions of adverse events and reactions

Adverse event (AE): Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product 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) or serious adverse reaction (SAR): Any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity or is a congenital anomaly or birth defect. If this reaction is unexpected suspected towards the use medication, this reaction is deemed by the term SUSAR (Suspected Unexpected Serious Adverse Reaction).

7.2 General considerations

Inclusion in the intervention group should be done with high respect to potential adverse events and reactions of the therapy. As vasopressor therapy currently is not routine therapy in Danish EDs, the clinical personnel will receive education in the handling, use and evaluation of the therapy. Also, the clinical personnel will have specific areas to assess during the study regarding possible adverse effects of the intervention.

The summary of product characteristic of Noradrenalin "Fresenius Kabi" is presented in Appendix 5 as the reference safety information of the IMP. This lists several AR due to treatment with noradrenaline, a few of these with a risk of SAR.

The studied patients are critically ill with hypotension and shock. Therefore, events regarding deterioration of this patient group will not be considered an adverse event due to the intervention. Fatal outcomes are expected and are therefore also an expected known risk regardless of treatment protocol.[5-8,24,62] The reporting of adverse events, reactions and serious adverse events and reactions, will therefore be focused on the risk involved in using noradrenaline, risk of noradrenaline in a peripheral catheter and the risk of fluid therapy, as excessive infusion can lead to complications.

7.3 Assessment of adverse events

Prior decided adverse events and serious adverse events occurring while the patient is in the emergency department will be registered. The trial will use noradrenaline from any manufacturer that supply this to the individual trial site. There are several manufacturers, where one of the most used formulations in Denmark is marketed by "Fresenius Kabi". The summary of product characteristic for this formulation is supplemented in Appendix 5.

Registration of AE and SAE in the trial will be completed in both the intervention and control group. If any AE or SAE are observed, the staff will note these on the paper-CRF. If SAE or SUSAR are suspected, the trial staff will also report these to the Sponsor following the description in section 7.4. Some of the adverse events will not be of issue in the control group, such as extravasation of peripheral noradrenaline infusion or subsequent skin necrosis and are therefore not expected. Regarding fluid therapy, the trial does not dictate the use of fluid other than inclusion criteria. Therefore, we do not mandate a certain fluid volume, fluid type, infusion rate or other considerations after inclusion in the study. Some adverse events due to fluid resuscitation are evaluated in the outcomes of the trial, but are not part of the safety reporting unless the clinical staff consider these as AE or SAE in relation to the trial. However, the amount of fluid administered for both the intervention and control group will be registered throughout the intervention period.

The assessment and registration of adverse events will be handled for noradrenaline infusion from inclusion to end of intervention, defined as 30 minutes after full termination of the noradrenaline infusion in the ED. If a patient is transferred to the ICU, by ICU staff (e.g. ICU registrar or attending), while still receiving peripheral noradrenaline, the assessment will be terminated as soon as the patient leaves the ED and treatment responsibility will be handled by the ICU staff in consideration of local guidelines. If escorted by the ED staff, the assessment will be terminated as soon as the patient arrives at the ICU and patient responsibility is transferred to the ICU staff.

The staff can at any time report any suspected AE or SAE on the paper-CRF and further reporting are handled according to the reporting guidelines in section 7.4.

The following AE or SAE will be specifically evaluated during the intervention period due to possible severe SAE from treatment with the IMP and for some, due to the peripheral infusion:[36,41,42,46,49,51,52,61,63]

- New onset cardiac arrhythmia
- New onset bradycardia
- Myocardial infarction

- Severe hypertension
- Extravasation of noradrenaline infusion
- Skin necrosis at infusion site
- Acute ischemia (limb or intestinal)

The following known AR and SAR to the IMP as mentioned in the summary of product characteristic and could be either mild AR or SAR due to the critical condition of the patient. The clinical staff will report any of these to the Sponsor following the procedures in section 7.4 if they suspect an SAE to the intervention. The Sponsor will then handle the reporting in relation to the clinical state and disease process of the participant, as these AR and SAR are considered possible in both treatment groups.[5,6,9,17,19,20,24-26,35,39,47,48,64-68] All AE will be registered on the paper-CRF.

- Change in plasma glucose levels
- Anxiety, confusion or psychosis
- Difficulty urinating or urinary retention
- Dyspnoea
- Cerebral haemorrhage
- Acute heart failure
- Cardiac arrest
- Stress cardiomyopathy
- Acute glaucoma

The infusion of noradrenaline can cause other AR than mentioned above. The following AR to the IMP as mentioned in the summary of product characteristic are known AR. These AR requires normal observation by the clinical staff and are therefore not considered as SAE, SAR or SUSAR.

- Palpitations
- Sinus tachycardia
- Nausea
- Vomiting
- Increased saliva production
- Fatigue
- Unrest

- Headache
- Irritability
- Sleep disorders
- Sweating

7.4 Reporting

Any suspected SAE during trial intervention will be reported within 24 hours of occurrence to the Sponsor. Sponsor will evaluate if the SAE is a SAR or SUSAR, and report SUSAR to the central European register EudraVigilance within 7 days if fatal or life-threatening, and 15 days for other SUSAR. A follow-up will be completed by the Sponsor no more than 8 days after reporting and will inform if the follow-up shows either life-threatening or fatal SUSAR. If the SUSAR poses risk to continuation of the trial- due to patient risk concerns, the Sponsor will inform all trial sites immediately.[1,69]

Following the registration of AE and SAE, all events will be reported to the Sponsor at least once a week by each trial site. If no patients are included or no AE of any type is registered during this week, the trial site will not be required to inform the Sponsor. This will ensure frequent relevant reporting and registration of any AE prior to the annual safety report.

Once a year, the Sponsor will submit an annual safety report to CTIS including a list of all SAR including SUSAR that have occurred on all sites. The annual safety report includes a risk-benefit assessment for all trial participants. All SAE will be included in the overall risk assessment. [1]

When the end of trial is reached, defined by the last patients last visit, the Sponsor, or by delegation, the Coordinating Investigator, will notify the authorities through CTIS that the trial has ended no more than 15 days after the last patients' last visit. The Sponsor is responsible for upload of the summary of results to CTIS as soon as possible and no later than 1 year after completion of the trial.[1,69] If the trial is ended earlier than planned, the reason for termination of the trial will be described.

8.0 Sample size and statistical analysis plan

8.1 Sample size calculation

Our sample size calculation is based on data from the CENSER trial.[48] The median time from "initial treatment to achieving the target of mean arterial blood pressure + tissue perfusion goal" for the intervention group was 4h:45 min and 6h:02 min for the controls. Given this difference, and considering a log normal distribution of the data, an alpha value of 0.05, and power of 90%, a sample size of 80 persons per groups is necessary.[70] Due to the nature of our primary outcome, including a higher blood pressure target and allowing the treating physicians to individualize treatment goals for the patients, we will include a larger number of patients, as it is not possible to calculate the specific sample size for this end goal specifically. Also, powering the study towards preventing patients being admitted to the ICU is not sufficiently possible, as it has not currently been tested in a Danish setting and in the international setting, this has not been evaluated before. Taking this into account, we will include 160 patients in each group (320 in total). This will also prevent skewing of data due to patient dropout or loss to follow-up.

8.2 Statistical analysis plan

8.2.1 General considerations

Primary outcome will be presented as numbers (proportions). Secondary and tertiary outcomes (see above) will be presented as either numbers (proportions) for categorical values or mean (SD) for numerical outcomes. Continuous variables will be analysed using a parametric test such as a paired t-test or Pearson Correlation and for categorical values such as the chi-square test or Fisher exact test, where appropriate. The primary outcome and mortality will also be presented using Cox regression and Kaplan-Meier curves. Our main analysis will be intention-to-treat with per protocol as sensitivity analysis.

Patient inclusion and exclusion will be illustrated in a CONSORT flow diagram. See Appendix 1 for CONSORT flow chart draft.

A full statistical analysis plan will be described before the final patient has been included.

8.2.2 Missing data

Missing data will be reported in all relevant publications. We do not expect missing data regarding the primary outcome of the trial or key secondary outcomes. We do expect some missing data in other

outcomes, as well as missing data or loss to follow-up for the long-term outcomes in the trial. We do not expect missing data for AE or SAE.

9.0 Data collection and management

9.1 Data collection methods

Data collection will be completed and managed using a secure web-based software platform REDcap (Research Electronic Data Capture) hosted at University of Southern Denmark via OPEN. All data will be entered using the secure web-form and from there extracted for data management. Data entered during randomization are cross checked during identification of the patient. All data entered from the paper CRF will be double entered into the eCRF, as well as upload of the scanned paper CRF.

The investigators will enter limited data into the REDCap database prior to randomization, this includes the date and time of screening and the patient's social security number.

Bedside collection will be completed using a paper Case Report Form (CRF) or collection of data throughout the patients' treatment period of up to 24 hours. The CRF will include data as mentioned under section 9.4: Data to be collected. All used CRF (Partly or fully completed) will be stored locally as specified under section 8.3: Data Management and uploaded to the electronic CRF for each patient.

Further data will be collected using relevant national registries and electronic patient records, as well as follow-up data from the individual patient. The data will, when applicable, be either manually entered in the electronic CRF or sampled into the database.

9.2 Participant retention and ensuring complete follow-up

All participants will be included using their social security number. For inclusion in the study and participant retention, the study will include relevant outcomes that can be extracted from the participant's personal health record and relevant national registries. Blood pressure, pulse, fluid type and amount of fluid given will be captured on paper using a CRF that will follow the patient until the end of their treatment period in the ED, for both the intervention and control group. If possible, the clinical staff can register saturation, respiratory rate, and GCS on the paper-CRF, though they aren't mandated in the study.

Complete follow-up in the trial will be ensured through Danish national registries, as only people with a Danish identification number will be included.

9.2.1 Replacement of data from participants no longer enrolled in the trial

Patients included in the trial, that subsequently withdraws consent for participation can decide either to only accept the use of data up until their withdrawal or if all data should be withdrawn from the trial participation. If the patient dies during the trial without providing consent, the data from the patient will be used in accordance with the trial protocol unless the deceased participants legal representative objects to use of the participants data.

9.2.2 Replacement of participants withdrawn during the trial

With the current planned participant inclusion of 320 patients, risk of patient withdrawal influencing the trial should be minimal. If all data are withdrawn during the interventional trial period by the patient, we will replace with one new randomization, but do not expect to replace patients with partly complete data in the trial. If we see a part dropout of ≥20% i.e., at least 64 patients, the steering committee will decide if more patients will be needed for completion of the trial.

9.3 Data management

Data will be stored on a secured electronic database through REDCap via OPEN at Odense University Hospital, Denmark. All access to data will be logged on a person level complying with the European code for handling person data and according to Danish law[71-73].

Relevant parameters for patients during inclusion, exclusion and randomization will be entered bedside by the clinical staff and investigators, using double entry with range and relevant checks by predefined coding to ensure highest possible data completion. Screening of patients will be conducted using a screening log for each trial site, where all patients screened will be registered as described in section 10.3.3. Only patients fulfilling inclusion criteria will be identified on the log using the generated unique patient identify number in REDCap. Patients not included, and therefore not randomised, will be registered anonymously with only age, gender, and reason for exclusion.

eCRF in REDCap for all data will be handled by either the trial sites principal investigator, Coordinating Investigator, Sponsor, or research nurse by assessing relevant information in the patient's electronic health records after study inclusion, supplemented with data extracted from relevant Danish registers to ensure full data records in the eCRF. The eCRF will be supplemented with both data input and scan of the paper CRF and consent forms used during the trial period of up to 24 hours.

The paper CRF will be used during the trial period of up to 24 hours bedside, during the patient treatment. When the trial period is completed, by any reason, the CRF will be stored locally in a secured locker in the department, in accordance with Danish legislation. The Principal Investigator or research nurse at each trial site, will upload the specific paper CRF for each patient to their specific eCRF, including entering the recorded data into the eCRF. After the upload of this form and entering the data, another research staff will enter the data as well, as double entry. This person is either the Principal Investigator, Research Nurse or Coordinating Investigator, whomever was not the first one entering the data from the paper CRF. The paper CRF will, when possible, be transferred to the Research Unit for Emergency Medicine at Odense University Hospital and stored in a secured locker. All data will be stored for at least 25 years after study inclusion as required by the EU regulation.[1]

The trial will not create a biobank as no additional trial specific blood samples are collected throughout this trial. Any blood analysis are collected and stored through the patients treatment are handled in accordance with usual ED local guidelines and patient management.
Blood sample analysis data, will however, be extracted from the patient electronic medical records as mentioned in section 9.4 Data to be collected. All these data from blood sample analysis are standard analysis used in the treatment of patients in the departments.

9.3.1 Data access

Each patient will be identified in REDCap by both their CPR number and a unique trial identification number. During the trial period, the Sponsor and Coordinating Investigator will have access to the entire database, while principal investigators, research nurses and other employed study personnel will have access to data from their own sites. Clinical staff, who conduct inclusion, allocation, and treatment of patients under guidance and supervision of the principal investigator, will have access to the REDCap database for the patients they include so they can include and randomize, where each individual have a personal username and password. The GCP unit, regulatory agencies and other relevant entities will have direct access to all relevant trial data as needed.

9.4 Data to be collected

9.4.1 Data collected bedside and thus only available in the paper Case Report Form before entry to the electronic Case Report Form

- Pulse and blood pressure measurements during the intervention period.
- Fluid administration time, type, and volume (mL)
- NA infusion dose concentration, including time of infusion start and termination and change of dosing.

