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 2.1

09-12-2024

EU CT ID: 2023-504584-16-00

Clinicaltrials.gov ID: NCT05931601

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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

_____

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

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

_____

Mikkel Brabrand, M.D., Ph.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

_____

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

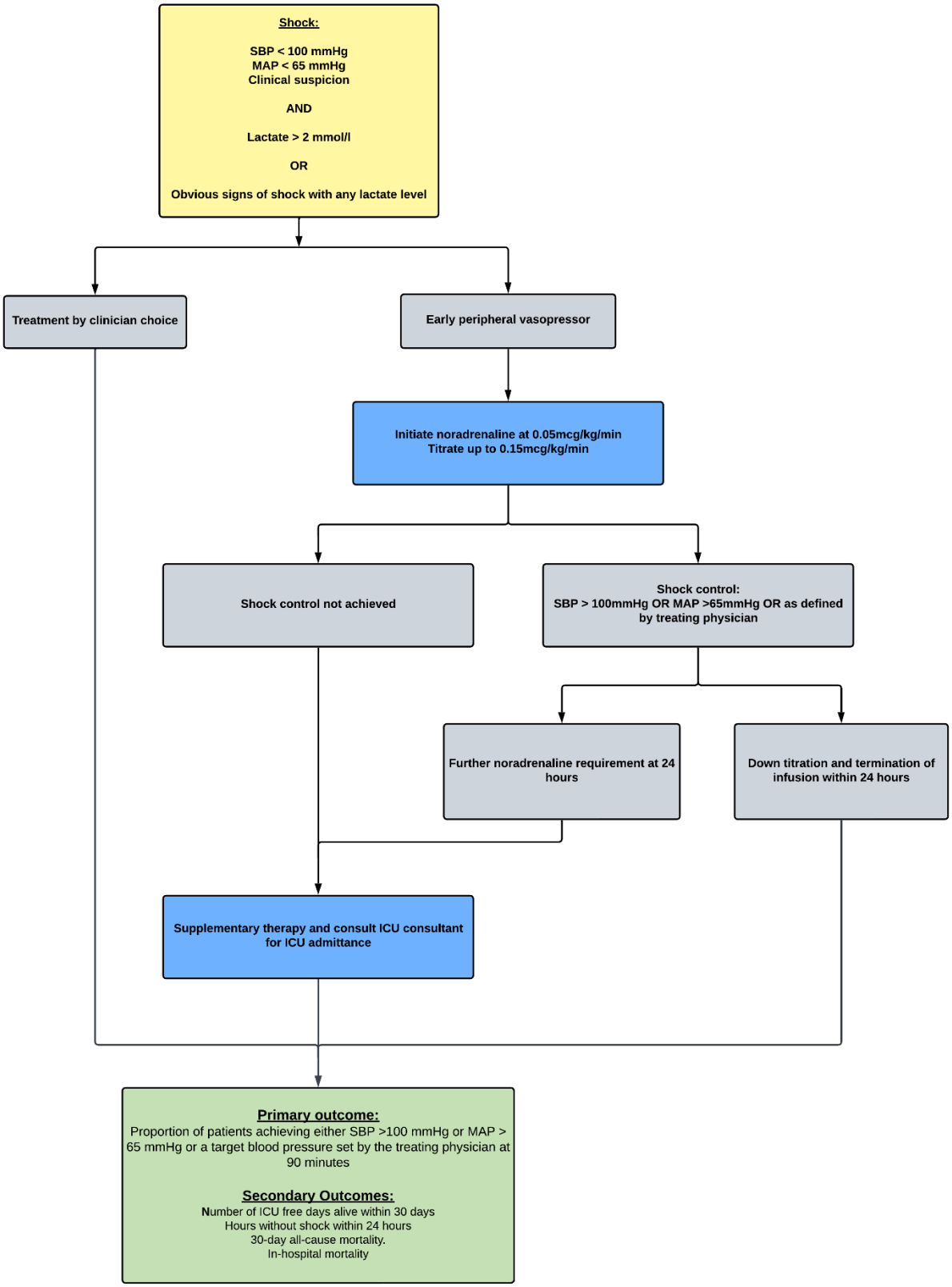
Overview

Protocol version	**Version 2.1**
Trial registrations	EU CT ID: 2023-504584-16-00 Clinicaltrials.gov ID: NCT05931601
Date of registration	13-06-2023
Start of trial	08-12-2023
Planned end of trial	31-08-2026
Planned biobank termination	31-08-2031
Funding	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 Sponsor-Investigator Clinical Professor and Senior Consultant Department of Emergency Medicine Odense University Hospital mikkel.brabrand@rsyd.dk
Contact	Lasse Paludan Bentsen Coordinating Investigator Registrar and PhD-Fellow Department of Emergency Medicine Odense University Hospital lasse.paludan.bentsen@rsyd.dk
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 2. Signs or suspicion of hypotension or shock (of any

	type such as septic, vasodilatory or hypovolemic not included in the exclusion criteria) defined as: a. SBP < 100mmHg or MAP < 65 mmHg combined with lactate > 2.0 mmol/L, b. Physician defined blood pressure for the individual patient combined with a lactate > 2.0 mmol/L c. Either SBP < 100mmHg or MAP < 65mmHg with obvious signs of shock with any lactate level evaluated by either two non-specialist physicians (e.g. registrar medical doctors) or one specialist physician. 3. Received at least 500ml of intravenous fluid before study inclusion (Including prehospital administration) 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 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. Severe organ failure outside circulatory failure that requires immediate ICU admission.

	5. Known allergy to noradrenaline. 6. Previously enrolled in the trial
Study type	Interventional study Allocation: Block Randomized (1:1) Intervention model: Parallel group Blinding: None
Target sample size	320
Recruitment status	Recruiting
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 (±15) minutes after inclusion
Key secondary outcomes	Number of ICU free days alive within 30 days Time without shock within 24 hours 30-day all-cause mortality. In-hospital all-cause mortality

Trial flow chart



Steering committee

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Trial sites and investigators

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

List of abbreviations

AE: Adverse Event

APTT: Activated Partial Thromboplastin Time

AR: Adverse Reaction

CFS: Clinical Frailty Score

CI: Cardiac Index

CO: Cardiac Output

CRF: Case Report Form

CTIS: Clinical Trial Information System

CVC: Central Venous Catheter

DBP: Diastolic Blood Pressure

DIC: Disseminated Intravascular Coagulopathy

DMP: Data Management Plan

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

INR: International Normalized Ratio

MAP: Mean Arterial Pressure

NIBP: Non-invasive Blood Pressure

OUH: Odense University Hospital

PVC: Peripheral Venous Catheter

RSI: Reference Safety Information

SAP: Statistical Analysis Plan

SBP: Systolic Blood Pressure

SAE: Serious Adverse Event

SAR: Serious Adverse Reaction

SCC: Surviving Sepsis Campaign

SD: Standard Deviation

SmPC: Summary of Product Characteristics

SOP: Standard Operating Procedure

SpO_2: Peripheral Saturation of O_2

SUSAR: Suspected Unexpected Serious Adverse Event

SV: Stroke Volume

SVR: Systemic Vascular Resistance

TMF: Trial Master File

Modifications and amendments

13-06-2023: Version 1.0

25-08-2024: 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.

15-03-2024: Version 1.2

- Updated the primary outcome for a more feasible time frame without altering the aim
- Updated secondary outcomes to me more specific
- Updated the inclusion criteria for shock

- Updated the start of trial in the overview
- Updated the background section
- Updated the table for the mixing dose of noradrenaline removing formatting errors
- Added description of sub-studies and updated the background, data collection and management and ethics section accordingly.
- Updated the funding section
- Updated appendix 2 (Clinical Frailty Scale) to the Danish version.
- Added the clinicaltrials.gov identifier
- Updated the Steering Committee to include Gerhard Tiwald, who was previously missing by formatting error
- Changed PI in Gødstrup from Larshan Perinpam to Malik Kalmriz.
- Added Bispebjerg Hospital with Jens Henning Rasmussen as Site PI.
- Updated the list of abbreviations, the trial-flow chart and the timeline
- Updated the authorship section
- Updated the intervention section in relation to intervention period to account for local organisation differences between sites'

11-11-2024: Version 2.0

- The protocol is revised with reorganization of several parts of the protocol to applicable sections following a more standard approach and clearing up certain sections that was previously placed incorrectly. Sections which was only moved are not part of the tracked changes. Sections revised, also after relocation, are tracked.
- Minor updates on grammar throughout the document.
- Internal bookmarks and cross-links is updated throughout the document.
- The document has been revised throughout to describe current Scandinavian practices instead of Danish only.
- Trial sites now refer to the CTIS registration.
- Section 1, background, added a section about mRNA analysis is to describe a new sub-study addition.
- Section 3, trial design, is updated with changes to the intervention procedures as current local practices might provide the opportunity for more secure line insertion and usage (such as midline) or better monitoring (such as arterial lines).

