Goal-directed fluid removal with furosemide in intensive care patients with fluid overload: a randomised, blinded, placebo-controlled trial (GODIF)

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Abstract

Background: Fluid overload is a common and serious complication in patients admitted to the intensive care unit (ICU). A core element of therapy in the ICU is resuscitation with crystalloid solutions. In many patients fluid accumulates, and they become fluid overloaded. This is especially true in patients with acute kidney injury (AKI), since they often have impaired ability to excrete salt and water. Several observational studies indicate a detrimental effect of fluid overload in different clinical settings, including patients with AKI. It is unknown whether this association is causal or if the increased tendency to accumulate fluid is a marker of disease severity and thereby a higher risk of death.

Objectives: To assess the benefits and harms of goal-directed fluid removal with furosemide versus placebo on patient-important outcomes in adult ICU patients with fluid overload.

Design: An investigator-initiated, international, multi-centre, centrally randomised, blinded, stratified, parallel-group trial of furosemide versus placebo in adult ICU patients with moderate-to-severe fluid overload.

Inclusion criteria: Acute admission to the ICU, **AND** age ≥ 18 year of age, **AND** fluid accumulation corresponding to ≥ 5 % of ideal body weight estimated from fluid charts, body weight, and clinical assessment, **AND** clinical stable.

Exclusion criteria: Allergy to furosemide or sulphonamides, advanced chronic kidney disease, ongoing renal replacement therapy, anuria ≥ 6 hours, rhabdomyolysis with an indication for forced diuresis, life-threatening bleeding, acute burn injury > 10 % of the body surface area, severe dysnatraemia, severe hepatic failure, patients undergoing forced treatment, pregnancy or unable to obtain informed consent.

Intervention: The experimental intervention is goal-directed fluid removal aimed at neutral fluid status achieved as fast as possible and maintained throughout the entire ICU stay. Neutral fluid status is achieved by furosemide according to a specific algorithm to achieve the therapeutic goal (negative fluid balance ≥ 1 ml/kg/h) with a maximum infusion rate of 40 mg/h. The control intervention will be a matching placebo (saline), which will be administered according to the same goals and algorithm. Safety variables are monitored continuously and if there is an indication of inadequate circulation a resuscitation algorithm can be activated.

Outcomes: The primary outcome is days alive and out of hospital at day 90. Secondary outcomes are days alive at day 90 without life support, all-cause mortality at day 90, all-cause mortality 1 year after randomisation, and serious adverse events and reactions in the ICU.

Trial size: A total of 2 x 500 patients are required to show an 8 % improvement or worsening of the mean days alive out of the hospital at day 90, assuming a 90-day baseline mortality of 27 % (α = 0.05, two-sided and β = 0.1). We will have 90 % power to detect a drop of 8.5 %-point corresponding to a risk ratio of 0.68 on 90-day mortality.

Administrative information

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Clinical trial sites and investigators

A list of clinical trial sites and investigators will be available in the Clinical Trials Information System (CTIS) and will be continuously updated during the trial.

Methodological trial sites

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Independent Data Monitoring Committee (DMC)

DMC consist of a statistician, a trialist, and an intensivist.The members of the DMC are listed in the DMC charter in (Appendix 4).

List of abbreviations

ADQI = acute dialysis quality initiative
AKI = acute kidney injury
ANP= atrial natriuretic peptide
BUN = blood urea nitrogen
CDC = centres for disease control and prevention
CI: cardiac index
CKD = chronic kidney disease
CO = cardiac output
COPD = chronic obstructive pulmonary disease
CRF = case report form
CRO = contract research organisation
CVC = central venous catheter
CVP = central venous pressure
CRRT = continuous renal replacement therapy
DMC = Data Monitoring Committee
FB = fluid Balance
FO = fluid overload
FiO_2 = fraction of inspired oxygen
GCS = Glasgow coma scale
GFR = glomerular filtration rate
HGC = human chorionic gonadotropin
HRQoL = health-related quality of life
IBW = ideal body weight
ICU = Intensive care unit
IHD = intermittent haemodialysis
IV = Intravenously
KDIGO = kidney disease improving global outcome
LOS = length of stay
MAP = mean arterial pressure
MC = management committee
MDRD = modification of diet in renal disease
MoCA = Montreal Cognitive Assessment score
MV = mechanical ventilation
$PaCO_2$ = partial pressure of arterial carbon dioxide
PaO_2 = partial pressure of arterial oxygen
PaOP = pulmonary artery occlusion pressure
PEEP = positive end-expiratory pressure
RBF = renal blood flow

RRT = renal replacement therapy
SAE = serious adverse event
SAR = serious adverse reaction
SBE = standard base excess
SMS-ICU = simplified mortality score for the intensive care unit
SPC = summary of product characteristic
TBSA = total burned surface area

1. Introduction and background

1.1 The patient population

Fluid overload (FO) is common in critically ill patients and often as a result of fluid therapy both prior to and after admittance to the intensive care unit (ICU). Fluid therapy is a cornerstone in the treatment of many conditions including hypovolemic shock, sepsis, septic shock, and acute kidney injury (AKI). More and more evidence shows that FO is an independent risk factor for mortality in critically ill patients[1–3]. FO is also a risk factor for organ dysfunctions (lungs, cardiovascular system, gastrointestinal tract, kidney, central nervous system)[4], most frequently respiratory failure, intraabdominal hypertension/compartment, and AKI in response to increased interstitial fluid - all leading to increased mortality.