9.4.2 Data collected from the registered AE or SAE reporting or the medical records

- Extravasation event (Time, duration, current infusion dose before termination, signs of necrosis, treatment for extravasation)
- New cardiac arrhythmia. (Time, duration, further investigation, and intervention if undertaken)
- Severe hypertension (Time, duration and further investigation or intervention if undertaken)
- Myocardial infarction (Time, further investigation and intervention if undertaken)
- Limb or intestinal ischemia (Time, duration, further investigation, and intervention if undertaken)

9.4.3 Data extracted from the medical records or beside and entered in the electronic Case Report Form

- Patient social security number
- Time of ED arrival including length of stay
- Time of screening
- Time of randomization
- AE, SAE and SUSAR and all necessary registrations in relations to these
- Time of death of applicable within 30 days
- Re-admission within 30 days
- Any admission to the ICU including length of stay of each admission
- Hospital admittance including length of stay
- Each initiation of mechanical ventilation (either invasive or non-invasive) including time of initiation, duration, and termination within 30 days
- Need for renal replacement therapy within 30 days

- All blood sample analysis measurements (either venous, arterial or capillary), during admission within the first 72 hours
- Development of acute kidney injury within 72 hours of hospital arrival (Defined as an absolute increase of creatinine ≥26.5µmol/L or ≥1.5 fold from baseline).
- Development of pulmonary oedema within 72 hours of hospital arrival (Diagnosed by physician in accordance with local guidelines, e.g., clinical decision including evaluation with paraclinical imaging such as x-ray or lung ultrasound).
- EQ-5L-5D[74,75] level at inclusion, or as soon as possible and at 1 year.
- Time to need for home nursing care or nursing home from inclusion and up to 1 year after
- Re-admission within 30 days
- Admission to the ICU including length of stay
- Hospital admittance including length of stay
- Need for renal replacement therapy within 30 days
- Death, if applicable within 30 days
- Time of death within 30 days

  Charlson co-morbidity index at 0, 14 and 30 days.

  Co-existing conditions at trial inclusion (e.g., diabetes)

9.4.4 Data collected in the screening log

- Screened patients not included in the study will be registered in the screening log with the following:
  - Age
  - Gender
  - Reason for not reaching inclusion and therefore randomization

9.5 Reporting of the summary of results

As soon as possible and no more than 1 year after the End of Trial, the Sponsor will upload the results to CTIS for the trial including a layman's resume as required in the EU regulation.[1]

10.0 Ethics

The study will be submitted to the European Medicines Agency (EMA) through CTIS. EMA will forward the application to The Danish Medicines Agency for evaluation of the clinical part of the protocol and the Danish Medical Research Ethics Committees for ethical approval. It will be conducted under the rules for research in emergency situations. The research protocol is written in accordance with the SPIRIT guidelines and the trial results will be reported following the CONSORT guidelines.[76,77] The study will be registered in both the European Clinical Trials Information System (CTIS) and Clinicaltrials.gov.

The trial will adhere to the revised Declaration of Helsinki[78] as well as European and National Danish Laws and regulations as applicable including following regulations on data protection and security in accordance with the Danish Data Protection Act and GDPR regulations[1,69,71-73,79,80].

10.1 General considerations

Shock and hypotension are emergent and critical conditions for patients and even though the conditions and treatments have been researched extensively, the mortality remains high.[5,20,24,35,39] Current guidelines considers fluid therapy as a first line treatment before initiation of vasopressor therapy, though the newest guidelines from the SSC mentions consideration for early initiation of vasopressor therapy.[24,29,37-39] Currently, the optimal time for initiation of vasopressor therapy has not been fully established, but it is reasonable to expect, that early stabilization of patients could potentially lead to shorter LOS, duration of the critical condition and reduced risk of complications due to excessive fluid therapy.[11,12,26,37,39,62] Current evidence does not address this, as early ED stabilization and therefore, possibly, decrease the necessity for ICU admittance among this patient group is evaluated in settings where vasopressor treatment initiated in the ED, will deem a quick admittance to the ICU.[28,48] Most other relatable countries, such as the USA, Canada and United Kingdom, have used ED initiated vasopressor therapy for several years, and are therefore used to earlier initiation if deemed necessary by the treating physician.[29,35,36,38,47,50,64] With the current organization and guidelines in Denmark, especially considering the use of fluid therapy for hypotension in the EDs, there is a unique opportunity to see if early initiated vasopressor therapy can improve patient outcomes. This could lead to more knowledge on whether the early treatment can reduce time to shock control and by that reduce LOS and less admittance to the ICU. Subsequently, it could lead to better understanding, if fluid therapy is lowered by the clinical staff due to earlier shock control, and therefore, possibly reduce the risk of complications to fluid therapy.

As the patient group is frequent in the ED[6,9], we consider this trial of great interest to the general society and public, not just for the individual patient, but also considering the extensive economical costs of ICU treatment compared to ED treatment.

Research in shock and hypotension provides challenges in ethics and patient consent. This is due to several reasons:

1. Patients are acute and critically ill, often with impaired cognition due to the low blood pressure and shock.
2. Patients can be emergently distressed due to the quick treatment interventions and team collaboration when stabilizing the patient's conditions.
3. Treatment for the condition requires prompt and swift decision and initiation, limiting the possibility for obtaining informed consent from the patient extensively.

Due to the necessity of research in improving both mortality and related outcomes in these conditions, there are no other patient groups that can give consent, who can be used as a substitute in the research area. Therefore, this trial will be conducted as an "Acute Drug Trial" where enrolment will be carried out from a pre-accepted enrolment without consent. See section 10.3 Procedures for further elaboration.

10.2 Danish regulations

Current Danish regulations regarding ethical requirements and enrolment of patients are following international EU law and regulations prior to conduction of the trial.[1,69] European regulations require the trial to be authorized through the CTIS database. Data will be handled as described in section 9.3, section 10.3.5 and section 10.3.6.

10.3 Procedures

10.3.1 Ethical review committee

The trial will require ethical approval by the Danish Medical Research Ethics Committees.

10.3.2 Trial-specific procedures

As the trial is conducted as an "Clinical trial in relation to emergency situations" and as an "acute drug trial" in accordance with European and Danish regulations, chapter V, article 35,[1] the patient will be enrolled in

the study when the clinical staff screens and finds the patient applicable for inclusion in accordance with the inclusion and exclusion criteria. The considerations for acute drug trials are necessary to use this inclusion method:

1) Due to the severity of the illness and condition, the patient is not expected to be able to provide informed consent prior to inclusion.
2) There is scientific evidence that enrolment and treatment in the trial will improve the patient's clinical condition and health.
3) It's not possible to wait for informed consent from the patient or their legally appointed representative, due to the therapeutic initiation of the intervention being too short.
4) The investigators attest, that they have no prior knowledge whether the person has refused to take part in clinical trials.
5) That the clinical condition is critical and emergent, therefore, that the intervention can only be conducted in acute situations.
6) That enrolment in the trial provides minimal risk and burden to the patient and their condition.

10.3.3 Screening and enrolment

The following patients will be screened by treating physician at each site: All patients ≥18-year-old with signs of hypotension or shock are screened. If patients are screened and evaluated as eligible for enrolment, the treating physician will discuss the patients' condition and fulfilment of the trial requirements for enrolment with the investigator under the right to transmission following the Danish Healthcare Act. [71] The investigator is responsible for decision of fulfilment of inclusion and exclusion criteria and if fulfilled then randomize in accordance with the trial enrolment procedure. Consent is handled as mentioned in section 10.3.4.

Due to the nature of the disease process, it is necessary for the investigator to receive information from the the treating physician about the patient in addition to oral information received by other healthcare personnel such as emergency medicine technicians or paramedics without prior consent to ensure correct screening prior to inclusion in the trial. This evaluation of possible participants will include their current health status including known diagnoses, medications, any decision on intensive care eligibility, their current home status and personal life circumstances related to their ability in daily living for evaluating clinical frailty score. As patients' prior healthcare records can be often or rarely updated due to frequent or seldom hospital admittance, data will be evaluated from the most recent hospital admissions that

elaborate these data. As mentioned in Section 13.0, we expect to include every 8th patient that arrive with hypotension or shock in the emergency department, and therefore, it can be necessary to screen up towards 2500 patients to identify possible participants.

Patients who have been screened will be noted on the trial screening log at each trial site, without any patient identifiable data other than time of screening, sex, age, reason for exclusion if applicable and if inclusion was possible or not. No other data will be collected for patients not eligible for trial participation. If a patient is included in the study, the unique trial identification number will be noted in the database and screening log.

10.3.4 Consent for participation

The trial is following the regulation for "acute drug trial"[1] and treatment needs to be initiated immediately. It is therefore not possible to obtain consent prior to enrolment, randomization and treatment initiation from either the patient or their next of kin (closest relative).[1,69] Consent will always be obtained from the legal guardian. The legal guardian is a physician with no relation to the trial, but with knowledge in handling of acute and emergent situations in patient treatment, see section 10.3.4.2.

After the enrolment is completed, the informed consent must be obtained as quickly as possible and without unnecessary delay in accordance with Danish law.[1,69] Consent is achieved through the following individuals:

- The legal guardian: Before consent can be obtained from the patient, or supplementary to consent obtained from the patient or the patient's next of kin/legal representative.
- The patient: If not deceased before consent could be obtained.
- Next of kin/legal representative: If consent is not possible to obtain from the patient due to their physical or cognitive state and critical condition or if the patient is deceased.

If the patients next of kin, or the legal guardian, will not provide consent for participation in the trial, they will be informed that they can refuse the inclusion of the patient's data that were collected during the trial.

10.3.4.1 Next of kin or legal representative

The patients next of kin or legal representative will be identified from the patient's electronic medical

records. These records contain information including name and contact for the patients closest relative. If the next of kin is attainable for consent, the consent will be obtained from the closest relative such as their spouse. If no spouse is available, the patients' parents, children or siblings will be contacted. If none of these are registered any other registered contact will be contacted to obtain consent, either through them (if registered as such) or by attaining information on any closer relative to the patient. If no relative can be contacted and the patient survives during the treatment, the patient will be contacted for consent as soon as possible following the usual procedure of the trial. If the patient is deceased before obtaining consent, this will be obtained following the procedures described in section 10.3.4.4.

10.3.4.2 Legal guardian

The legal guardian is a physician with no relation to the trial, but with knowledge in handling of acute and emergent situations in patient treatment. Prior to conduction of the trial, at least one physician from each Danish region with an active trial site will be identified by the Sponsor and informed of the trial and procedures of informed consent in emergency situations. Any questions and thoughts on the project will be discussed beforehand with the legal guardian and followed-up if any modifications to the trial is implemented. The physicians will be either an anaesthesiologist, intensivist or emergency physician not employed at any of the trial sites. After patient inclusion and randomization the legal guardian will be contacted as soon as possible and without unnecessary delay to obtain their consent following the procedures mentioned in section 10.3.4 and 10.3.4.5.

10.3.4.3 Procedures on information on the trial

Information about the trial, inclusion and need for consent will be presented in both oral and written form. Information for consent will be delivered by either the principal investigator or their delegate, such as another investigator or sub-investigator, who is also a physician or any physician who has been informed, educated and have signed agreement with the principal investigator on the trial. If possible, the consent should be given in a room with minimal risk of disturbance during the conversation, to give optimal surroundings for the decision. The patient or their next of kin/legal representative will have any necessary and requested time to consider providing consent for participation. Prior to fully obtaining the consent, the investigator will ensure that the patient or their next of kin understand the information presented. This is usually achieved through discussion with the informed person and ensuring that they can reference the relevant information of the trial. Due to the nature of the investigated intervention, continuation of

treatment will be conducted during this period, unless the patient or next of kin/legal representative refuses.

Patients already included in the trial, who are not able to speak and understand Danish due to insufficient language skills (e.g., immigrant with no or sparse education in Danish) will receive the oral information with the help from a professional interpreter. As patients will be enrolled without prior consent, it is not possible to translate the participant information to all possible necessary languages, thus this will only be available in Danish.

10.3.4.4 Consent for deceased participants prior to obtained consent

In case of death of the participant prior to consent being obtained by either the patient or next of kin/legal representative, the investigators will make reasonable attempts to contact the next of kin/legal representative of the patient. This is most likely achieved through prior registration of contact information in the participants electronic medical records as explained in section 10.3.4.1. If no such information is available, the investigators will try to reach out through usual procedures for informing relatives and next of kin of deceased patients completed by the departments when such information is unavailable. If no contact at any point can be established, the participants trial data will be used in the trial in accordance with the Danish law.[69]

10.3.4.5 Registration of obtained consent for participation

The consent will be signed either in paper form (which will be scanned and uploaded to the eCRF) or directly as an electronic signed consent form through REDCap, using a device, e.g., tablet signed by both the consenting individual, investigator, and the legal guardian. The electronic signature can be completed either with direct signature on an electronic copy of the paper form or using the personal electronic signature validation MitID hosted by The Danish Agency for Digital Government.[80] The touch-screen written signature for electronic signature will require same security validation level as required for MitID.

10.3.5 Protection of patient data

Patient data will be stored in compliance with the European and Danish laws and regulations for handling of personal data safety including the General Data Protection Regulation (GDPR), The Danish Data Protection Act, the Clinical Trial Regulations and the Danish Health Act.[1,2,69,71,72,79]

Data will be collected partly in writing, such as the paper case report form (paper-CRF) and written consent, and partly using the electronic CRF (eCRF). All data will be uploaded and stored in the eCRF using the web-based software platform REDCap hosted at Odense University Hospital via OPEN. Data are secured in accordance with the European General Data Protection Regulation and Danish Data Protection Act[73,79] and all data access are logged at a person level.
The database will be built to only allow personal access the relevant parts of the database, such as the Sponsor and GCP monitoring unit having full access. Sub-investigators will be able to access patients related to their own trial site and inclusion. The primary investigator and research nurse for each trial site will have access to the full eCRF for their own trial site, but not access to patients or data included from other trial sites.