    - Termination of treatment has been updated to be more precise.
    - Added a subsection for mRNA from plasma and urine samples as part of the biobank sub-study.
- Section 4, setting and patient population, has new exclusion criteria added to ensure more clarity on which patients not being enrolled in the trial. Also, the inclusion criteria on fluid therapy has had the time restriction removed.
- Section 5, outcomes, revised with removal of lactate at inclusion as outcome (it's baseline data) and revision of currently planned outcomes. Specified which outcomes are considered safety outcomes.
- Section 6, pharmacovigilance, is updated to provide a more pragmatic approach that considers the different local practices in medication handling, while still ensuring the same level of patient safety as previously mandated.
- Section 6.6., added section on choice of infusion route, allowing other routes than peripheral if used in accordance with current local site practices. The previous approach to peripheral lines and safety are unchanged.
- Section 7, safety and harm, is extensively revised to implement a risk proportionate approach as part of the low-intervention trial.
- Section 9, data management, updated to be more clear and concise on how data is handled, including storage of consent forms to conform with different national regulations. Also, data collected has been revised to be more concise.
- Section 10, ethical considerations, is thoroughly updated to emphasize the planned addition of a new member state concerned. The section is now divided into a Danish and Swedish section that describes the procedures for consent for each country. The Danish procedures, even after the update, is unchanged.
- Section 11, monitoring, is updated for the Swedish GCP monitoring.
- Section 14, authorship, is revised for the co-author criteria.
- Section 17, tasks and responsibilities, is updated with description of a national coordinator in Sweden.

09-12-2024: Version 2.1

- Section 6.4 has been updated to clarify the timing of IMP mixing prior to administration and how batch numbers will be available for full traceability.

- Retracted the change of exclusion criteria 2.
- Section 7.2 added a statement for SAE reporting and how this is handled by the investigators and Sponsor.
- Section 7.7 added statement for description of safety reporting in the annual safety report.

1. Background

1.1. Shock and hypotension in 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 the (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] and amount of fluid infusion can vary greatly among patients.[12].

1.2. Evaluation of fluid therapy responsiveness in shock

Shock identification can be complex and requires several parameters including abnormal vital signs, clinical evaluation and laboratory values including interpretation of acid-base disturbances.[13-34] If a condition of shock is not evident, there is a risk of missing it and thereby fail to provide the appropriate treatment. Even though abnormal vital signs can accurately predict critical illness and mortality, they are unspecific for shock and can miss the condition in the early stages.[27,31,35-38] Evaluation of fluid responsiveness in a clinical setting can be complicated.[39,40] 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).[41] 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.[42-44] Other than MAP, these measurements are not universally available in the Scandinavian 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.[45].
In Scandinavian EDs, the most common current practice of hemodynamic monitoring is limited to regular non-invasive blood pressure measurement using oscillometric air-filled pressure cuffs.[15,16]

However, this method is close to, but not as precise as, invasive methods and risk of overestimating blood pressure during hypotensive events.[46-49] Advanced hemodynamic measuring using invasive techniques like the pulmonary artery catheter and arterial cannulation is recommended for the monitoring of critically ill patients,[50] but is not always available in the ED due to local guidelines. Newer equipment has been developed that can perform advanced hemodynamic measurements non-invasively, potentially providing clinicians with a more precise understanding of the patients' hemodynamic status without the need for invasive procedures.[51] In addition, these methods provide continuous monitoring of parameters including blood pressure and therefore provides direct data of current hemodynamic measurements when compared to current intermittent methods.[14] This equipment presents an opportunity for improved patient monitoring with far fewer complications than invasive measurements; however, the knowledge of the implications has only been sparsely studied in the ED setting.[52]

Thermography is another tool which has shown possible prognostication of mortality in patients including correlation to systematic vascular resistance, stroke volume and other parameters. However, thermography has not yet been investigated specifically in the setting of shock and for evaluating treatment response.[53-55]

1.3. Excessive fluid therapy and current practice in Scandinavian EDs

Liberal fluid resuscitation, such as more than 5 litres over a short period of time, may cause harm[56-59] and hypotension that is not responsive to fluid therapy require earlier infusion of vasopressors such as noradrenaline[60]. Previous studies evaluating a restrictive approach to fluid therapy, such as less than 2-3 litres, seems feasible in both the ED for septic patients and the ICU for septic shock.[61,62] 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.[63] The most recent study in restrictive use of fluid in septic shock, CLOVERS, did not show a benefit in this subgroup in regards to a more restrictive fluid approach compared to a more liberal approach.[64] 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[60,65], at least until the CLOVERS study was published.[64]

Current treatment of hypotensive patients in the ED varies by department, which could be due to the different organizational models in Denmark and Scandinavia.[11,12,66,67] Emergency Medicine as a

specialty was founded in Denmark 2017, though the current organization of EDs 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.[66] For the rest of Scandinavia, the implementation of Emergency Medicine as a specialty ranges back to 2006 in Sweden but is not currently a fully-fledged specialty in Norway.[68,69]

There are currently no national guidelines in Scandinavia, 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.[60] Others are written as local guidelines directed at a specific subgroups, such as patients already admitted to the ICU.

In Scandinavia, 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.[70,71] Admittance to the ICU is usually by decision of 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.[72]

For many 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.[11,12,62] 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. [11,12,58,62,63,73-77] Choice of fluid can differ by department, though normal saline and balanced crystalloids such as Ringers Acetate or Lactate, are the most commonly used.[12,78] 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.[60,74,79,80]

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.[81] 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[60,64,65,73,74,76,77,82-85].

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[60,86]. Likewise, delayed initiation of vasopressor therapy in septic shock is associated with increased mortality.[73] 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.[65,73,74,76,80,82-85,87-90] 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.[60,74,76] At the same time, complications and adverse events from use of vasopressor infusion through peripheral catheters is miniscule.[64,79,80,84,91] Other catheter choices can include the use of midline catheters, intraosseous cannulas and PICC lines, all of which has been found with at least the same level of safety as peripheral catheters or CVC.[92-96]

The CLOVERS trial[64], 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 Scandinavia.

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 fewer 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. Hyperlactatemia and lactate clearance in shock

Lactate, under physiological conditions is a normal product of cell metabolism and is cleared by the liver. Lactate production can outpace its clearance leading to an increased blood lactate levels in shock. [97 98 99 100] Elevated lactate level, usually defined as > 2mmol/L, is usually the result of anaerobe glycolysis, which is the body's response to hypoxia and decreased tissue perfusion, but also can be derived from inefficient lactate clearance, an increase in protein degradation, or increased glycolysis, i.e. increased metabolic state that is associated with hypotensive shock. [101 102 103] Even though lactate is often used as a parameter for diagnosis of sepsis and shock, patients still present with normal lactate levels in the early course of the conditions, still providing substantial mortality, though not as high as patients with hyperlactatemia.[104] Repeated measurements of serum lactate levels of critically ill patients is used in clinical practice to monitor treatment efficacy, and as a guide to optimize treatment, [105 99 100] and considered a predictor of mortality [97,106 103 107] . As of today, there are different opinions regarding the optimal timing of these measurements, however most studies agree on that they should follow the time window of the cells to normalize with the return of normal perfusion and oxygen supplies. [99] Studies suggest that measurement of lactate levels need to take place at least 2, 6, 12 and 24 hours after initializing treatment [99,106]. However, the frequency of measurements is based on the severity of the patient's condition and can therefore differ significantly. This consensus does not consider whether fluid or vasopressor therapy as primary choice influence these changes.

In addition, the choice of either arterial or venous blood gas analysis can differ between departments and countries. Even though arterial gas analysis is considered the best option for correct measurement, venous blood gas samples are well correlated for lactate measurement. [108 109 110 111 112] However, venous punctures can be a better choice than arterial, when considering risk of the procedure including less pain and technically less demanding. [109,113 110]

1.6. Biochemical, neuroendocrinal, hormonal and acid-base changes in critical illness

Critical illness and especially shock imposes widespread systemic responses in the host organism including changes in biochemical, neuroendocrinal, hormonal and coagulation processes. [5,114-121] These processes are usually vital parts of the human homeostasis and regulation but can pose risks if these intrinsic parts are malfunctioning. [114,119,120,122] The maintenance of hormonal and coagulation balance is critical in the treatment of shock, however, the understanding of how treatment using only fluids compared with supplementary noradrenalin infusion might influence these, is not fully established. [116-121,123-128]

A key component of sepsis and especially septic shock is the systemic inflammatory response syndrome where inflammatory cytokines are released resulting in an increase in Adrenocorticotropic Hormone (ACTH) concentration to improve hormone production of Adrenaline and Noradrenaline. This release results in increased blood pressure, heart rate and peripheral vasoconstriction to stabilize the cardiovascular demise. [115,117,118]

Other pathways, such as the Renin-Angiotensin-Aldosterone pathway, are part of the intrinsic regulation of blood pressure. Low blood pressure increases renal Renin release which in the end increases aldosterone release from the adrenal gland leading to renal salt and water retention. [117-120] However, pro-inflammatory mediators decrease the secretion of vasopressin, and nitric oxide, subsequently decreasing the effect that angiotensin imposes on its receptors – thereby suppressing the compensatory mechanisms to hypotension. [114,115,117,118] Coagulation parameters can be destabilized in these critical conditions and lead to severe systemic responses such as disseminated intravascular coagulation (DIC) [125-128] with excessive changes to coagulation parameters [116,122,129] while also leading to more severe disease presentations and outcomes for patients. [114,130,131] Due to the excessive impact on the organism, other factors have also been associated with both disease severity and possibly prediction of patient outcomes.[132-138] Changes are especially seen in areas such as the cytokine system and signaling pathways, including changes in endocrine system especially for septic patients.[132,134-136,138] In addition, recent research suggests a possible tool of diagnosing sepsis, which can be difficult to identify in certain situations, using flow-cytometry and immune cells.[139] Even the use of micro-RNA evaluation in patients have been suggested as a possible pathway for better treatment precision and personalized regimens for the individual patient.[140,141]

Cells exposed to high metabolic stress secrete a higher number of extracellular vesicles. These extracellular vesicles contain mRNA, which can be used to identify its parental cell type. The EV RNA fingerprint in plasma and urine samples can therefore be used to identify possible host responses to critical illness and treatment regimens.[142]
Shock can affect all these parts of the human organism and even though research have look extensively into these areas, a more profound understanding of how different treatment strategies might influence them are not yet fully established.