Fluid therapy leads to interstitial fluid accumulation for several reasons. A study on healthy individuals showed that only about 20 % of infused Ringers lactate stays in the intravascular compartment after 75 minutes[5]. In sepsis the inflammation causes the endothelial glycocalyx to degrade and induce capillary leakage[6]. Aggressive fluid resuscitation can cause a release of atrial natriuretic peptide (ANP) which also causes shedding of the endothelial glycocalyx with capillary leak to follow[7]. This is one of the reasons why less fluid administered during resuscitation in sepsis/septic shock is expected to stay in the intravascular compartment compared to healthy individuals.

A study in healthy volunteers has shown that infusion of 2 L crystalloid leads to renal swelling[8]. Renal interstitial volume and pressure are correlated in an exponential manner, suggesting that a “renal compartment” exists[9] and increased interstitial pressure has been linked to a decline in renal blood flow (RBF), glomerular filtration rate (GFR), and sodium excretion[10,11]. FO is a risk of intraabdominal hypertension and compartment syndrome, which could further compromise RBF and GFR and increase the risk of AKI[12–14]. Most crystalloid solutions contain supraphysiologic concentrations of sodium and chloride, high levels of which have been linked to increased morbidity, mortality, and risk of AKI[15,16].

AKI is very common with an incidence of 16 % to 57 % in intensive care units[3,17–20]. FO is associated with the development of AKI[4,21–24], and FO in patients with AKI is associated with increased mortality[25–28]. FO is a risk factor for AKI but at the same time, fluid therapy is a part of the treatment of AKI. This makes the treatment complex. Just 5 % of FO (calculated based on the weight on admission to the ICU) is shown to make a difference in outcome on mortality and renal recovery[29]. It is still unknown if FO is a marker of disease severity or a direct cause of harm. There is some evidence that de-resuscitation by fluid removal in patients with FO is important and reduces the ventilator-free days, decreases the length of stay in the ICU[30], and reduces the mortality in critical illness[31]. There is, however, no evidence for how fluid removal should be conducted.

1.2 Current treatment (or current practice)

Over the last few years, the trend in fluid therapy has changed with an increasing awareness of FO as a risk factor for morbidity and mortality. Synthetic colloids are used less frequently and there is a trend towards less liberal fluid therapy. Fluid resuscitation in the newest surviving sepsis campaign[32] is much more restrictive compared to former guidelines. The current guidelines recommend an initial fluid administration of 30 mL/kg of IV crystalloid, and that subsequent fluid administration should be guided by dynamic measures of fluid responsiveness with a goal to maintain mean arterial pressure (MAP) $\geq$ 65 mmHg and normalise lactate.

A randomised pilot trial investigated fluid therapy in patients with septic shock in a restrictive group versus a standard of care group and demonstrated how difficult minimising fluid administration can be. On day 5 after randomisation, the total fluid input in the restrictive group was 12,411 mL versus 13,687 mL in the standard of care group[33]. This is a relatively small difference after 5 days and might indicate that FO will happen in most critically ill patients treated in the ICU even when restrictive fluid administration is the intention.
Thus, FO is still a problem, and international guidelines on treating FO do not exist. The evidence for using diuretics is sparse and insufficient. The treatment of FO today is at the treating physician's discretion and the practice varies widely.

1.3 Trial interventions

1.3.1 Clinical data on the experimental intervention

Goal-directed fluid removal

The goal of fluid administration and removal in critically ill patients is to achieve circulatory stability by restoring circulating volume. No studies have specifically evaluated the optimal timing for initiating fluid removal and no randomised trials have been performed to examine the effect of goal-directed fluid removal in patients with fluid overload.

Few randomised trials have been performed with a restrictive versus a liberal fluid therapy in critical illness. The landmark FACTT trial analysed the effect of restrictive (including furosemide therapy) versus liberal fluid therapy in 1000 patients with acute lung injury. The trial showed a difference in fluid balance of 7 L between groups, but no difference in the primary outcome of 60-day mortality, however, there was significantly faster weaning from mechanical ventilation in the restrictive therapy group[34]. Subgroup analysis of patients with AKI showed increased mortality in the liberal fluid group, and further analysis revealed a beneficial effect of diuretic use when it was associated with a resolution of FO[35].

A small trial of 10 mechanically ventilated patients with AKI, has been performed to test a protocol of goal-directed fluid removal[36]. The protocol consisted of fluid removal by ultrafiltration and hourly evaluation of haemodynamic status according to predefined criteria of mean arterial pressure, cardiac index, central venous saturation, lactate, base excess, capillary refill time and peripheral

skin temperature. Patients in this study were allowed to receive vasopressor therapy with norepinephrine to a maximum of 600 µmol/hour. The investigators managed to achieve a median fluid removal of -59 (-85 to -31) ml/kg/day. This resulted in a median negative fluid balance of -10,806 mL (range: -19,788 to -7,422) over the course of 36 to 72 hours.