Data stored in paper form such as the paper-CRF will be stored in a secured locker at each trial site only accessible by the relevant trial parties. Any original physical source data (e.g., the paper-CRF) will be copied and the copy stored at each trial site, so each trial site investigator has access to their relevant trial data. All original physical source data will be transferred to the Research Unit for Emergency Medicine at Odense University Hospital after inclusion and intervention has ended. All data storage will be handled for at least 25 years as mandated by the EU regulation.[1]

10.3.6 Measures in case of breach of data security

If any data breach is identified, the Sponsor, by delegate the Coordinating Investigator or other relevant trial staff with the delegated responsibility, will handle the data breach according to the European Guidelines on Personal Data Breach under Regulation 2016/679 and Danish Data Protection Act.[71,72] This includes informing the regulatory authority with no unnecessary delay and no more than 72 hours after the breach has been identified, including informing any affected individuals.

As soon as possible, the Sponsor and Coordinating Investigator will carry out a risk assessment and handling procedure in collaboration with relevant parties (such as OPEN), including decision on what further measure or handlings necessary to prevent further data breach or individual identification.

10.3.7 Insurance

The patients included in the trial, are covered by the Danish patient insurance.

11.0 Monitoring

11.1 Data monitoring

The study will be monitored by the regional Good Clinical Practice monitoring unit affiliated with OPEN at Odense University Hospital. Prior to study commencement there will be developed a detailed monitoring plan in collaboration with the Good Clinical Practice Unit at the University of Southern Denmark.

A Sponsor statement regarding data monitoring, audit, and access to trial data is attached after the Preface of the protocol.

11.2 Interim analysis and data monitoring committee

As this study is a pragmatic trial it is planned as a close resemblance to regular treatment regimens and protocols, and other studies have showed that the use of peripheral infused vasopressor therapy is a safe approach, we will not be completing an interim analysis during the trial period. Therefore, no data monitoring committee will be implemented.

11.3 Auditing

Audit during the trial period will be completed if deemed necessary or of the trial is taken out for auditing due to random sampling of trials. The audit will be completed in collaboration with the GCP-unit, Odense University Hospital, but auditors will not be part of the trial nor be part of the monitoring team for the trial.

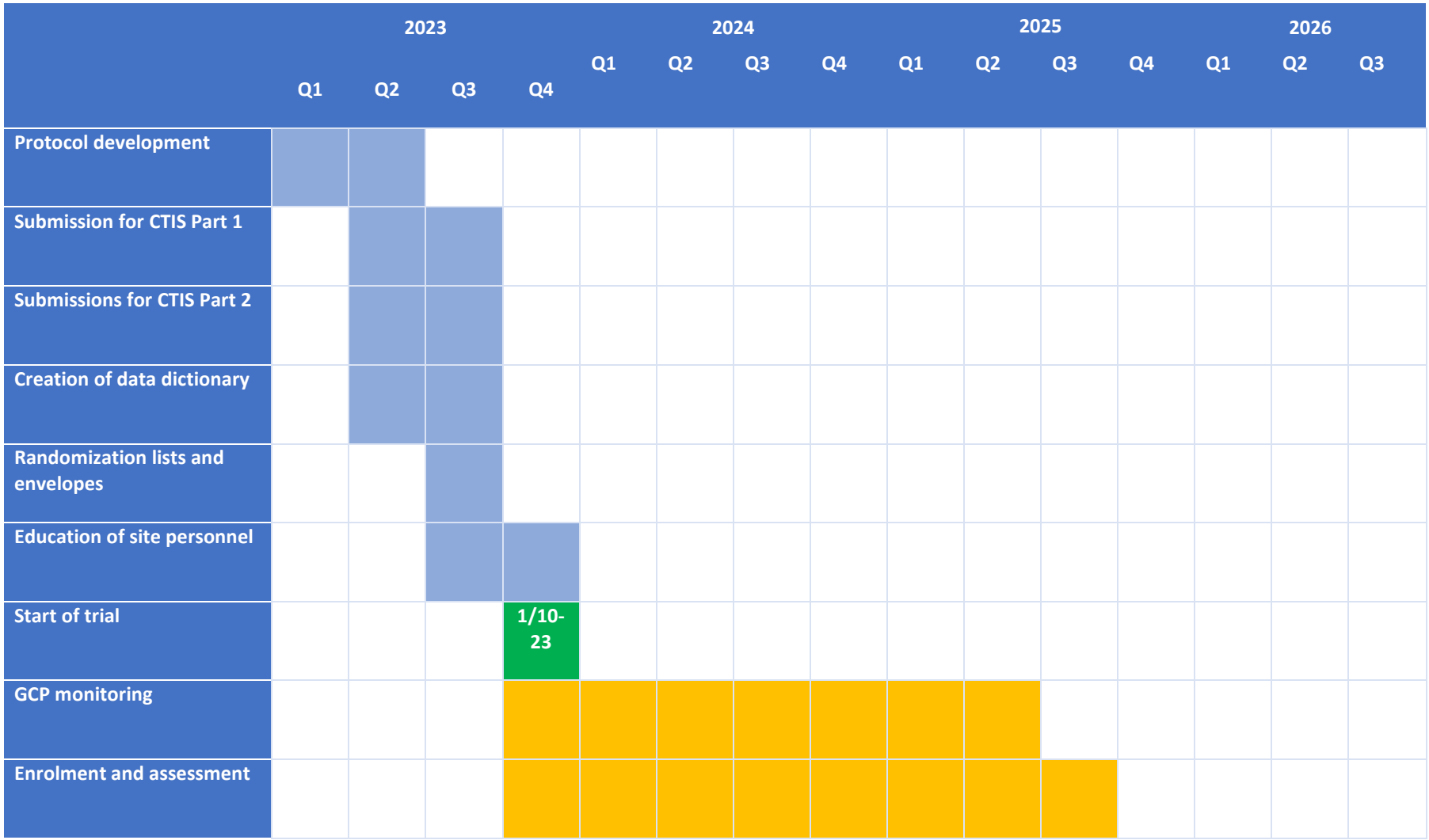
GCP-enheden

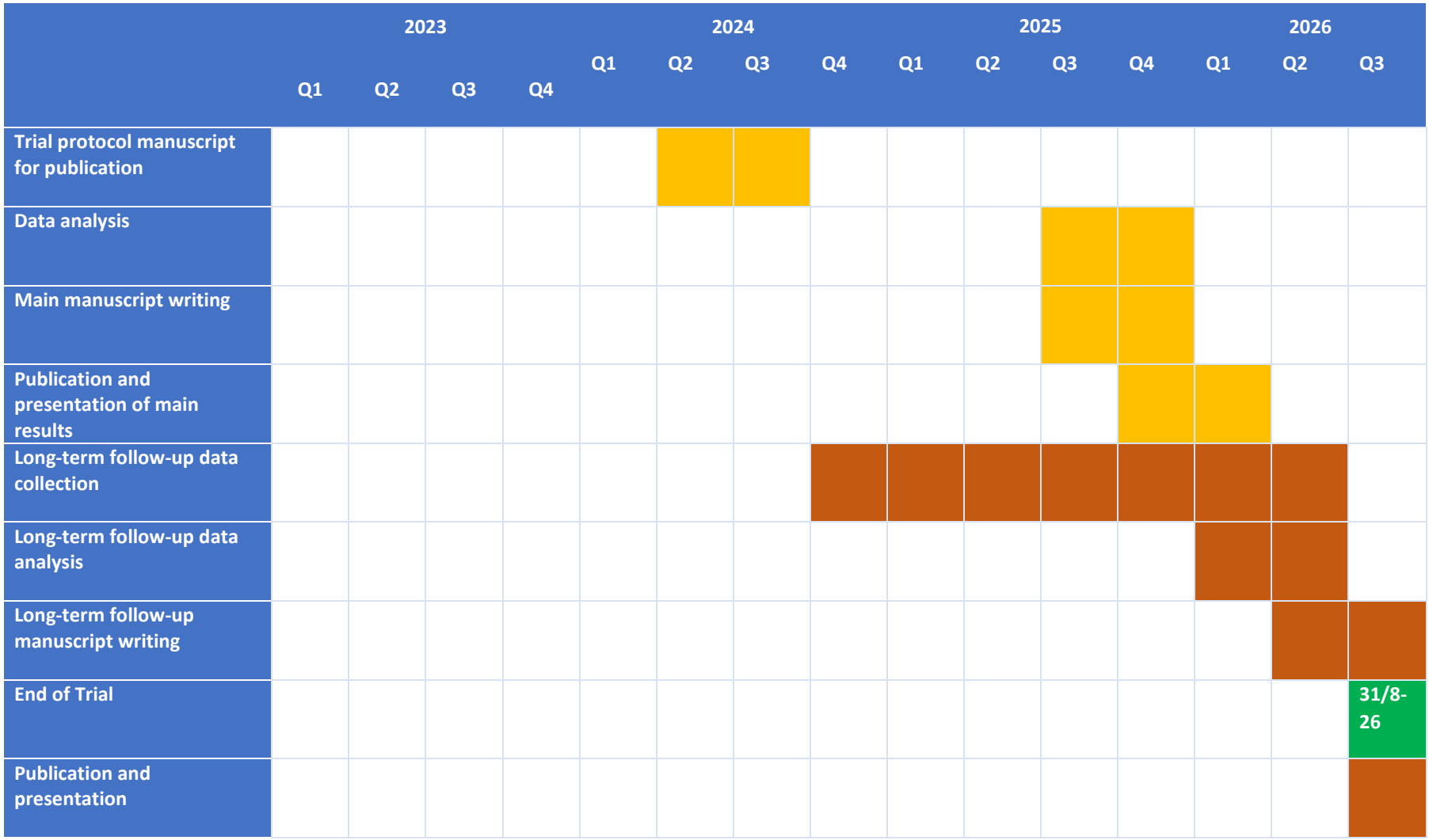
Odense University Hospital

J.B. Winsløws Vej 19, 2. sal

DK-5000 Odense C

12.0 Timeline

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Trial protocol manuscript for publication
Data analysis
Main manuscript writing
Publication and presentation of main results
Long-term follow-up data collection
Long-term follow-up data analysis
Long-term follow-up manuscript writing
End of Trial
31/8-26
Publication and presentation

13.0 Feasibility

Previous data on relevant patients in a Danish setting, have not been published. The previous studies on number of hypotensive patients at Odense University Hospital[7] does not stratify the patient groups according to clinical frailty score, or if they are eligible for ICU admittance or not. In the same manner, the national database for intensive care[32] does not register number of patients evaluated for ICU admittance. Therefore, we cannot say how many patients were deemed ineligible before the selection of the current ICU cohort in Denmark.

At the ED of OUH, more than 2,000 patients were admitted from Odense Municipality with an initial SBP of <100mmHg over a 3 year period.[8] This is equal to two patients/day at OUH alone, not considering patients admitted from other municipalities, considering that OUH does receive and treat patients from other municipalities on Funen. Not all hypotensive patients are admitted due to undifferentiated shock and hypotension, but due to suspected haemorrhagic shock, upper gastrointestinal bleeding, obstructive shock, and other causes. Patients admitted to OUH over a 12 year period showed 45.7% of patients were admitted due to the before mentioned conditions and 30.8% were due to hypovolemic shock including dehydration and trauma.[6] These patients might need other emergent interventions than treatment with vasopressor therapy and will not be included.

To ensure generalizability of the patient population, we will include several departments in the study. These departments will be a mix of both urban and rural populations, as well as university and regional hospitals. All departments will be receiving patients with suspicion of causes for hypotension such as infections and sepsis and will be able to assess, diagnose and treat these conditions to a modern standard, including relevant paraclinical studies such as blood tests, X-rays, CT-scans and so forth. All hospitals will have available ICUs, if necessary for patient admittance.

Including every 8th hypotensive patient admitted would, in Odense alone, enable the study to be completed within 4 years. However, we will include at least 4 sites, and expect completion within 12 months. If possible, more sites will be included in the study during the intervention period, therefor further improving the possibility for completion within a shorter time frame. The current trial is estimated to run over a period of 2-3 years, so slow inclusion can be improved over time and smaller sites with expected slower inclusion rate, will not challenge the completion of the study.

As the study is planned as a pragmatic study, we aim to make the inclusion and completion of the intervention as safe and easy as possible for the sites and trial participant, so the restrictions on trial

inclusion will most likely be due to either lack of eligible patients for inclusion or low participation of screening from each trial site. The latter will be sought improved by partly employing research nurses part time at each site, to both extract data and follow-up on patients included, while also improving the participation of clinical staff to screen and include relevant patients admitted to the department.

14.0 Publication and dissemination plan

Patients participating in the study will be able to note if they wish to be informed of the study results after conclusion of the trial period.

The study will be presented at national and international conferences and the publication divided into at least two main papers, firstly, one from the main study period and secondly, one for the long-term follow up of participants (see Appendix 6). Thirdly, the study protocol is expected to be published in a short version at a relevant international scientific journal. The manuscript will adhere to the CONSORT guidelines for reporting of randomized clinical trials.[81] All planned results of the study will be published either positive, negative, or inconclusive.

14.1 Authorship

The coordinating investigator, Lasse Paludan Bentsen, will be first author on the main papers of the study, the sponsor will be last author. The rest of the participants will be given authorship appropriately in accordance with International Committee of Medical Journal Editors rules for authorship.[3] Members of the steering committee and the site principal investigator for sites with at least one participant inclusion will take part in the authorship. Sites including more than 40 patients will receive an additional authorship for the main study paper if applicable as authors. Sites with more than 70 inclusions can have one additional author, if such a person is part of the study inclusion.

15.0 Data sharing

There will be no prior decision on formal data sharing other than required upload of results to CTIS and relevant authorities. Any further data sharing, if necessary, will be made available as de-identified data in accordance with EU and Danish regulations and national law.[1,2,69,71,73]

16.0 Funding

The trial funding is granted by The PhD Fund of The Region of Southern Denmark (592,000 DKK), The Medicine Fund of The Danish Regions (2,676,000 DKK) and The Region of Southern Denmark and Region Zealands Research Fund (440,000 DKK).