1.7. Rationale for studying early initiated peripheral noradrenaline in the Scandinavian 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 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 Scandinavian ED's. 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.

1.8. 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[64,86] and two studies currently recruiting patients, EVIS and ARISE.[143,144]

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

The CENSER[86] 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.[64] 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 patients), 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[144] and EVIS[143] 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 alone 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 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 (of any type such as septic, vasodilatory or hypovolemic not included in the exclusion criteria) defined as: a. SBP < 100mmHg or MAP < 65 mmHg combined with lactate > 2.0 mmol/L, b. Physician defined blood pressure for the individual patient combined with a lactate > 2.0 mmol/L c. Either SBP < 100mmHg or MAP < 65mmHg with obvious signs of shock with any lactate level evaluated by either two non-specialist physicians (e.g. registrar medical doctors) or a specialist physician.	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	In the ED if patient received necessary fluid.	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
ED vasopressor use before trial	No	Yes	Yes
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 (±15) minutes after inclusion	Days alive out of hospital at 90 days	30-day all-cause mortality

2. Trial objectives and hypotheses

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.

3. Trial Design

3.1. Overview

This study will be a pragmatic,[145,146] 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.[147]

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. 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. Interventions

Eligible patients will be randomized to receive noradrenaline starting at 0.05microg/kg/min 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.

Route of initiation is preferred to be the first available secure route of infusion, usually a peripheral venous catheter (PVC), but other methods can be used if these are standard care. Other more secure access types, such as midline catheters, central venous catheters, peripherally inserted central catheters (PICC) is also allowed if these are standard care in the individual department, as long as the line is secure and with a minimal risk of extravasation. For trial

Decision for dosing regimen can be seen in section 6.2. Dosing regime and rationale for dosing levels.

Monitoring of patients' blood pressure is recommended with at least use of 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. If department standard care includes the use of more invasive methods for blood pressure monitoring, such as arterial lines, these can be used as well without requiring concurrent use of non-invasive methods.

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 severe multi-organ failure requiring ICU treatment, 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 research staff employed either full or 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 site principal investigator.

3.3.1. 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 the ICU, is dead during the

intervention period, or consent is withdrawn. Intervention is also fully terminated if the patient is admitted to another department, except in the situation for other departments participating in the trial as described in department as described in section 3.3.3 Treatment during 24-hour intervention in other departments.

3.3.2. 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 or in a department as described in section 3.3.3 Treatment during 24-hour intervention in other departments.
Time of termination or recommencing should be clearly noted in the paper-CRF.

3.3.3. Treatment during 24-hour intervention in other departments

As local ED organisations are different across the country, not all ED's are able to treat patients for up to 24 hours during their participation in the trial. This could possibly require that patients are either quickly weaned off the noradrenaline infusion risking hemodynamic collapse, or that further treatment even after a few hours would require ICU admittance. Due to these organizational restrictions, the trial allows continuation of the treatment at same hospitals departments if the following conditions are met:

1. The department have sufficient staffing and capacity to treat and monitor the patients by at least the same minimum standard as the ED in the same hospital.
2. Staff handling the early intervention of noradrenaline prior to complete wean off or necessary post 24 hours ICU admittance are educated in the same manner in the trial as the staff in the ED.
3. The treatment protocol and standard operating procedures set by either the Sponsor or local Principal Investigator is followed as if the patients were still in the ED.
4. The investigators at the local site can be contacted and necessarily evaluate the patients

when needed in accordance with the protocol.

3.3.4. Early termination of intervention

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. Data collection and management and 10.4.4. Consent for participation. This is considered in the following situations:

1. The patient or their legally designated representative withdraws their consent to participate prior to completing the necessary intervention.
2. The patients next of kin, for countries where consent can be partly obtained from these, withdraws the consent for the patient to participate prior to completing the necessary intervention. This is only possible, if the patient are yet to provide consent for participation.
3. 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.

3.4. Control group

The control group will be receiving standard care as ordered by the treating physician according to local guidelines at the ED. Current Scandinavian practices are mentioned in section 1. Background.

3.5. 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.

3.6. Sub-studies

The VASOSHOCK trial consists of several sub-studies applicable. The long-term follow-up study will be completed for all participants in VASOSHOCK. For other sub-studies, prior to

randomization, the investigators will register which, if any, of the specific sub-studies that the participant will be enrolled in. This is to ensure that participants are not selected for specific sub-studies based on group allocation. Not all sites participate in these sub-studies.

3.6.1. Sub-study 1: 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 homecare. See Appendices , appendix 6.

3.6.2. Sub-study 2: Non-invasive hemodynamic monitoring of patients with hypotension and shock

The aim of this study is to evaluate changes in hemodynamic parameters for patients with hypotension or shock receiving peripheral vasopressor therapy compared to standard fluid resuscitation. Hemodynamic parameters will be evaluated using non-invasive measurement of MAP, stroke volume (SV), CO and systematic vascular resistance (SVR) in patients admitted to the ED and enrolled in the VASOSHOCK trial.

Patients in this sub-study will be monitored with usual non-invasive measurement of vital parameters as available in the ED as recommended in VASOSHOCK. Patients included in this sub-study will furthermore be monitored using the HemoSphere™ monitoring system with the ClearSight™ (Edwards Lifesciences, Irvine, USA)[148,149] finger cuff for non-invasive continuous hemodynamic parameters. Hemodynamic monitoring will be conducted from patient inclusion in the trial and until the end of participation in VASOSHOCK.

Data from the monitor will be extracted and stored securely in either the eCRF or the trials' secure electronic SharePoint site.

3.6.3. Sub-study 3: Lactate normalization in hypotensive shock patients

Patients included will have an arterial or venous blood puncture performed at study inclusion as required in the main trial followed by measurements at 2, 6 12, 18 and 24 hours after inclusion or until termination of the treatment period in the main trial. Each sample requires a collection of 1-

2ml of blood, i.e. between 1 and 12mL of blood in total over the course of the trial. All samples are analysed using the departments', or hospital laboratories', usual equipment for these measurements. Data are then extracted and stored following the data collection methods. eCRF prior to analysis.

3.6.4. Sub-study 4: Biochemical, neuroendocrinal, hormonal and acid-base changes in shock and hypotension

Patients included will have venous blood samples drawn at the following time points: Baseline at inclusion, at 90 minutes and at morning rounds the next day, day 2 of admittance and day 5 if the patient is still admitted.

Blood samples are drawn to be analyzed for pro- and anti-inflammatory proteins (interleukins, C-reactive protein, tumor-necrosis factor alfa), hormones for hemodynamic regulation (adrenaline, noradrenaline, renin, angiotensin), coagulation factors (INR, APTT, antithrombin, thrombocytes, d-dimer, fibrinogen, ROTEM), anabolic and catabolic hormones (cortisol, insulin, growth-hormones including the insulin-like growth factors), immune-profiling, flow-cytometry, micro-RNA, mRNA and acid-base measurements by either venous or arterial blood gas analysis.

Blood samples at baseline and the next day's morning round include blood drawn up to a total of 66.5 mL at each time-point. Blood samples at 90 minutes include blood drawn up to a total of 36.5 mL. Blood samples drawn at the morning round of day 2 and 5 each consist of up to 30 mL of blood at each time-point. In total up to 229,5mL blood collected over the course of 5 days from inclusion. Additionally, we will collect 1-2 ml of urine at each time point for additional analysis for the mRNA analysis, see section 3.6.4.1 mRNA.

Samples will be stored locally at the trial site in a secure manner before either analysis or transfer to the research biobank. Samples requiring analysis shortly after collection due to inability of storage (such a coagulation parameters or acid-base measurements) will be analyzed at each trial sites laboratories or by using point-of-care diagnostics if needed. Blood samples eligible for storage not requiring immediate analysis are either rested a room temperature or cooled using either an applicable refrigerator or ice, then centrifuged before being frozen and stored in a freezer prior to transfer to the biobank. Analysis will then be completed either locally when the necessary facilities are available in the local laboratory or analyzed in hospital department laboratories for specialized analyses (such as interleukins or micro-RNA) or at specialized research laboratories at the University of Southern Denmark (for mRNA). Samples, other than samples not possible to freeze

and store or not possible to analyze locally, are expected to be analyzed at Odense University Hospital or their regional biochemical department at Vejle Hospital for tests not possible to analyze in Odense. Samples will be prepared and stored in the research biobank prior to analysis within the timeframe of the biobank's lifespan and prior to biobank termination.

3.6.4.1. mRNA from plasma and urine samples

The mRNA from extracellular vesicles are isolated and sequenced from plasma and urine samples. Each sample requires 1-2ml of plasma or serum stored in a EDTA tube, and 1-2 ml for urine samples prior to being frozen to -80°C. Analysis is completed using the exoRNAeasy midi kit (QIAGEN, Hilden, Germany). The isolated RNA is sequenced to quantify the amount of RNA transcripts. The identified nucleotide sequence is only used to computational identify the origine gene. The RNA sequencing is completed using an Illumina platform (Illumna, San Diego CA, United States of America) and from this the specific RNA transcript quantity is identified from genes in the host, through dedicated software such as R project (https://www.r-project.org/). The RNA sequencing data are then analyzed to identify the correct quantity of extracellular vesicles of different cell types using a transcriptome deconvolution method.
Through the methods applied in the trial, the total amount of mRNA is identified, but the specific sequences are not used as part of the analysis.