The funding is administered at the Research Unit of Emergency Medicine, Department of Emergency Medicine, Odense University Hospital, The Region of Southern Denmark. Funding will be used for salary support for the Coordinating Investigator and relevant research personnel, monitoring of the study, equipment, medications, and other operational expenses during the study completion. Further applications will be sent to public or private funders before and during the trial if necessary. None of the funding institutions or organizations, including possible pharmaceutical companies, will have any role in design and conduction of the study, collection, management, analysis, or interpretation of the data. They will have no role in preparation, review, or approval of manuscripts or any decision related to manuscript content and results for publication.

17.0 Tasks and responsibilities

17.1 Sponsor-Investigator and Coordinating Investigator

The Sponsor has overall responsibility for the trial. In close collaboration with the sponsor, the coordinating investigator will develop and take responsibility for the protocol including revision, funding, budget overview, ethical approval, trial registration, daily management, trial oversight, contact to Good Clinical Practice monitoring unit, assessment of overall recruitment of patients, education of clinical staff in relation to the trial, potential recruitment of additional sites, data analysis, dissemination and presentation of results. The Coordinating Investigator or Sponsor, where applicable, will take responsibility of contact to relevant authorities in relation to the study and updating the main Trial Master File.

17.2 Steering committee

Protocol development, funding, budget overview, trial oversight, dissemination of results and if necessary, responsibilities of either Sponsor or Coordinating Investigator for short time periods.

17.3 Project coordinator

The project coordinator will handle necessary tasks delegated by the Sponsor and Coordinating Investigator in relation to the trial. The project coordinator will assist with protocol development and revision, funding, budget overview, ethical approval, trial registration, daily management and oversight, contact to the GCP unit, communication with trial sites and research staff, organization and management of trial documents including the trial master file, production and revision of relevant standard operating procedures, organization of meetings and other administrative tasks related to the coordination and management of the trial. Tasks delegated to the project coordinator are always carried out in close collaboration with the Sponsor and Coordinating Investigator.

17.4 Principal Investigators at each trial site

Responsible for site-specific screening and enrolment, in collaboration with clinical staff on site, evaluation of eligible patients not included education and follow-up of clinical staff on trial site, reporting to Sponsor or Coordinating Investigator on site-specific issues or challenges, participant consent for data collection and follow-up data collection for the data collection in the 30-day follow-up part of the trial. The Principal

Investigator will, in collaboration with the Coordinating Investigator, handle update and handling of the trial site specific part of the Trial Master File.

17.5 Research nurses

Support for the principal investigator and clinical staff at the trial sites, education, and follow-up for clinical staff, contact to Good Clinical Practice monitoring unit, data collection, entry and management including patient follow-up for at least the 30-day follow-up part of the trial.

17.6 Clinical team

Screening and enrolment of patients, obtaining informed consent after receiving education to do this, deliver of care for both intervention and control group according to the trial protocol, registering of data on the paper-CRF after randomization and up until end of treatment period (24 hours).

17.7 Good Clinical Practice-unit

See section 11.0.

18.0 References

1. The European Parliament and the Council of the European Unit. Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC 2014. Accessed 1st March 2023.
2. Committee For Human Medicinal Products. ICH Guideline for good clinical practice E6(R2). 2016 (https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-good-clinical-practice-e6r2-step-5_en.pdf).
3. International Committee of Medical Journal E. Defining the Role of Authors and Contributors. 2017.
4. Chan AW, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med 2013;158(3):200-7. DOI: 10.7326/0003-4819-158-3-201302050-00583.
5. Vincent JL, De Backer D. Circulatory shock. N Engl J Med 2013;369(18):1726-34. DOI: 10.1056/NEJMra1208943.
6. Gitz Holler J, Jensen HK, Henriksen DP, et al. Etiology of Shock in the Emergency Department: A 12-Year Population-Based Cohort Study. Shock 2019;51(1):60-67. DOI: 10.1097/SHK.0000000000000816.
7. Pedersen PB, Henriksen DP, Brabrand M, Lassen AT. Prevalence of organ failure and mortality among patients in the emergency department: a population-based cohort study. BMJ Open 2019;9(10):e032692. DOI: 10.1136/bmjopen-2019-032692.
8. Holler JG, Henriksen DP, Mikkelsen S, Pedersen C, Lassen AT. Increasing incidence of hypotension in the emergency department; a 12 year population-based cohort study. Scand J Trauma Resusc Emerg Med 2016;24(1):20. DOI: 10.1186/s13049-016-0209-4.
9. Holler JG, Bech CN, Henriksen DP, Mikkelsen S, Pedersen C, Lassen AT. Nontraumatic hypotension and shock in the emergency department and the prehospital setting, prevalence, etiology, and mortality: a systematic review. PLoS One 2015;10(3):e0119331. DOI: 10.1371/journal.pone.0119331.
10. Finfer S, Liu B, Taylor C, et al. Resuscitation fluid use in critically ill adults: an international cross-sectional study in 391 intensive care units. Crit Care 2010;14(5):R185. DOI: 10.1186/cc9293.
11. Jessen MK, Simonsen BY, Thomsen MH, Andersen LW, Kolsen-Petersen JA, Kirkegaard H. Fluid management of emergency department patients with sepsis-A survey of fluid resuscitation practices. Acta Anaesthesiol Scand 2022;66(10):1237-1246. DOI: 10.1111/aas.14141.
12. Jessen MK, Andersen LW, Thomsen MH, et al. Twenty-four-hour fluid administration in emergency

department patients with suspected infection: A multicenter, prospective, observational study. Acta Anaesthesiol Scand 2021;65(8):1122-1142. DOI: 10.1111/aas.13848.

13. Hernandez G, Ospina-Tascon GA, Damiani LP, et al. Effect of a Resuscitation Strategy Targeting Peripheral Perfusion Status vs Serum Lactate Levels on 28-Day Mortality Among Patients With Septic Shock: The ANDROMEDA-SHOCK Randomized Clinical Trial. JAMA 2019;321(7):654-664. DOI: 10.1001/jama.2019.0071.
14. Kattan E, Ospina-Tascón GA, Teboul JL, et al. Systematic assessment of fluid responsiveness during early septic shock resuscitation: Secondary analysis of the ANDROMEDA-SHOCK trial. Critical Care 2020;24(1):1-9. DOI: 10.1186/s13054-020-2732-y.
15. Maurer C, Wagner JY, Schmid RM, Saugel B. Assessment of volume status and fluid responsiveness in the emergency department: a systematic approach. Med Klin Intensivmed Notfmed 2017;112(4):326-333. DOI: 10.1007/s00063-015-0124-x.
16. Pierrakos C, Velissaris D, Scolletta S, Heenen S, De Backer D, Vincent JL. Can changes in arterial pressure be used to detect changes in cardiac index during fluid challenge in patients with septic shock? Intensive Care Med 2012;38(3):422-8. DOI: 10.1007/s00134-011-2457-0.
17. Kattan E, Ospina-Tascon GA, Teboul JL, et al. Systematic assessment of fluid responsiveness during early septic shock resuscitation: secondary analysis of the ANDROMEDA-SHOCK trial. Crit Care 2020;24(1):23. DOI: 10.1186/s13054-020-2732-y.
18. Chaves RCF, Correa TD, Neto AS, et al. Assessment of fluid responsiveness in spontaneously breathing patients: a systematic review of literature. Ann Intensive Care 2018;8(1):21. DOI: 10.1186/s13613-018-0365-y.
19. Bihari S, Prakash S, Bersten AD. Post resusicitation fluid boluses in severe sepsis or septic shock: prevalence and efficacy (price study). Shock 2013;40(1):28-34. DOI: 10.1097/SHK.0b013e31829727f1.
20. Marik PE, Linde-Zwirble WT, Bittner EA, Sahatjian J, Hansell D. Fluid administration in severe sepsis and septic shock, patterns and outcomes: an analysis of a large national database. Intensive Care Med 2017;43(5):625-632. DOI: 10.1007/s00134-016-4675-y.
21. National Heart L, Blood Institute Acute Respiratory Distress Syndrome Clinical Trials N, Wiedemann HP, et al. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med 2006;354(24):2564-75. DOI: 10.1056/NEJMoa062200.
22. Silversides JA, Major E, Ferguson AJ, et al. Conservative fluid management or deresuscitation for patients with sepsis or acute respiratory distress syndrome following the resuscitation phase of critical illness: a systematic review and meta-analysis. Intensive Care Medicine: Springer Verlag;

2017:155-170.

23. Perner A, Cecconi M, Cronhjort M, et al. Expert statement for the management of hypovolemia in sepsis. Intensive Care Medicine: Springer Verlag; 2018:791-798.
24. Evans L, Rhodes A, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 20212021.
25. Meyhoff TS, Hjortrup PB, Wetterslev J, et al. Restriction of Intravenous Fluid in ICU Patients with Septic Shock. New England Journal of Medicine 2022. DOI: 10.1056/nejmoa2202707.
26. Jessen MK, Andersen LW, Thomsen MH, et al. Restrictive fluids versus standard care in adults with sepsis in the emergency department (REFACED): A multicenter, randomized feasibility trial. Acad Emerg Med 2022;29(10):1172-1184. DOI: 10.1111/acem.14546.
27. Harris T, Coats TJ, Elwan MH. Fluid therapy in the emergency department: an expert practice review. Emerg Med J 2018;35(8):511-515. DOI: 10.1136/emermed-2017-207245.
28. National Heart L, Blood Institute P, Early Treatment of Acute Lung Injury Clinical Trials N, et al. Early Restrictive or Liberal Fluid Management for Sepsis-Induced Hypotension. N Engl J Med 2023;388(6):499-510. DOI: 10.1056/NEJMoa2212663.
29. Djogovic D, Macdonald S, Wensel A, et al. Vasopressor and inotrope use in canadian emergency departments: Evidence based consensus guidelines. Canadian Journal of Emergency Medicine: Decker Publishing; 2015:1-16.
30. Moellekaer A, Kirkegaard H, Vest-Hansen B, et al. Risk of death within 7 days of discharge from emergency departments with different organizational models. European Journal of Emergency Medicine 2020;27(1):27-32. DOI: 10.1097/MEJ.0000000000000596.
31. Moellekaer A, Duvald I, Obel B, Madsen B, Eskildsen J, Kirkegaard H. The organization of Danish emergency departments. European Journal of Emergency Medicine 2020:295-300. DOI: 10.1097/MEJ.0000000000000554.
32. Hulegaard Sørensen H, Dyrvig A-K. Dansk Intensiv Database Årsrapport 2019/2020. 2021(april):5-6. (http://www.did1.dk/upl/9153/DIDrsrapport2010.pdf).
33. Garde K, Christiansen ML. Dansk Anæstesi Database - National årsrapport 2021. 2021(december 2021):1-130. (www.rkkp.dk).
34. Dansk Selskab for Anæstesiologi og Intensiv M. Generelle rekommandationer for intensiv terapi i Danmark. 2020(April).
35. Colon Hidalgo D, Patel J, Masic D, Park D, Rech MA. Delayed vasopressor initiation is associated with increased mortality in patients with septic shock. J Crit Care 2020;55:145-148. DOI: 10.1016/j.jcrc.2019.11.004.

36. Delaney A, Finnis M, Bellomo R, et al. Initiation of vasopressor infusions via peripheral versus central access in patients with early septic shock: A retrospective cohort study. Emerg Med Australas 2020;32(2):210-219. DOI: 10.1111/1742-6723.13394.
37. Finfer S, Myburgh J, Bellomo R. Intravenous fluid therapy in critically ill adults. Nat Rev Nephrol 2018;14(9):541-557. DOI: 10.1038/s41581-018-0044-0.
38. Keijzers G, Macdonald SP, Udy AA, et al. The Australasian Resuscitation In Sepsis Evaluation: Fluids or vasopressors in emergency department sepsis (ARISE FLUIDS), a multi-centre observational study describing current practice in Australia and New Zealand. Emerg Med Australas 2020;32(4):586-598. DOI: 10.1111/1742-6723.13469.
39. Self WH, Semler MW, Bellomo R, et al. Liberal Versus Restrictive Intravenous Fluid Therapy for Early Septic Shock: Rationale for a Randomized Trial. Ann Emerg Med 2018;72(4):457-466. DOI: 10.1016/j.annemergmed.2018.03.039.
40. Ellekjaer KL, Perner A, Svan KB. Issuing of isotonic crystalloid solutions to Danish public hospitals in 2021 — A retrospective nationwide observational study. 2022(October):1-8. DOI: 10.1111/aas.14176.
41. Nguyen TT, Surrey A, Barmaan B, et al. Utilization and extravasation of peripheral norepinephrine in the emergency department. Am J Emerg Med 2021;39:55-59. DOI: 10.1016/j.ajem.2020.01.014.
42. Tran QK, Mester G, Bzhilyanskaya V, et al. Complication of vasopressor infusion through peripheral venous catheter: A systematic review and meta-analysis. American Journal of Emergency Medicine: W.B. Saunders; 2020.
43. Tank AW, Lee Wong D. Peripheral and central effects of circulating catecholamines. Compr Physiol 2015;5(1):1-15. DOI: 10.1002/cphy.c140007.
44. Ospina-Tascón GA, Hernandez G, Bakker J. Should we start vasopressors very early in septic shock? Journal of Thoracic Disease 2020;12(7):3893-3896. DOI: 10.21037/jtd.2020.02.21.
45. Russell JA. Vasopressor therapy in critically ill patients with shock. Intensive Care Med 2019;45(11):1503-1517. DOI: 10.1007/s00134-019-05801-z.
46. Tian DH, Smyth C, Keijzers G, et al. Safety of peripheral administration of vasopressor medications: A systematic review. Emerg Med Australas 2020;32(2):220-227. DOI: 10.1111/1742-6723.13406.
47. Black LP, Puskarich MA, Smotherman C, Miller T, Fernandez R, Guirgis FW. Time to vasopressor initiation and organ failure progression in early septic shock. J Am Coll Emerg Physicians Open 2020;1(3):222-230. DOI: 10.1002/emp2.12060.
48. Permpikul C, Tongyoo S, Viarasilpa T, Trainarongsakul T, Chakorn T, Udompanturak S. Early Use of Norepinephrine in Septic Shock Resuscitation (CENSER). A Randomized Trial. Am J Respir Crit Care

Med 2019;199(9):1097-1105. DOI: 10.1164/rccm.201806-1034OC.

49. Araiza A, Duran M, Varon J. Administration of vasopressors through peripheral venous catheters. CMAJ 2022;194(21):E739. DOI: 10.1503/cmaj.211966.
50. Gamper G, Havel C, Arrich J, et al. Vasopressors for hypotensive shock. Cochrane Database of Systematic Reviews: John Wiley and Sons Ltd; 2016.
51. Lewis T, Merchan C, Altshuler D, Papadopoulos J. Safety of the Peripheral Administration of Vasopressor Agents. J Intensive Care Med 2019;34(1):26-33. DOI: 10.1177/0885066616686035.
52. Loubani OM, Green RS. A systematic review of extravasation and local tissue injury from administration of vasopressors through peripheral intravenous catheters and central venous catheters. J Crit Care 2015;30(3):653 e9-17. DOI: 10.1016/j.jcrc.2015.01.014.
53. Lewis SR, Pritchard MW, Evans DJ, et al. Colloids versus crystalloids for fluid resuscitation in critically ill people. Cochrane Database Syst Rev 2018;8(8):CD000567. DOI: 10.1002/14651858.CD000567.pub7.
54. Early Vasopressor In Sepsis (EVIS). Sepsis Research FEAT. (https://sepsisresearch.org.uk/evis/).
55. Australasian Resuscitation In Sepsis Evaluation: Fluid or Vasopressors In Emergency Department Sepsis: ARISE FLUIDS. ANZICS Clinical Trials Group. (https://www.arisefluids.org/).
56. Gamerman V, Cai T, Elsäßer A. Pragmatic randomized clinical trials: best practices and statistical guidance. Health Services and Outcomes Research Methodology 2019;19(1):23-35. DOI: 10.1007/s10742-018-0192-5.
57. Zwarenstein M, Treweek S, Gagnier JJ, et al. Improving the reporting of pragmatic trials: An extension of the CONSORT statement. Bmj 2008;337(7680):1223-1226. DOI: 10.1136/bmj.a2390.
58. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: Building an international community of software platform partners. Journal of Biomedical Informatics 2019;95(April):103208-103208. DOI: 10.1016/j.jbi.2019.103208.
59. Fløjstrup M, Bogh SB, Henriksen DP, Bech M, Johnsen SP, Brabrand M. Increasing emergency hospital activity in Denmark, 2005-2016: A nationwide descriptive study. BMJ Open: BMJ Publishing Group; 2020.
60. Ekeløf SA, Ekeløf S, Bech JN, Ekeløf P. Administration of norepinephrine in peripheral venous catheter on surgical patients. Ugeskr Laeger 2017;179(34) (In dan).
61. Pancaro C, Shah N, Pasma W, et al. Risk of Major Complications After Perioperative Norepinephrine Infusion Through Peripheral Intravenous Lines in a Multicenter Study. Anesth Analg 2020;131(4):1060-1065. DOI: 10.1213/ANE.0000000000004445.
62. Klastrup V, Hvass AM, Mackenhauer J, et al. Site of infection and mortality in patients with severe

sepsis or septic shock. A cohort study of patients admitted to a Danish general intensive care unit. Infect Dis (Lond) 2016;48(10):726-31. DOI: 10.3109/23744235.2016.1168938.

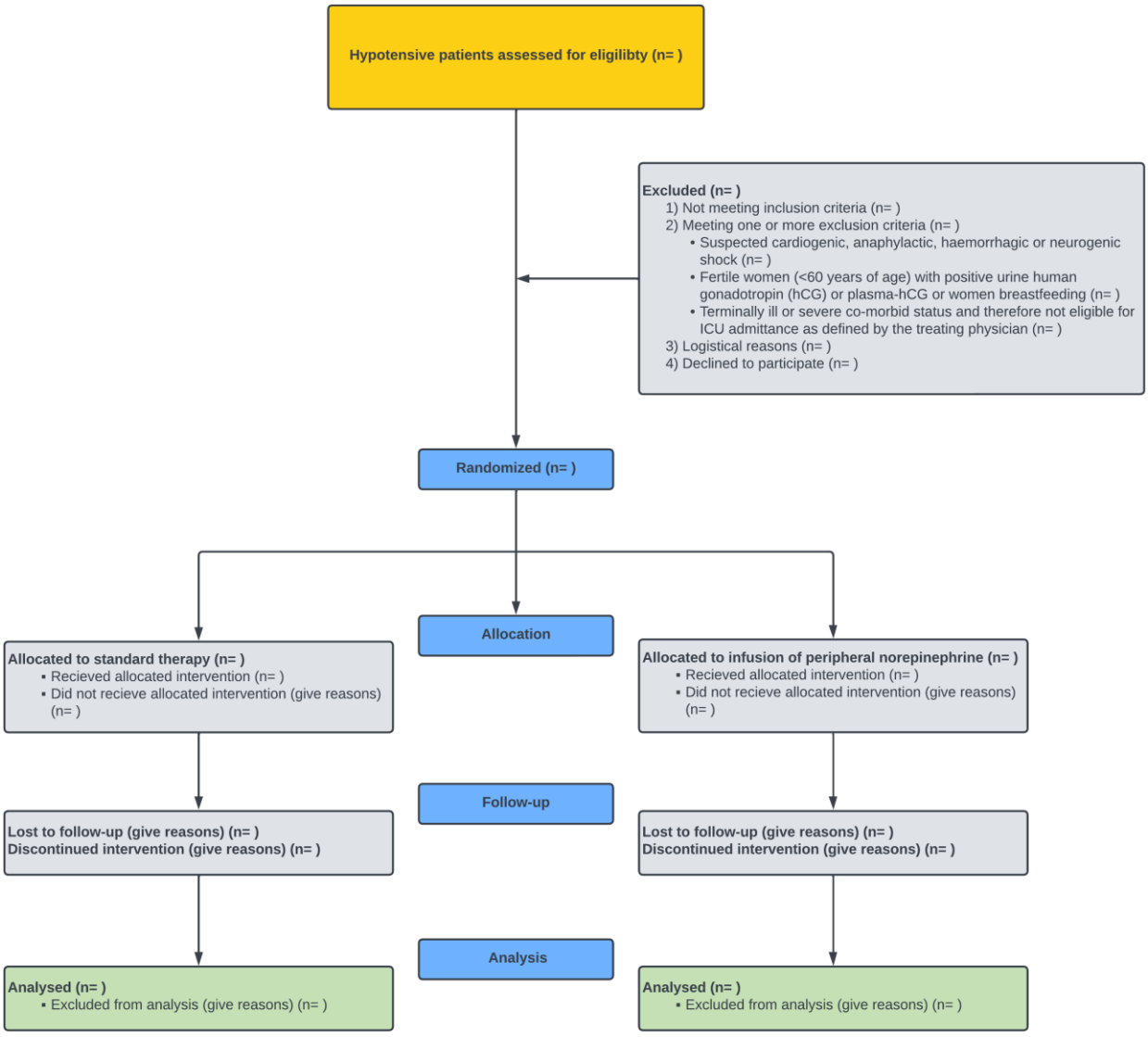
63. Owen VS, Rosgen BK, Cherak SJ, et al. Adverse events associated with administration of vasopressor medications through a peripheral intravenous catheter: a systematic review and meta-analysis. Crit Care 2021;25(1):146. DOI: 10.1186/s13054-021-03553-1.
64. Ospina-Tascon GA, Hernandez G, Alvarez I, et al. Effects of very early start of norepinephrine in patients with septic shock: a propensity score-based analysis. Crit Care 2020;24(1):52. DOI: 10.1186/s13054-020-2756-3.
65. Bakker J, Kattan E, Annane D, et al. Current practice and evolving concepts in septic shock resuscitation. Intensive Care Med 2022;48(2):148-163. DOI: 10.1007/s00134-021-06595-9.
66. Marik PE, Linde-Zwirble WT, Bittner EA, Sahatjian J, Hansell D. Fluid administration in severe sepsis and septic shock, patterns and outcomes: an analysis of a large national database. Intensive Care Medicine 2017;43(5):625-632. DOI: 10.1007/s00134-016-4675-y.
67. Li Y, Li H, Zhang D. Timing of norepinephrine initiation in patients with septic shock: A systematic review and meta-analysis. Critical Care 2020;24(1):1-9. DOI: 10.1186/s13054-020-03204-x.
68. Annane D, Maxime V, Ibrahim F, Alvarez JC, Abe E, Boudou P. Diagnosis of adrenal insufficiency in severe sepsis and septic shock. American Journal of Respiratory and Critical Care Medicine 2006;174(12):1319-1326. DOI: 10.1164/rccm.200509-1369OC.
69. Sundheds- og Ældreministeriet. Bekendtgørelse af lov om kliniske forsøg med lægemidler. LBK nr 1252 af 31/10/2018. Accessed 20th May 2023.
70. O'Keeffe AG, Ambler G, Barber JA. Sample size calculations based on a difference in medians for positively skewed outcomes in health care studies. BMC Medical Research Methodology 2017;17(1):1-11. DOI: 10.1186/s12874-017-0426-1.
71. The Danish Health Ministry. The Danish Health Act. LBK No. 1011 of 17 June 2023. 2023.
72. Guidelines on Personal data breach notification under Regulation 2016/679. 2017.
73. Regulation (EU) 2016/679 of The European Parliament and of The Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation). 2016.
74. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011;20(10):1727-36. DOI: 10.1007/s11136-011-9903-x.
75. Janssen MF, Pickard AS, Golicki D, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. Qual Life Res 2013;22(7):1717-27. DOI:

10.1007/s11136-012-0322-4.

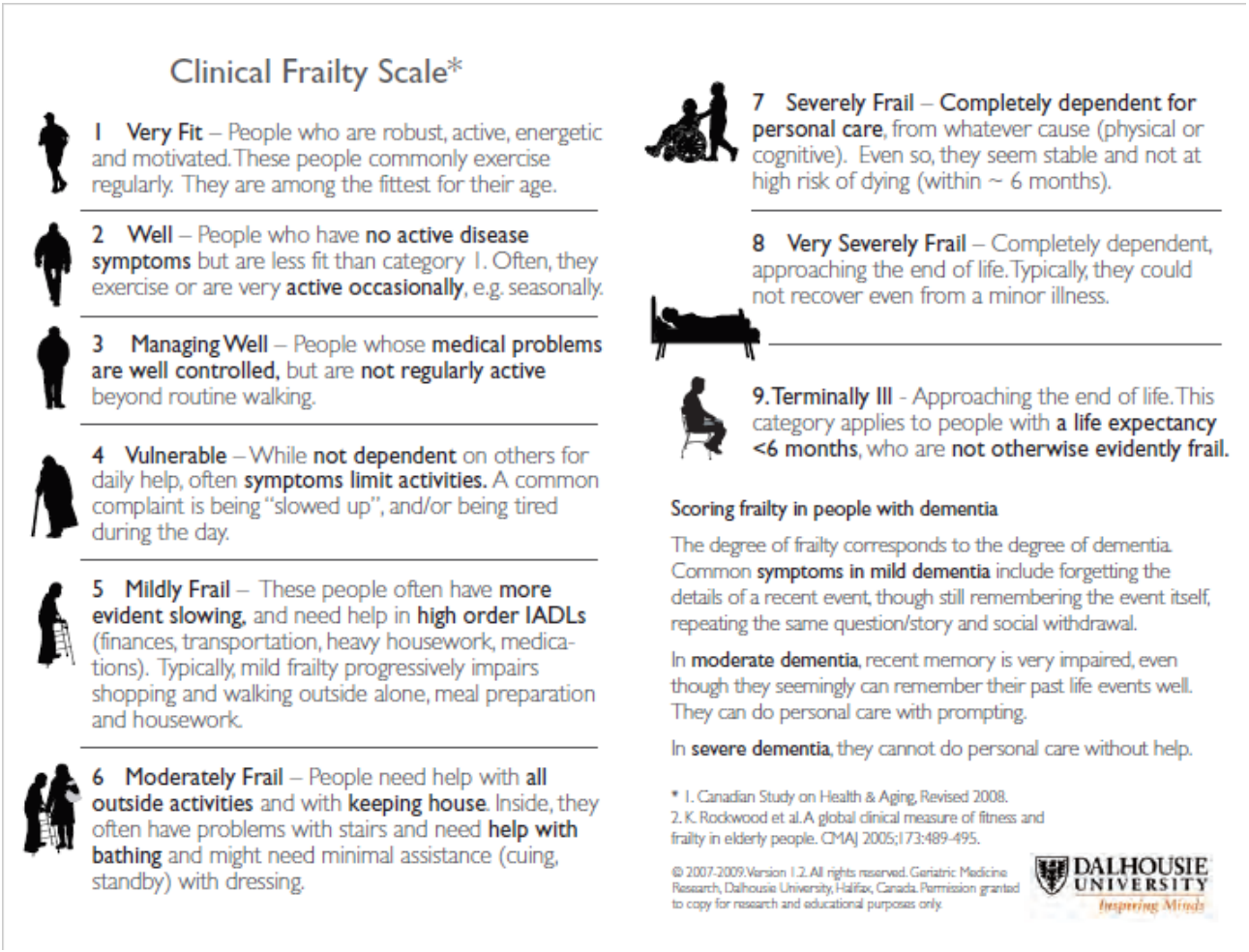
76. Schulz KF, Altman DG, Moher D, Group C. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ 2010;340(7748):c332. DOI: 10.1136/bmj.c332.
77. Tetzlaff JM, Chan AW, Kitchen J, Sampson M, Tricco AC, Moher D. Guidelines for randomized clinical trial protocol content: A systematic review. Systematic Reviews 2012;1(1):1-11. DOI: 10.1186/2046-4053-1-43.
78. World Medical A. WMA Declaration of Helsinki: ethical principles for medical research involving human subjects. 1974;353(1):1418-1419. (http://www.wma.net/en/30publications/10policies/b3/index.html).
79. Datatilsynet. The Danish Data Protection Act No. 502 of 23 May 2018. 2018.
80. The Ministrity of Finance of Denmark, The Danish Agency for Digital Government. Bekendtgørelse om MitID til privatpersoner. BEK nr 1778 af 01/09/2021. 2021.
81. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 explanation and elaboration: Updated guidelines for reporting parallel group randomised trials. International Journal of Surgery 2012;10:28-55. DOI: 10.1016/j.ijsu.2011.10.001.
82. Fournaise A, Nissen SK, Lauridsen JT, et al. Translation of the updated clinical frailty scale 2.0 into Danish and implications for cross-sectoral reliability. BMC Geriatrics: BioMed Central Ltd; 2021.
83. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth Universal Definition of Myocardial Infarction (2018). Circulation 2018;138(20):e618-e651. DOI: 10.1161/CIR.0000000000000617.