3.6.5. Sub-study 5: Thermography changes in early treatment of hypotension and shock

Patients included will have thermographic images taken and bed-side measurement of the capillary refill time done at inclusion and after 90 minutes. If possible, further images and capillary refill measurements will be conducted repeatedly (maximum once every hour) while the patient is included in the intervention period of the study.
Data from the monitor will be extracted and stored securely in either the eCRF or the trials' secure electronic SharePoint site.

4. Setting and patient population

4.1. Setting

Scandinavian ED's 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.).[66,67,69,150]

The patients will be included under the regulation for "Acute drug trial" – See section 10.1.1. General considerations 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 (of any type such as septic, vasodilatory or hypovolemic not included in the exclusion criteria) defined as:
    a. SBP < 100mmHg or MAP < 65 mmHg combined with lactate > 2.0 mmol/L,
    b. Physician defined blood pressure for the individual patient combined with a lactate > 2.0 mmol/L
    c. Either SBP < 100mmHg or MAP < 65mmHg with obvious signs of shock with any lactate level evaluated by either two non-specialist physicians (e.g. registrar medical doctors) or one specialist physician.
3. Received at least 500ml of intravenous fluid before study inclusion (Including prehospital administration)
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.

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. Severe organ failure outside circulatory failure that requires immediate ICU admission.
5. Known allergy to noradrenaline.
6. Previously enrolled in the trial

4.5. Co-enrolment

The trial has no restrictions regarding co-enrolment in other trials.

5. Outcomes

5.1. 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 (±15) minutes after inclusion

5.2. Secondary outcomes

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

5.3. Tertiary and exploratory outcomes

- Proportion of patients receiving vasopressor at any point within 24 hours.
- Time to vasopressor initiation during hospitalization
- Duration of vasopressor infusion during hospitalization
- Re-admission for any reason within 30 days of inclusion
- ED length of stay
- Proportion of patients admitted to the ICU during hospitalization
- Hospital length of stay
- ICU length of stay during hospitalization
- Need for mechanical ventilation (either invasive or non-invasive ventilation) within 30-days
- Need for renal replacement therapy (continuous renal replacement therapy or dialysis) within 30-days
- Organ support-free days within 30 days (defined as mechanical ventilation, vasopressor or inotropic therapy, or dialysis).
- Amount of fluid therapy received within the first 24 hours

5.4. Safety outcomes

- Proportion of patients developing pulmonary oedema at any point within 72 hours from randomization (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 at any point within 72 hours from randomization (Defined as an absolute increase of creatinine ≥26.5μmol/L or ≥1.5 fold from baseline)
- Proportion of patients experiencing extravasation of peripheral noradrenaline
- Proportion of patients having serious complications due to extravasation (Defined as a serious complication fulfilling the criteria for a serious adverse reaction, e.g. skin necrosis necessitating surgical intervention)
- Proportion of patients experiencing overdosing due to noradrenaline infusion in the trial (Defined as severe hypertension, and reflex bradycardia suspected by the staff or investigators)
- Proportion of patients experiencing any SAE, SAR or SUSAR related to the trial intervention or procedures registered during the trial

6. Pharmacovigilance

6.1. Choice of IMP

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 is 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:

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

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.[151] However, this publication is before further knowledge on the safety of peripheral noradrenaline were published.
Recent studies[64,84,89] 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.[89] 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[86] 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[64] 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. Early vasopressor therapy for hypotension and shock. The trial details for the intervention are specified in 3.3. Interventions.
Choice of dosing regime, considering the above data, will be up to 0.15mcg/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 the IMP

Most Scandinavian 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 as well as The European 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, the trial implements the following considerations as necessary for each department:

1. The medication will be stored in accordance with local department or hospital guidelines.
2. If required locally for conducting clinical trials involving pharmacological products, the individual site is allowed to repackage the medication along with necessary utensils if deemed possible and allowing for easier handling for the clinical staff.
3. If local packaging in clinical trials is used, the box has to be easy easily identifiable as storage of medication for the trial, by either use of colours or labelling so it is distinguishable to other medications or packages. The trial name and trial identification number are clearly marked on the box, including a list of stored contents.

6.3.1. Infusion pumps

Infusion pumps used in the trial is the usual infusion pump equipment that are routinely used in each department. However, the trial mandates the use of infusion pumps that have auto-stop functions which prevents unintentional infusion of medications if the infusion sets are disconnected from the infusion pump. If no such pumps are part of standard care, the trial site has to ensure the availability of these pumps for the trial including teaching and supervision for these to the related clinical staff participating in the treatment with noradrenaline.
The infusion pumps used in the trial will be cleaned before use for another patient and are handled in accordance with local requirements.

6.4. Preparation of the IMP

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 used mixing dose used in the trial is derived from the standard guidelines from the intensive care unit and operating theatres at Odense University Hospital. As this trial is a low-intervention trial, see section 10.3 Low intervention trial, the staff will register patient weight, the dose of NA used for the individual patient, time and infusion rate during infusion of NA the paper-CRF. Batch numbers are registered as part of the local standard safety procedures for pharmaceutical products to ensure full traceability, if necessary, in cases such as recalls from the manufacturer. The IMP is mixed just prior to administration and the timing will therefore not be registered directly in the trial, but only on the labels for mixed medications in conjunction with any other registrations following local standard procedures.

6.4.1. 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		0.06mg x patient weight in kg mixed with isotonic NaCl or Glucose to a total volume of 100ml. 1ml/hour = 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 the IMP

When the intervention is terminated, either due to stabilization of the patient or admittance to the ICU, the end of treatment should be noted on the paper-CRF. These data will be transferred to REDCap with the rest of the paper-CRF data as detailed in section 9.1. Data collection methods and a total dose is calculated in the REDCap database.

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

6.6. Choice of infusion route

Any type of secure infusion route for medication infusion is allowed in the trial, if they are part of the departments standard care. This includes catheters such as midlines, PICC and central venous catheters. Intravenous access may also be used for a short period of the time prior to achieving a more secure access route.

All lines should be secure for safe infusion of the medication with a minimal risk for extravasation.[92-96] For PVC use, the trial requires that the departments follow the considerations as explained in 6.7 Insertion of peripheral catheters.

6.7. 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 of 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.

6.8. 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.[74,80,84,87,90,91,152,153]. This risk has not previously been studied in the Scandinavian 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.

6.9. Unintended overdose of noradrenaline

Noradrenaline overdose can cause 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).
Events are registered as described in 7. Safety and harm.

7. Safety and harm

7.1. Definitions

Adverse Event (AE): An untoward medical occurrence after exposure to a medicine, which is not necessarily caused by that medicine.

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

Serious Adverse Event (SAE): An untoward medical occurrence after exposure to a medicine, which is not necessarily caused by that medicine:

1. Requires inpatient hospitalisation or prolongation of existing hospitalisation
2. Results in persistent or significant disability or incapacity
3. Results in a congenital anomaly or birth defect
4. Is life-threatening
5. Results in death.

Serious Adverse Reaction (SAR): An adverse reaction that:

1. Requires inpatient hospitalisation or prolongation of existing hospitalisation, results in
2. Results in persistent or significant disability or incapacity
3. Results in a congenital anomaly or birth defect
4. Is life-threatening
5. Results in death.

Suspected Unexpected Serious Adverse Reaction (SUSAR): A serious adverse reaction, the nature, severity or outcome of which is not consistent with the reference safety information.

7.2. General considerations and risk proportionate approach

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 Scandinavian 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 trial will use noradrenaline from any manufacturer that supply this to the individual trial site. The summary of product characteristic of Noradrenalin "Fresenius Kabi" is presented in Appendix 5 as the reference safety information of the IMP, but other manufacturers equivalent noradrenaline solutions are used following local pharmaceutical storage.

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.[5-8,60,154] Noradrenaline is commonly used in different treatment settings, including in the setting of shock conditions, through peripheral lines, as mentioned in section 1.4 Early vasopressor therapy for hypotension and shock. This administration route for noradrenaline has been proven safe if handled correctly. Current evidence has established that risk of adverse events from peripheral infusion is even lower than for central venous catheters.[74,79,80,84,87,89,90,152,153,155,156]
In previous trials investigating noradrenaline as an intervention, the occurrence of SAE and SAR were significantly lower than in the standard care groups. As such, the CENSER trial had more patients in the standard care arm experiencing cardiogenic pulmonary oedema, 27.7% vs. 14.4%, RR 0.70 (0.56-0.87) and new onset cardiac arrhythmia, 20% vs. 11%, RR 0.74 (0.56-0.94) with no difference between other SAE or SAR (such as skin necrosis, limb or intestinal ischemia).[86] The CLASSIC 2 trial investigated the use of restrictive versus liberal fluid therapy regimes randomizing a total of 1554 participants in the ICU admitted for septic shock. There were no difference in SAE or SAR with the different fluid therapy approaches.[61] The CLOVERS trial had comparable 90-day mortality, with no significant difference between groups for ventricular arrhythmias.[64]

As this trial is a low-intervention trial, see section 10.3. Low intervention trial, as the infusion rate is low, see section 6.2. Dosing regime and rationale for dosing levels and as noradrenaline is not a medication with strict reporting obligations, the trial will implement a risk proportionate approach in the trial.[1,157]
The risk proportionate approach follows the current recommendations provided by the Danish Medicines Agency in accordance with the EU regulation for low intervention trials.[1,158]

This approach will specifically include registration of events and reactions related to peripheral noradrenaline infusion as well as possible overdose.[74,79,80,84,87,89,90,152,155] No other AE, AR, SAE or SAR as described in the SmPC is required for reporting to the Sponsor.
Investigators will be able to report any SAE to the Sponsor immediately, and not later than 24 hours from such occurrence, at their own discretion. This includes any SAE that the investigator deems necessary to report though not predefined as stated in section 7.3 Assessed adverse events and reactions.
The Sponsor will assess and follow up on any reports from investigators and include these in the annual safety report. All SUSARs will be registered and reported to the authorities. Apart from investigator reported events and all SUSARs, only the predefined SAE or SAR will be registered and reported to the authorities. See section 7.7 Reporting.