19.0 Appendices

Appendix 1: CONSORT diagram draft



Appendix 2: Clinical Frailty Scale (Danish)



Clinical Frailty Scale*

1 **Very Fit** – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2 **Well** – People who have **no active disease symptoms** but are less fit than category 1. Often, they exercise or are very **active occasionally**, e.g. seasonally.

3 **Managing Well** – People whose **medical problems are well controlled,** but are **not regularly active** beyond routine walking.

4 **Vulnerable** – While **not dependent** on others for daily help, often **symptoms limit activities.** A common complaint is being "slowed up", and/or being tired during the day.

5 **Mildly Frail** – These people often have **more evident slowing,** and need help in **high order IADLs** (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

6 **Moderately Frail** – People need help with **all outside activities** and with **keeping house**. Inside, they often have problems with stairs and need **help with bathing** and might need minimal assistance (cuing, standby) with dressing.

7 **Severely Frail** – **Completely dependent for personal care**, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).

8 **Very Severely Frail** – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

9. **Terminally Ill** - Approaching the end of life. This category applies to people with **a life expectancy <6 months**, who are **not otherwise evidently frail.**

Scoring frailty in people with dementia

The degree of frailty corresponds to the degree of dementia. Common **symptoms in mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia**, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In **severe dementia**, they cannot do personal care without help.

* 1. Canadian Study on Health & Aging, Revised 2008.
2. K. Rockwood et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489-495.

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English version of the Clinical Frailty Scale. A Danish version are expected to be used. This version is translated and validated by Fournaise et al.[82] (64)

Appendix 3: Conflict of interests for steering committee

Lasse Paludan Bentsen: LPB is funded by the same research grants as this trial; The PhD Fund of The Region of Southern Denmark (592,000 DKK), The Medicine Fund of The Danish Regions (2,676,000 DKK) and The Region of Southern Denmark and Region Zealand Research Fund (440,000 DKK). All grants are restricted to LPBs PhD study and LPB is not funded by any other sources.
LPB declares no conflicts of interests.

Mikkel Brabrand: MB declares no conflicts of interests.

Thomas Strøm: TS declares no conflicts of interests.

Peter Biesenbach: PB declares no conflicts of interests.

Gerhard Tiwald: GT declares no conflicts of interests.

Larshan Perinpam: LP declares no conflicts of interests.

Appendix 4: Procedure for reporting AE and SAE

All AE or SAE will be registered within the intervention period from randomization and up to 24 hours inclusion to end of intervention, defined as 30 minutes after full termination of the noradrenaline infusion in the ED. If a patient is transferred to the ICU, by ICU staff (e.g. ICU registrar or attending), while still receiving peripheral noradrenaline, the assessment will be terminated as soon as the patient leaves the ED and treatment responsibility will be handled by the ICU staff in consideration of local guidelines. If followed by the ED staff, the assessment will be terminated as soon as the patient arrives at the ICU and patient responsibility is transferred to the ICU staff.

The clinical staff will be educated on specific SAEs mentioned in section 7.3 and will be reported within 24 hours to the Sponsor. If SUSAR is suspected, the Sponsor will handle this in accordance with section 7.4. A flow-chart is attached for the reporting pathway and refers the below mentioned AE and SAE.

Observed AE and SAE during the intervention period that will require reporting within 24 hours:

1) New onset cardiac arrhythmia (New onset tachyarrhythmia such as atrial fibrillation/flutter, ventricular tachycardia, or ventricular fibrillation) during noradrenaline infusion)
2) New onset bradycardia (Defined as pulse < 40 beats/min after and during noradrenaline infusion due to any cause)
3) Myocardial infarction (Defined by European or Danish guidelines for acute myocardial infarction[83] with confirmation from the on-call cardiologist if applicable)
4) Severe hypertension (Defined as a sudden onset blood pressure levels ≥180/110 mmHg)
5) Extravasation of noradrenaline infusion
6) Skin necrosis at infusion site
7) Acute ischemia of limb of infusion site or intestinal ischemia (Defined as
    a. Limb: New onset signs of restricted perfusion of the infusion related limb with a loss of pulse distal to the infusion site, or severely lowered ankle-pressure <50mmHg.
    b. Intestinal: Signs and symptoms of intestinal ischemia with a radiological diagnosis by imaging such as computerized tomography scan or diagnosed by surgeon during abdominal surgery).

If the clinical staff suspect any of the below possible SAE, could be due to the intervention, they should

report these within 24 hours to the Sponsor:

- Significant clinical change in plasma glucose level
- Anxiety, confusion, or psychosis
- Difficulty urinating or urinary retention
- Dyspnoea
- Cerebral haemorrhage
- Acute heart failure
- Cardiac arrest
- Stress cardiomyopathy
- Acute glaucoma

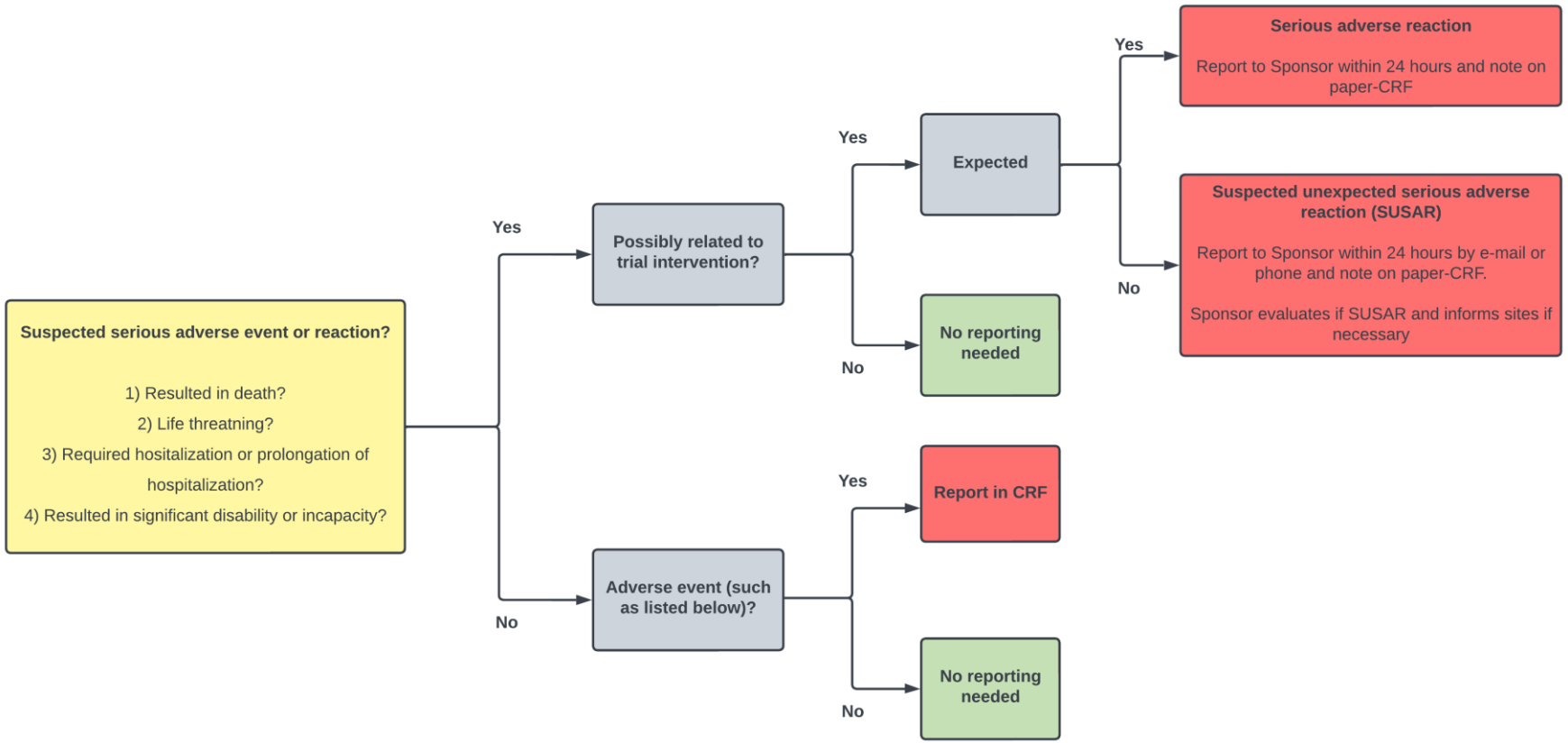
The following AE are known AE of the IMP and, for most, could be due to the disease process alone. They should be noted on the paper CRF:

- Palpitations
- Sinus tachycardia
- Nausea
- Vomiting
- Increased saliva production
- Fatigue
- Unrest
- Mild to moderate headache
- Irritability

  Sleep disorders

  Sweating

Flow chart for reporting AE, SAE or SUSAR during intervention period (24 hours)



Appendix 5: Summary of product characteristic for noradrenaline

LÆGEMIDDELSTYRELSEN
DANISH MEDICINES AGENCY

6. december 2021

PRODUKTRESUMÉ

for

Noradrenalin "Fresenius Kabi", koncentrat til infusionsvæske, opløsning

0. D.SP.NR.
32047

1. LÆGEMIDLETS NAVN
Noradrenalin "Fresenius Kabi"

2. KVALITATIV OG KVANTITATIV SAMMENSÆTNING
1 ml koncentrat til infusionsvæske, opløsning indeholder 1 mg noradrenalin base svarende til 2 mg noradrenalintartrat.

Kompositionen pr. ampul er givet i følgende tabel:

Mængden af koncentrat	Mængden af noradrenalin base	Mængden af noradrenalintartrat
1 ml	1 mg	2 mg
4 ml	4 mg	8 mg
5 ml	5 mg	10 mg
8 ml	8 mg	16 mg
10 ml	10 mg	20 mg

Hver ml indeholder 40 mikrogram noradrenalin base svarende til 80 mikrogram noradrenalintartrat, når fortyndet som anbefalet.

Hjælpestof, som behandleren skal være opmærksom på:
Dette lægemiddel indeholder 3,4 mg natrium pr. ml.
8 ml koncentrat til infusionsvæske, opløsning indeholder 27,2 mg natrium.
10 ml koncentrat til infusionsvæske, opløsning indeholder 34 mg natrium.

Alle hjælpestoffer er anført under pkt. 6.1.

3. LÆGEMIDDELFORM

Koncentrat til infusionsvæske, opløsning
En klar farveløs til svagt gul opløsning, praktisk talt fri for synlige partikler.
pH 3,0-4,0.
Osmolaritet: cirka 300 mOsm/l.

4. KLINISKE OPLYSNINGER

4.1 Terapeutiske indikationer

Noradrenalin "Fresenius Kabi" er indiceret til voksne til brug som en nødforanstaltning til genopretning af blodtryk i tilfælde af akut hypotension.

4.2 Dosering og indgivelsesmåde

Dosering

Voksne
Den endelige koncentration af infusionsopløsningen er 40 mg/liter noradrenalin base, som svarer til 80 mg/l noradrenalintartrat, når fortyndet som anbefalet i pkt. 6.6.

Nogle klinikere kan foretrække at fortynde til andre koncentrationer. Hvis der anvendes andre fortyndinger end 40 mg/l, skal beregningen af infusionshastighed tjekkes omhyggeligt før behandlingens start.

Initial infusionshastighed
Den initiale infusionshastighed bør være mellem 10 ml/time og 20 ml/time (0,16 til 0,32 ml/min). Dette svarer til 0,4 mg/time til 0,8 mg/time noradrenalin base (0,8 mg/time til 1,6 mg/time noradrenalintartrat).
Nogle klinikere kan ønske at starte med en lavere initial infusionshastighed på 5 ml/time (0,08 ml/min), svarende til 0,2 mg/time noradrenalin base (0,4 mg/time noradrenalintartrat).

Dosistitrering:
Når en infusion af noradrenalin er etableret, bør dosis titreres i trin af 0,05-0,1 µg/kg/min noradrenalin base i henhold til den observerede pressoreffekt. Der er stor individuel forskel på den dosis, der kræves for at opnå og vedligeholde normotension. Målet bør være at etablere et lavt normalt systolisk blodtryk (100-120 mm Hg) eller at opnå et tilstrækkeligt gennemsnitligt arterielt blodtryk (større end 65-80 mm Hg – afhængig af patientens tilstand).