7.3. Assessed adverse events and reactions

7.3.1. Noradrenaline extravasation

The following will be reported to the Sponsor as a potential SAE or SAR:

- Extravasation of noradrenaline infusion
- Skin necrosis at infusion site

Extravasation of noradrenaline will be reported to the Sponsor following the procedures for SAE reporting, as this requires the investigators to report any extravasations to the Sponsor within 24-hours. The subsequent assessment from the investigator and Sponsor might downgrade the extravasation event to an adverse event or reaction, if the event does not fulfil the criteria as described in 7.1 Definitions. This is implemented so the Sponsor always have oversight on potential risk issues mandating changes in oversight or safety handling during the trial.

Skin necrosis is always considered a SAR if identified due to extravasation from the trial intervention.

7.3.2. Suspected or evident overdose of noradrenaline

The occurrence of the following will be reported to the Sponsor as a potential SAE or SAR:

- Severe hypertension in combination with severe bradycardia with suspected or evident overdose of noradrenaline (Defined as a sudden onset blood pressure levels ≥180/110 mmHg in combination with a pulse < 40 beats/min)

7.4. Suspected Unexpected Serious Adverse Events (SUSAR)

If, at any point, the investigators are suspecting and unexpected serious adverse event (SUSAR) in either group, they are obligated to report this to the Sponsor within 24-hours following the procedures described in section 7.7. Reporting.

7.4.1. Fluid treatment

Fluid administration volume as well as outcomes such as acute kidney injury and pulmonary oedema are part of the outcome assessment described in section 5. Outcomes.
As decisions on fluid treatment for both the intervention and control group is not provided by the trial or protocol, we will not evaluate any AE, AR, SAE or SAR in relation to these treatments unless the event is a possible SUSAR.

7.5. Follow-up period for adverse events and reactions

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 or applicable departments as described in 3.3.3 Treatment during 24-hour intervention in other departments. 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, or related department participating, and treatment responsibility will be handled by the ICU staff in accordance with local guidelines. If escorted by the staff administrating the intervention, the assessment will be terminated as soon as the patient arrives at the ICU and patient responsibility is transferred to the ICU staff.

7.6. Registration

Registration of SAE, SAR or potential SUSARS as described earlier will be completed by direct contact through e-mail, telephone or REDCap to the Sponsor. The Sponsor or investigator will then register these in the REDCap database if this was not initially completed.

7.7. Reporting

Any previously stated and observed SAE or SAR 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.[1,159]

Once a year, the Sponsor will submit an annual safety report to CTIS including a list of all SAE, SAR or SUSAR that have occurred on all sites. The annual safety report will describe the rules of registration and reporting of adverse events as described in this protocol. The annual safety report includes a risk-benefit assessment for all trial participant and will be included in the overall risk assessment.[1]

8. Sample size and statistical analysis plan

8.1. Sample size calculation

Our sample size calculation is based on data from the CENSER trial.[86] 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.[160] 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 current data and previous studies has not evaluated this. We therefore plan to 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, either due to the death of the participant before the follow-up, or due to unavailability of direct contact. We do not expect missing data for SAE, SAR or SUSAR.

9. 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 is entered from the paper-CRF to the e-CRF.

The investigators will enter limited data into the REDCap database prior to randomization, this includes the date and time of screening.
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 paper-CRF will include data as mentioned under section 9.4. Data to be collected. All used paper-CRF (Partly or fully completed) will be stored locally as specified under section 9.3. Data management .

9.1.1. HemoSphere™ data

Data collected using the HemoSphere™ monitor for each participant will be extracted as an electronic file for each participant will be stored in the secure SharePoint site prior to data analysis. These data will not be entered in the eCRF.

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 eCRF or sampled into the database.

9.2. Participant retention and ensuring complete follow-up

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. Vital parameters, fluid type and amount of fluid given will be captured in the eCRF extracted from the patients' medical records or monitors used during treatment.

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 national law[161,162].
Relevant parameters for patients during inclusion, exclusion and randomization will be entered bedside by the clinical staff and investigators. 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 10.4.3. Screening and enrolment. 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 which in- and exclusion criteria applied at the time of screening.

The eCRF in REDCap for all data will be handled by either the trial sites principal investigator, Coordinating Investigator, Sponsor, site investigators or their dedicated research staff by assessing

relevant information in the patient's electronic health records after study inclusion, supplemented with data extracted from relevant registers to ensure full data records in the eCRF.

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, for any reason, the paper-CRF will be stored locally in a secured locker in the department in accordance with applicable national law.
The Principal Investigator, site investigators or dedicated research staff at each trial site will enter the recorded data form the paper-CRF to the eCRF. Data will be stored for at least 25 years after study inclusion as required by the EU regulation.[1]

Blood analyses that are drawn and analysed during patient treatment are handled according to local guidelines and registration. The analysis data are entered directly into the eCRF or extracted electronically from the electronic patient record before merging to the eCRF or uploaded and stored in the secure SharePoint site.

9.3.1. Data access

Each patient will be identified in REDCap by both their CPR number and a unique trial identification number if included in Denmark. Patients included in Sweden will be identified in the REDCap database by their unique trial identification number and can be identified locally from the local trial identification log only accessible at the specific site. During the trial period, the Sponsor and Coordinating Investigator will have access to the entire database, while principal investigators, research staff 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. Access to the REDCap database is handled by individual login credentials with mandated multi factor authentication. 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 on the paper-CRF

- NA infusion dose concentration, including time of infusion start and termination and change of dosing.

9.4.2. Data collected from the registered safety reporting or electronic patient records

- Extravasation event (Time, duration, current infusion dose before termination, signs of necrosis, treatment for extravasation)
- Severe hypertension and reflex bradycardia (Time, duration and further investigation or intervention if undertaken)
- Any necessary media for continuous evaluation of the safety event (Such as photographs of extravasations)
- Any other reported SAE including potential SUSAR.

9.4.3. Data extracted from the medical records and bedside, including from patient monitors for either identification log, papir-CRF, data entry directly in the eCRF or storage in the secure SharePoint site.

- Patient social security number or applicable unique patient identifier
- Time of ED arrival including length of stay
- Time of screening
- Time of randomization
- SAE, SAR and SUSAR and all necessary registrations in relations to these
- Vital parameters up to 24-hours post randomization
- Fluid administration time, type, and volume (mL) up till 24 hours post randomization
- Time of death, if applicable, from inclusion and up to 1 year
- Re-admission from inclusion and up to 1 year
- Any admission to the ICU including length of stay of each admission within 30 days

- Hospital admittance including length of stay within 30 days
- 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) up to 72 hours post randomization
- Development of acute kidney injury up to 72 hours post randomization (Defined as an absolute increase of creatinine ≥26.5µmol/L or ≥1.5 fold from baseline)
- Development of pulmonary oedema up to 72 hours post randomization (Diagnosed and registered in the patient medical records 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[163,164] level at inclusion, or as soon as possible and at 1-year.
- Need for home nursing care or nursing home within 1-year
- Re-admission within 30 days post randomization
- Charlson co-morbidity index at ED arrival
- Co-existing conditions at trial inclusion (e.g., diabetes)
- Source of infection (if investigated, e.g. blood urine cultures)
- Patient weight and height
- Diagnoses during the ED and hospital stay, including any follow-up visits within 30 days

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

9.4.5. Data collected from the HemoSphere™ monitor

- Blood pressure (Systolic, diastolic and mean)
- Stroke volume
- Stroke volume index
- Stroke volume variation
- Pulse pressure variation
- Cardiac output
- Cardiac index
- Systematic vascular resistance
- Systemic vascular resistance index

Including specific date and time of each measurement.

9.4.6. Data collected from blood or urine samples

- Blood or urine analyses parameters measured in the sub-studies at the site laboratory, point-of-care diagnostic equipment or from samples collected in the research biobank

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. Ethical considerations

The study will be submitted to the European Medicines Agency (EMA) through CTIS and from there assessed for the applicable parts of the protocol, including ethical committee review as applicable by each member state concerned. It will be conducted under the rules for research in emergency situations as described in section 10.4.2 Trial-specific procedures. The research protocol is written in accordance with the SPIRIT guidelines and the trial results will be reported following the CONSORT guidelines.[165,166] 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[167] as well as European and National laws as applicable, including following regulations on data protection and security in accordance with GDPR regulations[1,161,162].

10.1. Research in shock and hypotension

10.1.1. 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.[5,56,60,73,77] 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.[60,65,75-77] 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.[11,12,62,75,77,154] 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.[64,86] ED initiated vasopressor therapy has been used for several years, and are therefore used to earlier initiation if deemed necessary by the treating physician in countries such as the USA, Canada and United Kingdom.[65,73,74,76,85,88,168] With the current organization and guidelines in Scandinavia, 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. This approach might not be feasible from a patient safety standpoint in countries with established usage of ED vasopressors, as this could potentially lead worse outcomes. Subsequently, it could lead to better understanding of more restrictive fluid approaches, if this therapy is lowered by the clinical staff due to earlier shock control, and therefore, possibly reduce the risk of complications from fluid overload.

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 potential benefit to the individual patient, but also considering the extensive economical costs of ICU treatment compared to treatment in the ED or other hospital departments.