Tabel 1. Dosistitrering af noradrenalin infusionsvæske, opløsning

Noradrenalin infusionsvæske, opløsning 40 mg/l (40 µg/ml) noradrenalin base			
Patientens vægt	**Dosering (µg/kg/min) noradrenalin base**	**Dosering (mg/time) noradrenalin base**	**Infusionshastighed (ml/time)**
50 kg	0,05	0,15	3,75
	0,1	0,3	7,5
	0,25	0,75	18,75
	0,5	1,5	37,5
	1	3	75
60 kg	0,05	0,18	4,5
	0,1	0,36	9
	0,25	0,9	22,5
	0,5	1,8	45
	1	3,6	90
70 kg	0,05	0,21	5,25
	0,1	0,42	10,5
	0,25	1,05	26,25
	0,5	2,1	52,5
	1	4,2	105
80 kg	0,05	0,24	6
	0,1	0,48	12
	0,25	1,2	30
	0,5	2,4	60
	1	4,8	120
90 kg	0,05	0,27	6,75
	0,1	0,54	13,5
	0,25	1,35	33,75
	0,5	2,7	67,5
	1	5,4	135

Behandlingens varighed og overvågning
Noradrenalin infusionen skal fortsætte indtil tilstrækkeligt blodtryk og vævsperfusion kan opretholdes uden behandling. Patienten skal overvåges nøje under behandlingen med noradrenalin.
Noradrenalin skal kun administreres af sundhedspersonale, som er bekendt med dets brug og har egnede faciliteter til tilstrækkelig overvågning af patienten.

Seponering af behandling
Noradrenalin infusionen bør gradvist nedtrappes, da pludseligt ophør af behandlingen kan forårsage akut hypotension.

Nedsat nyre- eller leverfunktion
Der foreligger ingen erfaringer med behandling af patienter med nedsat nyre- eller leverfunktion.

Ældre patienter

Generelt skal dosis vælges med forsigtighed til en ældre patient, startende i den lave ende af dosisintervallet for at afspejle en større hyppighed af nedsat lever-, nyre- eller hjertefunktion og samtidig sygdom eller anden lægemiddelbehandling (se pkt. 4.4).

Pædiatrisk population
Sikkerheden og effekten af noradrenalin til børn og unge under 18 år er ikke klarlagt. Ingen data er tilgængelige.

Administration
Administrationsvej
Til intravenøs anvendelse kun efter fortynding.
For instruktioner om fortynding af lægemidlet før administration, se pkt. 6.6.
Infusionen bør ske ved en kontrolleret hastighed enten ved hjælp af en sprøjtepumpe, en infusionspumpe eller en dråbetæller.

Noradrenalin "Fresenius Kabi" bør administreres som en fortyndet opløsning og bør administreres via et centralt venekateter.
Hvis det ikke er muligt at anvende et centralt venekateter, bør noradrenalin infusionen administreres i en stor vene, særligt en antekubital vene, for at minimere risikoen for iskæmisk nekrose (hud, ekstremiteter) (se pkt. 4.4. Ekstravasation).

Hvis muligt skal fastgørelse af kateret undgås, eftersom blokering af blodgennemstrømningen omkring røret kan forårsage stase og øget lokal koncentration af lægemidlet.

4.3 Kontraindikationer

- Overfølsomhed over for det aktive stof eller over for et eller flere af hjælpestofferne anført i pkt. 6.1.
- Hypotension som følge af nedsat blodvolumen (hypovolæmi) (se pkt. 4.4).
- Må ikke anvendes med cyclopropan og halothan bedøvelsesmidler, idet disse kan forårsage alvorlige hjertearytmier herunder ventrikelflimmer. Se pkt. 4.5 vedrørende interaktioner.

4.4 Særlige advarsler og forsigtighedsregler vedrørende brugen

Må ikke anvendes ufortyndet.

Noradrenalin er kontraindiceret hos patienter med hypotension som følge af nedsat blodvolumen med undtagelse som nødbehandling for at opretholde koronar og cerebral arterieperfusion, indtil blodvolumenerstatningsterapi kan fuldføres (se pkt. 4.3).

Noradrenalin bør kun bruges sammen med egnet blodvolumenerstatning (se pkt. 4.8).

Hvis noradrenalin administreres kontinuerligt for at opretholde blodtryk i fravær af blodvolumenerstatning, kan følgende forekomme: alvorlig perifer eller visceral vasokonstriktion, nedsat nyreperfusion og urinproduktion, ringe systemisk blodcirkulation på trods af "normalt" blodtryk, vævshypoksi og laktisk acidose.
Blodvolumenerstatningsterapi kan administreres før og/eller samtidig med dette

lægemiddel. Hvis fuldblod eller blodplasma er indiceret for at øge blodvolumen, skal det dog administreres separat (f.eks. hvis det gives samtidig, brug Y-slange og individuelle beholdere).

Forlænget administration af enhver potent vasopressor kan resultere i reduceret plasmavolumen, som skal korrigeres kontinuerligt med egnet behandling af væske-og elektrolyterstatning. Hvis plasmavolumenet ikke bliver korrigeret, kan der opstå hypotension, når noradrenalin seponeres, eller blodtrykket kan opretholdes med risiko for alvorlig perifer og visceral vasokonstriktion (f.eks. nedsat nyreperfusion) med reduktion i blodcirkulation og vævsperfusion med efterfølgende vævshypoksi og laktisk acidose og mulig iskæmisk skade; gangræn i ekstremiteterne er rapporteret i sjældne tilfælde.

Når noradrenalin infunderes, bør blodtrykket og flowhastigheden kontrolleres ofte for at undgå hypertension, som kan være associeret med bradykardi så vel som hovedpine og perifer iskæmi, herunder i sjældne tilfælde gangræn i ekstremiteterne. Ekstravasation kan forårsage lokal vævsnekrose (se nedenstående afsnit ”Ekstravasation”).
Der skal udvises særlig forsigtighed hos patienter med koronar, mesenterial eller perifer vaskulær trombose, fordi noradrenalin kan øge iskæmien og udvide infarktområdet, med mindre den behandlende læge mener, at administration af noradrenalin er nødvendig som en livsreddende procedure. Tilsvarende forsigtighed skal udvises hos patienter med hypotension som følge af myokardieinfarkt og hos patienter med angina, særligt Prinzmetal’s angina variant, diabetes, hypertension eller hyperthyroidisme.

Forsigtighed tilrådes hos patienter med omfattende dysfunktion af venstre ventrikel associeret med akut hypotension. Understøttende behandling bør initieres samtidig med diagnostisk evaluering. Noradrenalin bør vær forbeholdt patienter med kardiogent shock og refraktær hypotension, særligt til patienter uden forhøjet systemisk vaskulær resistens.

Forekomst af hjerterytmeforstyrrelser under behandlingen skal medføre en dosisreduktion.

Hjertearytmier kan opstå, når noradrenalin anvendes sammen med hjertesensibiliserende midler, og kan være mere sandsynlige hos patienter med hypoksi eller hyperkapni.

Brug af pressoraminer med kloroform, enfluran eller andre halogenerede anæstetika kan medføre alvorlige hjertearytmier. På grund af muligheden for øget risiko for ventrikel-flimmer, bør noradrenalin anvendes med forsigtighed til patienter, der får disse eller andre hjertesensibiliserende midler eller som udviser dyb hypoksi eller hyperkapni (se pkt. 4.5). Samtidig anvendelse med cyklopropan og halothan anæstetika er kontraindiceret (se pkt. 4.3).

Noradrenalin bør anvendes med ekstrem forsigtighed til patienter, der får monoaminoxidase-(MAO)-hæmmere eller inden for 14 dage efter ophør af sådan behandling og hos patienter, der får tricykliske antidepressiva, adrenerge-serotoninerge lægemidler eller linezolid, idet det kan resultere i alvorlig forlænget hypertension (se pkt. 4.5).

Der skal udvises særlig forsigtighed hos patienter med leversvigt, alvorlig renal dysfunktion, iskæmiske hjertesygdomme og forhøjet intrakranielt tryk. Overdoser eller

konventionelle doser til hypersensitive personer (f.eks. hyperthyroide patienter) kan forårsage alvorlig hypertension med voldsom hovedpine, fotofobi, stikkende retrosternal smerte, bleghed, intens svedproduktion og opkastning. Hypertension kan eventuel føre til akut lungeødem, arytmi eller hjertestop.

Forsigtighed bør udvises ved diabetes, idet det øger niveauet af blodsukker (på grund af den glykogenolytiske virkning i leveren og hæmningen af insulinfrigørelse fra bugspytkirtlen).

Ældre patienter kan især være sensitive over for virkningerne af noradrenalin, hvilket skyldes den større hyppighed af lever-, nyre- eller hjertedysfunktion og samtidig sygdom eller anden lægemiddelbehandling.

Brug af noradrenalin til børn er ikke anbefalet (se pkt. 4.2 og 5.2).

Noradrenalin bør kun anvendes af læger, som er familiære med de selektive indikationer for dets brug.
Når det er indiceret, skal egnet blod-eller væskeerstatningsterapi sammen med brug af rygleje med elevation af benene iværksættes og vedligeholdes før og/eller under behandlingen med dette produkt. Når noradrenalin infunderes, bør blodtrykket og flowhastigheden tjekkes ofte for at undgå hypertension. Derfor er det ønskeligt at registrere blodtrykket hvert andet minut fra tidspunktet, hvor administrationen starter, og indtil det ønskede blodtryk er nået og derefter hvert femte minut, hvis administrationen skal fortsætte. Flowhastigheden skal overvåges konstant, og patienten må aldrig efterlades uden opsyn, imens vedkommende får noradrenalin. Hypertension kan eventuelt føre til akut lungeødem, arytmi eller hjertestop.

Infusionen af noradrenalin bør stoppes gradvist, idet et pludseligt ophør kan medføre et katastrofalt blodtryksfald.

Vasopressor effekten (som skyldes den adrenerge virkning på blodkarrene) kan reduceres ved samtidig administration af et alfablokerende middel, mens administration af et betablokerende middel kan resultere i en reduktion af produktets stimulerende virkning på hjertet og en stigning i den hypertensive effekt (via reduceret dilatering af arteriolerne), som følge af beta-1-adrenerg stimulering.

<u>Ekstravasation</u>
Infusionsstedet bør tjekkes ofte for frit flow. Der skal udvises forsigtighed for at undgå ekstravasation af norardrenalintartrat ind i vævet, da det kan føre til lokal nekrose på grund af lægemidlets vasokonstriktive effekt. Blegning langs den infunderede vene, nogle gange uden åbenbar ekstravasation, har været tilskrevet konstriktion af *vasa vasorum* med øget permeabilitet af venevæggen, hvilket tillader en vis lækage. I sjældne tilfælde kan dette udvikle sig til overfladisk nekrose (”slough”), særligt under infusion i vener i benene hos ældre patienter eller hos patienter, der lider af obliterativ vaskulær sygdom. Hvis blegning forekommer, bør det overvejes at ændre infusionsstedet med jævne mellemrum for, at virkningerne af den lokale vasokonstriktion kan aftage.

Okklusive vaskulære sygdomme (f.eks. aterosklerose, arteriosklerose, diabetisk endartiritis, Buergers sygdom) er mere sandsynlige for at forekomme i de lavere ekstremiteter end de øvre. Undgå derfor at anvende vener i benene hos ældre patienter eller hos patienter, der lider af disse sygdomme.

VIGTIGT – antidot til ekstravaskulær iskæmi
For at hindre "slough" og nekrose i områder, hvor ekstravasation har fundet sted, bør området infiltreres så hurtigt som muligt med 10 ml til 15 ml saltvandsopløsning, som indeholder fra 5 mg til 10 mg phentolamin, et adrenergt blokeringsmiddel. En sprøjte med en tynd hypodermisk kanyle bør anvendes sammen med opløsningen, der infiltreres rigeligt over hele området, hvilket identificeres let ved dets kolde, hårde og blege udseende. Sympatisk blokade med phentolamin giver umiddelbare og iøjnefaldende lokale hyperæmiske ændringer, hvis området infiltreres inden for 12 timer. Phentolamin skal gives så snart som muligt efter, at ekstravasationen er blevet opdaget, og infusionen skal stoppes.

Natrium
Dette lægemiddel indeholder 3,4 mg natrium pr. ml, svarende til 0,17% af den WHO anbefalede maximale daglige indtagelse af 2 g natrium for en voksen.

4.5 Interaktion med andre lægemidler og andre former for interaktion

Frarådede kombinationer

- Flygtige halogenerede anæstetika: alvorlig ventrikulær arytmi (stigning i hjertets excitabilitet) (se pkt. 4.3 og 4.4)
- Imipramin antidepressiva: paroksysmal hypertension med mulighed for arytmi (hæmning af sympatomimetikas indtrængen i sympatiske fibre)
- Serotoninerg-adrenerge antidrepressiva: paroksysmal hypertension med mulighed for arytmi (hæmning af sympatomimetikas indtrængen i sympatiske fibre)
- Digitalisglykosider
- Levodopa
- Chlorpheniraminhydrohclorid, tripelennaminhydrochlorid og desipramin: signifikant stigning i toksiciteten af noradrenalin.
- Antihistaminer, idet nogle kan blokere indtaget af katekolaminer via perifert væv og øge toksiciteten af injiceret noradrenalin.

Kombinationer, som kræver forholdsregler og tæt lægeligt tilsyn (se pkt. 4.4)

- Ikke-selektive monoaminoxidase (MAO)-hæmmere: stigning i vasopressoreffekten af sympatomimetika, som almindeligvis er moderat.
- Selektive MAO-A hæmmere: ved ekstrapolering fra non-selektive MAO-hæmmere, risiko for stigning i vasopressoreffekten.
- Linezolid: ved ekstrapolering fra non-selektive MAO-hæmmere, risiko for stigning i vasopressoreffekten.

Effekten af noradrenalin kan blive forøget af guanethidin, guanadrel, reserpin, methyldopa eller tricykliske antidepressiva, amfetamin, doxapram, mazindol, rauwolfia alkaloider.

Forsigtighed er påkrævet, når noradrenalin anvendes sammen med alfa- og betablokkere, idet det kan føre til alvorlig hypertension.

Forsigtighed er påkrævet, når noradrenalin anvendes sammen med følgende lægemidler, idet de kan medføre øgede hjerteeffekter: thyroidhormoner, hjerteglykosider, antiarytmika.

Ergotalkaloider (ergoloide mesylater, ergotamin, dihydroergotamin, ergometrin, methylergometrin og methylsergid) eller oxytocin kan forstærke de vasopressoriske- og vasokonstriktive virkninger.

Samtidig administration af propofol og noradrenalin kan føre til propofol infusionssyndrom (PRIS).

Desmopressin eller vasopressin: den antidiuretiske effekt reduceres.

Lithium reducerer effekten af noradrenalin.

Noradrenalin infusionsopløsninger bør ikke blandes med andre lægemidler (med undtagelse af de nævnte i pkt. 6.6).

4.6 Graviditet og amning

Graviditet
Noradrenalin kan nedsætte perfusion i placenta og foranledige bradykardi hos fosteret. Det kan også fremkalde sammentrækninger i den gravides livmoder, som kan føre til føtal asfyksi sent i graviditeten. Disse eventuelle risici for fosteret bør derfor vejes op imod den potentielle fordel for moderen.

Amning
Det vides ikke hvorvidt dette lægemiddel udskilles i modermælk. Amning er generelt ikke tilrådeligt ved brug af noradrenalin som nødbehandling ved akut hypotension.

Fertilitet
Ingen studier er blevet udført for at indsamle fertilitetsdata for noradrenalin.

4.7 Virkninger på evnen til at føre motorkøretøj eller betjene maskiner

Ikke mærkning.
Ingen information er tilgængelig. Det anbefales derfor ikke at føre motorkøretøj eller betjene maskiner.

4.8 Bivirkninger

Tabel 2 lister bivirkninger, som er rapporteret efter behandling med noradrenalin. Størstedelen af disse data er samlet ind fra spontan rapportering. På grund af problemer med at beregne rapporteringshyppighed fra spontan rapportering, er hyppigheden for de anførte bivirkninger "Ikke kendt" (kan ikke estimeres ud fra forhåndenværende data). Disse bivirkninger er anført efter faldende hyppighed indenfor hver systemorganklasse (SOC).

Tabel 2. Bivirkninger rapporteret med noradrenalin gennem spontan rapportering

Systemorganklasse	**Bivirkning**
Psykiske forstyrrelser	Angst, søvnløshed, konfusion, svaghed, psykotisk tilstand
Nervesystemet	Forbigående hovedpine, tremor
Øjne	Akut glaukom (meget hyppig hos patienter, der er anatomisk prædisponerede med lukning af den iridocorneale vinkel).
Hjerte	Bradykardi[1], arytmi (se pkt. 4.4), ændringer i elektrokardiogram (EKG), takykardi, kardiogent shock, stress kardiomyopati, palpitationer, stigning i kontraktiliteten i hjertemusklen som følge af den beta-adrenerge effekt på hjertet (inotrop og kronotrop), akut hjerteinsufficiens
Vaskulære sygdomme	Hypertension (se pkt. 4.4), perifer iskæmi[2] herunder gangræn i ekstremiteter, nedsat plasmavolumen ved langvarig brug
Luftveje, thorax og mediastinum	Dyspnø, respiratorisk insufficiens og åndedrætsbesvær
Mave-tarm-kanalen	Kvalme, opkastning
Hud og subkutane væv	Bleghed, ardannelse i huden, blålig hudfarve, hedeture eller rødmen, hududslæt, nældefeber eller kløe
Nyrer og urinveje	Urinretention
Almene symptomer og reaktioner på administrationsstedet	Ekstravasation, nekrose på injetionsstedet

[1]Bradykardi, sandsynligvis som en refleks som følge af en stigning i blodtrykket.
[2]Iskæmi, grundet potent vasokonstriktiv virkning og vævshypoksi

Hypertension kan forekomme, som kan være associeret med bradykardi så vel som hovedpine og perifer iskæmi herunder gangræn i ekstremiteter.

Kontinuerlig administration af vasopressor for at opretholde blodtryk i fravær af blodvolumenerstatning kan forårsage følgende symptomer (se pkt. 4.4):

- Alvorlig perifer og visceral vasokonstriktion
- Nedsat blodcirkulation i nyrerne
- Nedsaturinproduktion
- Hypoksi
- Øget laktatniveau i serum

Indberetning af formodede bivirkninger
Når lægemidlet er godkendt, er indberetning af formodede bivirkninger vigtig. Det muliggør løbende overvågning af benefit/risk-forholdet for lægemidlet. Sundhedspersoner anmodes om at indberette alle formodede bivirkninger via:

Lægemiddelstyrelsen
Axel Heides Gade 1
DK-2300 København S
Websted: www.meldenbivirkning.dk

4.9 Overdosering

Symptomer
Overdosering kan føre til alvorlig hypertension, refleks-bradykardi, markant stigning i perifer resistens og nedsat minutvolumen. Dette kan ledsages af voldsom hovedpine, hjerneblødning, fotofobi, retrosternale smerter, bleghed, feber, kraftig svedproduktion, lungeødem og opkastning.

Behandling
I tilfælde af utilsigtet overdosering, som fremgår af overdreven stigning i blodtrykket, skal lægemidlet seponeres, indtil patientens tilstand er stabiliseret.

4.10 Udlevering

B

5. FARMAKOLOGISKE EGENSKABER

5.0 Terapeutisk klassifikation

ATC-kode: C 01 CA 03. Hjerteterapi, adrenerge og dopaminerge midler.

5.1 Farmakodynamiske egenskaber

Virkningsmekanisme
De vaskulære virkninger i doser, som er sædvanlige i klinisk brug, skyldes samtidig stimulering af alfa- og beta-adrenerge receptorer i hjertet samt i det vaskulære system. Bortset fra i hjertet påvirker det overvejende alfa-receptorerne.

Farmakodynamisk virkning
Dette fører til en øgning i kraften (og i fravær af vagal inhibering) og hastigheden af myokardiekontraktion. Perifer resistens øges og diastolisk og systolisk tryk øges.

Klinisk virkning og sikkerhed
Stigningen i blodtrykket kan forårsage en refleksreduktion i hjertefrekvensen. Vasokonstriktion kan føre til reduceret blodgennemstrømning i nyrer, lever, hud og glatmuskulatur. Lokal vasokonstriktion kan føre til hæmostase og/eller nekrose.

Effekten på blodtrykket forsvinder 1-2 minutter efter ophør af infusionen.

5.2 Farmakokinetiske egenskaber

Der findes to noradrenalin-stereoisomerer. I Noradrenalin "Fresenius Kabi" 1 mg/ml koncentrat til infusionsvæske, opløsning er det den biologisk aktive L-isomer, der er til stede.

Absorption
- Subkutan: ringe.

- Oral: ved oral administration bliver noradrenalin hurtigt inaktiveret i mavetarmkanalen.
- Efter intravenøs administration har noradrenalin en halveringstid i plasma på cirka 1 til 2 minutter.

Fordeling
- Noradrenalin forsvinder hurtigt fra plasma gennem en kombineret cellulær genoptagelse og metabolisme. Det passerer ikke let blod-hjernebarrieren.

Biotransformation
- Methylering ved katekol-o-methyltransferase
- Deaminering ved monoaminoxidase (MAO)
- Den endelige metabolit fra begge er 4-hydroxy-3-methoxymandelsyre
- De mellemliggende metabolitter omfatter normetanephrin og 3,4-dihydroxymandelsyre.

Elimination
Noradrenalin elimineres hovedsageligt som glucuronid- eller sulfatkonjugering af metabolitterne i urinen. Op til 16% af en intravenøs dosis bliver udskilt uændret i urinen med methylerede eller deaminerede metabolitter i frie eller konjugerede former.

Pædiatrisk population
Ingen data er tilgængelige om erfaring fra farmakokinetiske studier hos pædiatriske aldersgrupper.

5.3 Prækliniske sikkerhedsdata
De fleste af de bivirkninger, der kan tilskrives sympatomimetika, kommer af overdrevet stimulering af det sympatiske nervesystem via de forskellige adrenerge receptorer.

Noradrenalin kan nedsætte perfusion i placenta og inducere føtal bradykardi. Det kan også forårsage sammentrækninger i livmoderen og føre til føtal asfyksi sent i graviditeten.

6. FARMACEUTISKE OPLYSNINGER

6.1 Hjælpestoffer
Natriumchlorid
Natriumhydroxid (til pH-justering)
Saltsyre (til pH-justering)
Vand til injektionsvæsker

6.2 Uforligeligheder
Noradrenalin "Fresenius Kabi" må ikke blandes med andre lægemidler end dem, der er anført under pkt. 6.6.
Infusionsopløsninger indeholdende noradrenalintartrat er rapporteret uforligelige med følgende stoffer: jernsalte, alkalier og oxiderende stoffer, barbiturater, chlorpheniramin, chlorthiazid, nitrofurantoin, novobiocin, phenytoin, natriumbicarbonat, natriumiodid, streptomycin, sulfadiazin, sulfafurazol.

6.3 Opbevaringstid

2 år

Holdbarhed efter åbning af ampul:
Lægemidlet skal anvendes straks efter første åbning.

Holdbarhed efter fortynding:
Kemisk og fysisk stabilitet ved brug er påvist i 24 timer ved 25 °C. Ud fra et mikrobiologisk synspunkt bør præparatet bruges med det samme.
Anvendelse af andre opbevaringstider og -betingelser er på brugerens eget ansvar og bør ikke overstige 24 timer ved 2 til 8 °C, medmindre fortyndingen er udført under kontrollerede og validerede aseptiske betingelser.

6.4 Særlige opbevaringsforhold

Må ikke opbevares ved temperaturer over 25 °C.
Opbevar ampullen i den ydre pakning for at beskytte mod lys.

Opbevaringsforhold efter fortynding af lægemidlet, se pkt. 6.3.

6.5 Emballagetyper og pakningsstørrelser

Type I klare glasampuller indeholdende:
1 ml koncentrat (i pakningsstørrelserne 5, 10 eller 50).
4 ml, 5 ml, 8 ml og 10 ml koncentrat (hver i pakningsstørrelse af 5 eller 10).

Ikke alle pakningsstørrelser er nødvendigvis markedsført.

6.6 Regler for destruktion og anden håndtering

Kun til engangsbrug.

Opløsningen skal visuelt inspiceres før brug. Opløsningen skal ikke anvendes, hvis den har en brunlig farve, eller hvis den indeholder synlige partikler.

Fortyndingsinstruktion:
Tilsæt enten 2 ml koncentrat til 48 ml fortyndingsvæske til administration med sprøjtepumpe eller tilsæt 20 ml koncentrat til 480 ml fortyndingsvæske til administration med dråbetæller. I begge tilfælde er den endelige koncentration af infusionsvæsken 40 mg/liter noradrenalin base (hvilket svarer til 80 mg/liter noradrenalintartrat).
Andre fortyndinger end 40 mg/liter noradrenalin base kan også anvendes (se pkt. 4.2).
Hvis der anvendes andre fortyndinger end 40 mg/liter noradrenalin base, skal beregningen af infusionshastighed tjekkes omhyggeligt før behandlingens start.

Følgende fortyndingsvæsker kan anvendes:
Natriumchlorid 9 mg/ml (0,9% w/v) med glucose 50 mg/ml (5% w/v) infusionsvæske.
Glucose 50 mg/ml (5% w/v) infusionsvæske.
Natriumchlorid 9 mg/ml (0,9% w/v) infusionsvæske

Ikke anvendt lægemiddel samt affald heraf skal bortskaffes i henhold til lokale retningslinjer.

7. INDEHAVER AF MARKEDSFØRINGSTILLADELSEN

Fresenius Kabi AB
Rapsgatan 7
75174 Uppsala
Sverige

Repræsentant
Fresenius Kabi
Islands Brygge 57
2300 København S

8. MARKEDSFØRINGSTILLADELSESNUMMER (NUMRE)

64365

9. DATO FOR FØRSTE MARKEDSFØRINGSTILLADELSE

7. juli 2021

10. DATO FOR ÆNDRING AF TEKSTEN

6. december 2021

Appendix 6: Long-term follow up study

After completion of the trial, a long-term follow-up study will be conducted. The long-term follow-up will include data collection from the electronic medical records and by direct telephone contact to the patient at 1-year after inclusion of each patient. The telephone number is registered in the patients' electronic medical records, which is updated every new visit to the hospital. If the patient is not reachable by this, follow-up will be sought through their next of kin.

Before follow-up is conducted, the patients electronic medical record will be evaluated, so any deceased patients or their next of kin are not contacted. This is due to consideration of ethical implications of being contacted during a mourning period and data for the trial at 1-year is not relevant if the participant is deceased.

Evaluation of the primary outcome and other data such as transfer to elderly care home facility and need for nursing care in private home will be collected through direct contact.

Data on number of ED contacts and Charlson Co-morbidity index is collected from the electronic medical records.

Primary outcome

Patient quality of life 1 year after inclusion measured by EQ-5D-5L scale evaluated by phone call to each participant.[74,75]

- Note: The primary outcome might not be achievable in all patients, especially patients that are deceased at follow-up.

Secondary outcomes

- 1-year mortality
- Number of ED contacts and hospital admissions within 1 year

Tertiary outcomes

- Charlson Co-morbidity index by 14 days and 1 year
- Transfer to elderly care home facility within 1 year
- Time for new need for home nursing care in private home from inclusion and up to until 1 year after

- Return to work at 30 days and 1 year for people with occupational position prior to inclusion