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

1. Patients are acutely and critically ill, often with impaired cognition due to low blood pressure and, consequently, reduced blood perfusion to the brain. Additionally, patients in shock due to conditions such as sepsis can have bacterial toxins and inflammatory responses that may result in cognitive deficits until the underlying sepsis is controlled.[169-171]
2. Patients may experience significant distress and anxiety due to the urgency of their situation, including rapid ambulance transport and the overwhelming environment upon arrival in the ED resuscitation area, where multiple healthcare providers simultaneously perform clinical assessments and initiate emergency interventions to stabilize their condition
3. Treatment for the condition requires prompt and swift decision and initiation, limiting the possibility for obtaining informed consent from the patient extensively.
4. Patients might be awake, while not being mentally present in a way to consider the information necessary to provide consent and are at a high risk of not having any remembrance of the situation when their condition is stabilized.

Due to the necessity of research in improving both mortality and related outcomes in these conditions, there are no other patient groups, who can be used as a substitute in the research area for a similar intervention in their early stabilization period. Therefore, this trial will be conducted as an “Acute Drug Trial” where enrolment will be carried out without prior consent before inclusion,

randomization and treatment initiation. The specific procedures for obtaining consent post-randomization are described in section 10.4 Informed consent procedures.

10.1.2. Research Biobank

A research biobank will be established at Odense University Hospital, and if necessary, additionally at local sites prior to transport to Odense, to store blood samples taken in the sub-studies. This biobank is only applicable for patients included in Denmark and no samples for the biobank will be collected outside Denmark. Blood samples not directly analyzed at the trial site of the included participants, will be stored in the biobank until all samples from all participants have been collected. Hereafter the samples will be analyzed. The blood samples stored in the research biobank will be destroyed no later than 5 years after the last patient's last visit. When all samples are destroyed the research biobank will then be terminated.

10.1.3. Collection of venous or arterial blood samples

This sub-study collects blood samples with a total expected volume of 229.5 mL over 5 days different time-points in one sub-study and between 1-12ml of blood in the lactate sub-study. Collection of blood samples can pose risks during collection, both with minimal patient impact other than small hematomas, but also with small risk of more severe complications.[172,173] However, to minimize these risks, the blood samples will, if possible, be collected at the same time as routine samples are collected from the participants. This will not always be possible due to inclusion and 90 minutes samples are not necessarily drawn at the same time as routine tests, but samples collected during the next day's morning round are. Blood samples will be collected by educated personnel from the clinical biochemistry laboratories at the trial sites, or by medical students with thorough education on the technique prior to performing the procedure. If venipuncture is deemed as a possible complicated procedure due to the participants clinical status, trained staff in ultrasound guided vein and arterial puncture procedures can assist the designated staff to improve success rate.[173] All personnel collecting the blood samples will follow the local guidelines for performing the procedure, including recommendations provided by the hospital on the safety to minimize risk and harm in the participants.

Collection of blood samples in critical ill patients are a frequent procedure to either diagnose or monitor their condition. A total of 229.5 mL of blood is a small sample for the patients, about 4% of

their expected total circulating blood volume. However, this sample collection is not completed at once, but over a 5-day period, allowing the participants to be stabilized and provide time for intrinsic volume replacement, including blood and plasma components. These patients usually receive a more extensive amount of fluid replacement therapy during their treatment. The relatively small negative disadvantages are outweighed by the fact that the trial seeks to better the understanding, and thereby the treatment of a serious, and deadly condition and the impact of different treatment regimens, and possible identify if there could be any risks of more severe complications due to treatment choice.

10.1.4. Urine samples for mRNA analysis

Urine at a volume of up to a total of 10 mL collected over three time points are collected during the collection of the blood samples as described in section 10.1.3 Collection of venous or arterial blood samples. The urine is then frozen and stored in the biobank prior to analysis.

10.1.5. Non-invasive hemodynamic monitoring of patients with hypotension and shock

The HemoSphere™ ClearSight™ finger cuff is a non-invasive method for measuring hemodynamic parameters and is not associated with any harm or side effects.[52,174] These data are only collected from patients included at specific sites in Denmark.

10.1.6. Thermography changes in early treatment of hypotension and shock

Thermography poses no risk for patients during capture of the images, nor does the measurement of capillary refill time. Pictures captured consists of both normal images and thermographic images, including relevant file metadata. Images are stored securely and will only be accessible for the trials research staff. These data are only collected from patients included at specific sites in Denmark.

10.2. National regulations

Regulations regarding ethicpal requirements and enrolment of patients are following international EU law and regulations including applicable national law in participating countries.[1,159] European regulations require the trial to be authorized through the CTIS database. Data will be handled as described in section 9. Data collection and management.

10.3. Low intervention trial

A low-intervention trial under the EU Regulation No. 536/2014 is defined with the following requirements:[1]

1. The investigational medicinal products, excluding placebos, are authorised;
2. According to the protocol of the clinical trial;
    a. The investigational medicinal products are used in accordance with the terms of the marketing authorisation; or
    b. The use of the investigational medicinal products is evidence-based and supported by published scientific evidence on the safety and efficacy of those investigational medicinal products in any of the Member States concerned; and
3. The additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned.

The trial fulfills the requirements for being defined and approved as a the low-intervention trial by the following considerations:

1. Noradrenaline as an IMP is authorized in the member states and has been in routine use for decades.
2. It is used in accordance with the marketing authorization other than the use of peripheral access as route of administration instead of central venous access.
   The choice of administration route and applicability in relation to international literature and evidence for this choice, including additional risk or burden to safety is thoroughly described in section 6. Pharmacovigilance and section 7. Safety and harm.

10.4. Informed consent procedures

10.4.1. Ethical review committee

The trial will require ethical approval by the national ethical research committees as applicable by each member state.

10.4.2. 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, chapter V, article 35,[1] the patient will be enrolled in the study when the clinical and research staff screens and finds the patient applicable for inclusion in accordance with the inclusion and exclusion criteria.
The considerations for acute drug trials following the EU regulation[1] are the following:

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.

As the patients' critical condition eliminates the possibility to achieve informed consent within the timeframe of the studied intervention, and as no other patient group that can provide consent is possible to identify, this trial fulfils the above criteria set by the regulation. For a full explanation of the trial considerations in the studied patient group and how this impairs the patients ability to provide consent within a therapeutical timeframe, see section 10.1 Research in shock and hypotension.

10.4.3. 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 following the rules for transfer of personal data I accordance with GDPR.[162] 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 10.4.4. Consent for participation.

Due to the nature of the disease process, it is necessary for the investigator to receive information from 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. Feasibility, 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.

10.4.4. 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 legal representative.[1]

After the enrolment is completed, the informed consent must be obtained as quickly as possible and without unnecessary delay in accordance European and national law[1]

10.4.5. Danish procedures

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.

10.4.5.1. 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 10.4.5.4 Procedures for deceased patients. **Error! Reference source not found.**. **Error! Reference source not found.**.

10.4.5.2. 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 are 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 10.4.4. Consent for participation.

10.4.5.3. 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 or from an investigator native in the patient's own language. 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 for sites in Denmark.

10.4.5.4. Procedures for deceased patients

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. 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 national law.

10.4.6. Swedish procedures

Informed consent is to be obtained from the patient and/or from the legal representative if the patient has a legal representative (with the authority to make healthcare decisions) registered prior to study inclusion.

Consent is achieved through the following individuals:

- The patient: If not deceased before consent could be obtained.
- The legally designated representative: For consent in patients who are incapacitated and by that not in a state where they can provide legal consent for participation.

10.4.6.1. Legally designated representatives

The legally designated representative is a natural or legal person, authority or body which, according to the law is empowered to give informed consent on behalf of a subject who is an incapacitated subject or a minor. In the trial, if such legally designated representative exists, they are sought out for consent as soon as possible and without unnecessary delay after inclusion in the trial.

The legally designated representative will usually be registered in the patients' medical records and the research staff will reach out to them if they are not present in the department at the time of inclusion. If uncertain whether a patient has a legally designated representative, The Chief Guardian

Board (Överförmyndarnämnden) will be contacted as early as possible during their opening hours. The information procedures are described in section 10.4.6.2 Consent for Swedish Patient Participation.

10.4.6.2. Consent for Swedish Patient Participation

In Sweden, most patients with a registered legal representative are those with cognitive impairments (such as dementia), and since this category is often not considered for specialised intensive care therapy—an exclusion criterion in the study—a registered legal representative would likely be a rare option for obtaining informed consent. Additionally, it is important to note that in Sweden, a legal representative does not necessarily have the authority to make healthcare decisions unless this right has been specifically granted. Therefore, obtaining patient consent as soon as possible after inclusion would, in practical terms, most often be the only option.

Informed consent should be obtained as soon as the patient's condition is stabilised, treatment of the underlying conditions is initiated, and the patient’s cognitive state has improved sufficiently for them to receive, understand, and make a decision about participating in the trial. It is anticipated that most patients will be able to provide informed consent within the first 24 hours. If the patient’s cognitive condition does not allow for informed consent within the first 24 hours (the intervention period), an attempt to obtain consent will be made each weekday while the patient remains hospitalised (in any department within the hospital). Every contact and assessment of the patient’s ability to consent will be documented in the medical record. The assessment of consent capacity will be conducted by the principal investigator or their delegate, such as another investigator or sub-investigator who is a physician, or by any physician who has been informed, trained, and has signed an agreement with the principal investigator for the trial to conduct informed consent (see section 10.4.6.3 Procedures on information on the trial) In the unlikely event that the patient is unable to provide consent during hospitalisation—such as if the underlying condition and shock lead to prolonged or chronic cognitive impairment—only data collected up until discharge and 30-day outcome data will be used.. If cognitive impairment persists throughout the hospitalisation, it is unlikely that the patient will fully recover cognitive function. However, an attempt will be made to contact the patient after 6 and 12 months to reattempt informed consent and enable a 12-month follow-up.

If the patient does not accept inclusion in the study, no more data will be registered after the time of this decision. Data from before this decision will still be used in the study. If the patient explicitly requests that no data be used in the study, then none of the patient's data will be included.
In the unlikely case that the patient has a registered legal representative with the authority to assist in healthcare decisions, this person will be contacted as soon as possible. The legal representative will be identified from the patient's electronic medical records. If uncertain whether a patient has a legally designated representative, The Chief Guardian Board (Överförmyndarnämnden) will be contacted as early as possible during their opening hours.

10.4.6.3. 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 trail. 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 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 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/legal representative refuses.
Patients already included in the trial, who are not able to speak or Swedish due to insufficient language skills (e.g., immigrant with no or sparse education in Swedish) will receive the oral information with the help from an 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 Swedish for sites in Sweden.

10.4.6.4. Procedures for deceased patients

In the event of the participant's death prior to consent being obtained from either the patient or the legal representative, the investigators will make reasonable attempts to contact the legal representative, if one exists. If no registered legal representative exists, the participant's trial data will be used in the study.

10.4.7. Registration of obtained consent for participation

The consent will be signed either in paper form and stored locally in the TMF 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.
In Denmark the electronic signature can be completed either with direct signature on an electronic copy of the paper form. For patients included in Denmark consent can also be sought using the personal electronic signature validation MitID hosted by The Danish Agency for Digital Government.[175] The touch-screen written signature for electronic signature will require same security validation level as required for MitID.
In Sweden, the obtained consent will be signed on a paper form and securely stored locally at the trial site.

10.4.8. Participation in sub-studies

Participants enrolled at sites conducting any of the VASOSHOCK sub-studies will receive information in relation to the inclusion in the specified sub-studies that they are enrolled in. This information will consist of supplemental informed consent appendices describing the relevant sub-studies if not otherwise described in the general consent form. No Swedish patients participate in sub-studies outside the long-term follow-up study.
Patients enrolled in the sub-studies related to blood samples stored in the research biobank receive a separate informed consent form in addition to the main trials consent form. This includes both written and oral information on the specific studies including a separate consent form that needs to be signed in addition to the form in the main trial.

10.5. Protection of patient data

Patient data will be stored in compliance with the European and national laws regulations for handling of personal data safety including the General Data Protection Regulation (GDPR) and the

Clinical Trial Regulations.[1,2,161] All data storage will be handled for at least 25 years as mandated by the EU regulation.[1]

10.5.1. Overall procedures

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. All data access are logged at a person level and access is handled with individual login credentials and multi factor authentication.
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.

10.5.2. Specific swedish procedures

Patients enrolled in Sweden will be allocated a unique study ID number according to the enrolment procedure. A patient enrolment log will include the study ID number and the Swedish identity number, and this file will be stored separately on a secure server with two-factor authentication, accessible only to the Swedish investigators. Data will be registered in the dedicated web-based software platform REDCap, hosted at Odense University, with reference to the study ID number. The Swedish identity number will not be registered or used outside Sweden. For data handled by any other organization, inside or outside the European Union, appropriate agreements and/or documentation will be established to ensure that data processing is performed in accordance with GDPR and other relevant legislation, before any data transfer takes place.[161,162]

10.5.3. 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[161] and applicable national law. 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.

10.5.4. Insurance

Danish patients included in the trial, are covered by the Danish patient insurance. Patients included in Region Skåne, Sweden, are covered by Region Skåne's patient insurance through “Landstingens Ömsesidiga Försäkringsbolag”.

10.5.5. End of trial

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.[1,159] If the trial is ended earlier than planned, the reason for termination of the trial will be described.

11. Monitoring

11.1. Good Clinical Practice

Danish trial sites will be monitored by the regional Good Clinical Practice monitoring unit affiliated with OPEN at Odense University Hospital. Swedish study sites will be monitored by Clinical Studies Sweden. 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 and Clinical Studies Sweden.
A statement regarding data monitoring, audit, and access to trial data is mentioned in the Sponsor Statement.

11.2. Independent Data Monitoring Committee (IDMC)

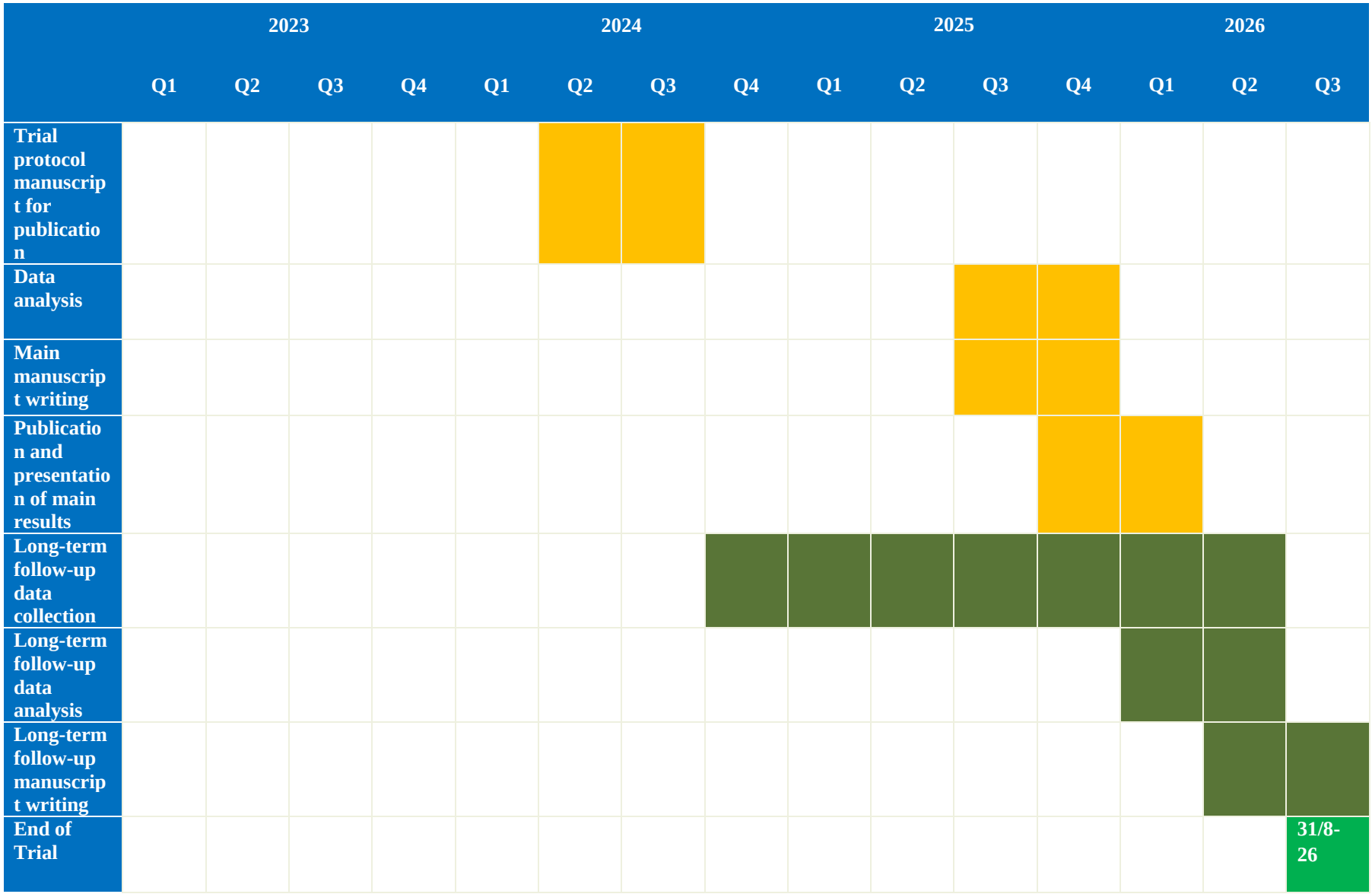
As this study is a pragmatic trial it is planned as a close resemblance to regular treatment regimens and protocols, and other studies have showed that the use of peripheral infused vasopressor therapy is a safe approach, we will not be completing an interim analysis during the trial period. Therefore,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

	2023				2024				2025				2026		
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3
Protocol development															
Submission for CTIS Part 1															
Submissions for CTIS Part 2															
Creation of data dictionary															
Randomization lists and envelopes															
Education of site personnel															
Start of trial				8/12-23											
GCP monitoring															
Enrolment and assessment															


2023
2024
2025
2026
Q1
Q2
Q3
Q4
Q1
Q2
Q3
Q4
Q1
Q2
Q3
Q4
Q1
Q2
Q3
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

	2023				2024				2025				2026		
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3
Publication and presentation															

12.1.1. Biobank Timeline

	2024	2025	2026	2027	2028	2029	2030	2031
Application for biobank								
Planning of blood sampling and biobank storage								
Collection of samples	**1/5-24**							
Analysis of samples								
GCP monitoring of biobank								
Latest destruction of samples and biobank termination								**31/8-31**

13. Feasibility

Previous data on relevant patients in a Scandinavian 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[70] 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 cohorts.

The ED at OUH therefore provides a baseline representation of the possible patient population, considering the similarity in demography's throughout Scandinavia.

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. However, the ED at OUH provides emergency treatment to a population of more than 300.000 inhabitants, including regional specialty treatment not available at regional hospitals. The patient population is therefore larger than most other trial sites expected to participate in the trial. Additional sites are therefore expected to participate in the trial during the intervention period, to further improve 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. Publication and dissemination

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 trial will be presented national and international conferences and manuscripts consisting of at least one main paper and a version of the trial protocol applicable for publication in international scientific journals. All sub-studies will at least be sought published as manuscripts in international scientific journals and if possible, presented at relevant national or international conferences and seminars. The main manuscript will adhere to the CONSORT guidelines for reporting of randomized clinical trials and any other manuscripts should adhere to the applicable recommendations for publication on the specific type of sub-study.[176] All planned results of the trial 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, including applicability in related sub-studies.[3] Members of the steering committee and the site principal investigator for sites with at least one participant inclusion in the main study, and relevant sub-studies, will take part in the authorship. Sites including more than 25 patients will receive an additional authorship for the main study paper if applicable as authors. Sites with more than 40 inclusions can have one additional author. Secondly, for the main paper, a trial consortium will be co-authored, consisting of site investigators with at least 5 individual participant inclusions. Other authorships will be handled in accordance with overall trial participation and individuals with substantial contribution in other areas than direct inclusion of patients can be eligible for authorship if they fulfil the ICMJE requirements.

15. 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, Danish regulations and national law.[1,2,159,162,177]

16. 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 (1,240,000 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. 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. National Coordinating Investigator in Sweden

The national coordinating investigator takes responsibility for the areas directly related to Sweden and works in close collaboration with the Sponsor and the Coordinating Investigator. The national coordinating investigator is responsible for any relation to trial sites in Sweden including daily management, contact to Good Clinical Practice monitor in Sweden, education of clinical staff, funding and protocol revision.

17.3. 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.

17.4. 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.

17.5. 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.

17.6. Research staff

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.

17.7. 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).

17.8. Good clinical practice unit:

See section 11.1 Good Clinical Practice.

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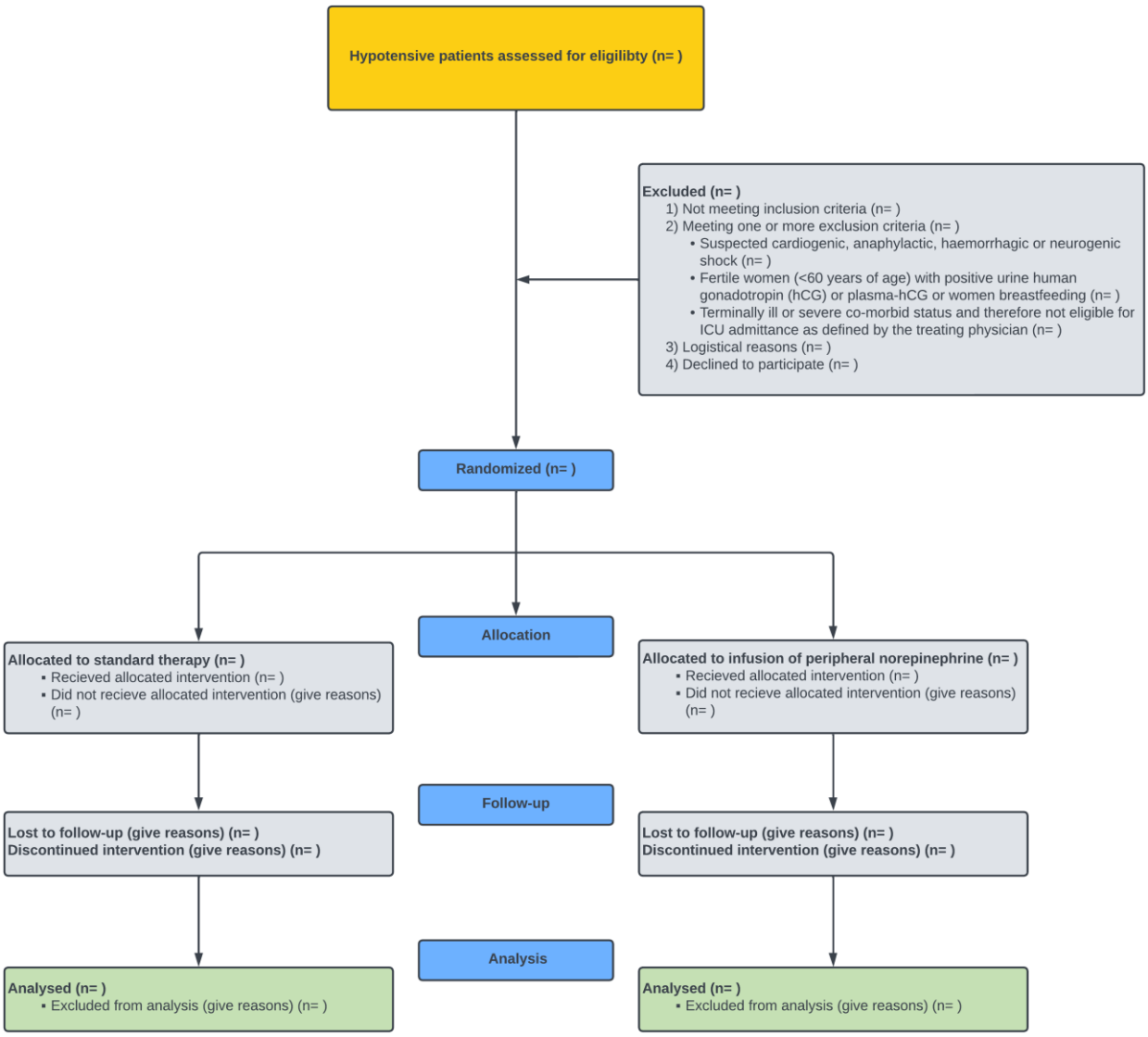
19. Appendices

Appendix 1: CONSORT diagram draft



Appendix 2: Clinical Frailty Scale (Danish)

CLINICAL FRAILTY SCALE

1 MEGET GOD FORM

Mennesker der er robuste, aktive, energiske og motiverede. De motionerer typisk regelmæssigt og er blandt dem i bedst form for deres alder.

2 GOD FORM

Mennesker **uden aktive symptomer på sygdom**, men i mindre god form end kategori 1. Ofte motionerer de eller er meget **aktive en gang imellem**, f.eks. på bestemte årstider.

3 KLARER SIG GODT

Mennesker med **velkontrollerede sygdomsproblemer**, selvom de indimellem har symptomer. Oftest er de **ikke regelmæssigt aktive** udover rutinemæssige gåture.

4 LEVER MED MEGET MILD SKRØBELIGHED

Denne kategori markerer en begyndende overgang fra komplet uafhængighed. Mennesker der **ikke er afhængige** af andre til daglige gøremål, men som ofte har **symptomer, der begrænser aktiviteterne**. En almindelig klage er at føle sig "langsom" eller træt i løbet af dagen.

5 LEVER MED MILD SKRØBELIGHED

Mennesker der ofte er **mere tydeligt langsomme**, og har behov for hjælp til **komplekse daglige gøremål** (*Instrumental Activities of Daily Living* – økonomi, transport, hovedrengøring). Typisk vil mild skrøbelighed i stigende grad hæmme indkøb, gåture alene udenfor, madlavning, medicin og begynde at begrænse let husarbejde.

6 LEVER MED MODERAT SKRØBELIGHED

Mennesker der har behov for hjælp til **alle udendørs aktiviteter** og med **at holde hus**. Ofte har de problemer med indendørs trappegang og behøver **hjælp til at gå i bad** og kan eventuelt have brug for minimal hjælp til påklædning (stikord, let støtte ved behov).

7 LEVER MED SVÆR SKRØBELIGHED

Fuldstændig afhængige af hjælp til egenomsorg, uanset årsag (fysisk eller kognitiv). Alligevel virker de stabile og ikke i høj risiko for at dø inden for ca. 6 måneder.

8 LEVER MED MEGET SVÆR SKRØBELIGHED

Fuldstændig afhængige af hjælp til personlig pleje og nærmer sig livets afslutning. Typisk vil de ikke engang komme sig efter let sygdom.

9 TERMINALT SYG

Mennesker der nærmer sig livets afslutning. Denne kategori gælder mennesker med en **forventet levetid på mindre 6 måneder**, som **ikke lever med svær skrøbelighed i øvrigt** (Mange terminalt syge mennesker kan stadig motionere helt indtil livets afslutning).

BEDØMMELSE AF SKRØBELIGHED HOS MENNESKER MED DEMENS

Mennesker med demens er oftest skrøbelige (scorer oftest minimum 5) og graden af skrøbelighed svarer som regel til graden af demens. Typiske **symptomer ved mild demens** er at glemme detaljer om en nylig begivenhed, selvom man kan huske selve begivenheden og at gentage det samme spørgsmål/ historie og social tilbagetrækning.

Ved **moderat demens** er hukommelsen for nylige begivenheder svært nedsat, selvom man kan huske gamle minder tydeligt. Man kan udføre personlig pleje med vejledning.

Ved **svær demens** kan man ikke udføre personlig pleje uden hjælp.

Ved **meget svær demens** er man ofte sengeliggende. Mange er nærmest ophørt med at tale.

DALHOUSIE UNIVERSITY

Clinical Frailty Scale © 2005-2020 Rockwood, Version 2.0 (EN). All rights reserved. For permission: **www.geriatricmedicineresearch.ca**

Rockwood K et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173;489-495.

Danish Version 2.0, 2020, translated by Anders Fournaise and Søren Kabell Nissen, University of Southern Denmark.

Appendix 3: Conflict of interests for steering committee

All conflicts of interest forms are available in the CTIS registration.

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.[163,164]

- 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