Both studies used invasive measurements (central venous pressure (CVP), pulmonary artery occlusion pressure (PaOP), and cardiac index (CI)) to assess haemodynamic stability. In our protocol, we will perform haemodynamic evaluation using three readily available and minimally invasive methods: lactate ≥ 4 mmol/L, mottling beyond the edge of kneecaps, and severe hypotension (MAP < 50 mmHg) resistant to vasopressors and inotropes. The cut-off value for lactate is based on the previous Surviving Sepsis Campaign guidelines[32]. Mottling of the lower extremities have been shown to be an easy-to-use, accurate, and highly reproducible method to evaluate haemodynamic adequacy in patients with septic shock[37] (Appendix 12).

In a recent pilot trial, we showed that forced fluid removal aimed at achieving a net negative fluid balance of 1 ml/kg/hour effectively reduces cumulative fluid balance by approximately 6 L after 5 days compared with standard care[38]. The rate of fluid removal in that trial was similar to the cut-off for beneficial outcomes identified by Murugan et al. in an observational study of ultrafiltration rates in critically ill patients with AKI and fluid overload above 5 % bodyweight[39]. This observational study showed that patients with a fluid removal rate > 25 ml/kg/day had better survival than patients receiving fluid removal at a rate < 25 ml/kg/day.

Overall, these data could suggest that a net fluid removal rate of 1 ml/kg/hour is optimal and effective in treating fluid accumulation in critically ill patients.

Trial drug - Furosemide

Furosemide is a widely used and well-known diuretic. The registered indications include oedema, hypertensive crisis, forced diuresis, and acute and chronic renal insufficiency. Furosemide can either be administered orally or intravenously as an intermittent bolus or continuous infusion. Several trials have examined the efficacy and safety of bolus therapy versus a continuous infusion in patients with acute decompensated heart failure. A systematic review from 2005 evaluated 8 trials including 258 patients and found a small increase in urine output (271 ml/24 hours) when continuous infusion was used. Furthermore, there were significantly lower rates of ototoxicity in the infusion group. However, the trials were small and heterogeneous and no definitive recommendations were made[40]. A later randomised trial (The DOSE-trial) included 308 patients in a two-by-two design. Patients were assigned to high (2.5 x usual daily loop diuretic dose) or low dose (equal to usual daily loop diuretic dose) intravenous furosemide administered as either intermittent bolus every 12 hours or as a continuous infusion. The trial showed no difference in efficacy or safety outcomes, however, there was a trend towards lower cumulative dose and fewer adverse events with continuous infusion[41]. Similar results have been shown in smaller trials of critically ill patients[42,43].

A systematic review with meta-analysis of 20 randomised trials and 2608 patients looked at the impact of furosemide on mortality and the requirement for renal replacement therapy in AKI. They found that furosemide had neither an impact on mortality nor the requirement for renal replacement therapy (RRT)[44].

The Danish Summary of Product Characteristics (SPC) provides no guidelines for continuous infusion doses. However, recommendations are available at www.uptodate.com[45]. These suggest that treatment of patients with severe kidney injury (eGFR < 30 mL/min) is initiated with a loading dose of 40-80 mg furosemide followed by an infusion rate of 20-40 mg furosemide/h.

The treatment regime for furosemide in the present trial consists of an initial bolus of 5 to 40 mg at the treating physician's discretion followed by an infusion starting at 20 mg/h and titrated to effect or a maximum dose of 40 mg/h (this equals a maximum daily dose of 960 mg/24 h). This regime is well within the safety limits described in the SPC with a maximum daily dose of 1500 mg. The adverse effects and complications of furosemide are well-known and well-described in the SPC. The main reactions include electrolyte disturbance, hypotension, agranulocytosis, pancreatitis, arrhythmia, circulatory collapse, seizures, Stevens-Johnson syndrome, toxic epidermal necrolysis, hearing impairment, and anaphylaxis. Monitoring of serious adverse reactions (SARs) is described in 8.2.

1.3.2 Clinical data on the escape intervention

Initiation of renal replacement therapy (RRT)

The optimal time for initiation of RRT remains controversial. A systematic review with meta-analysis of randomised clinical trials suggests that early initiation of RRT compared with standard initiation of RRT in critically ill patients with AKI provides no advantage[46]. Large multicentre randomised clinical trials must clarify the optimal time for starting RRT.

The Kidney Disease Improving Global Outcome (KDIGO) guidelines state that “RRT should be initiated emergently when life-threatening changes in fluid, electrolyte, and acid-base balance exist” (not graded), and when “… the broader clinical context, the presence of conditions that can be modified by RRT and trends of laboratory tests rather than single blood urea nitrogen (BUN) and creatinine thresholds, should be considered when starting RRT” (not graded).

In summary, we believe that current evidence does not favour either early or late RRT and we find it reasonable to perform a trial where patients receive RRT according to conservative indications as suggested in the KDIGO guidelines (described in 6.3).

Furosemide

Extra furosemide can only be used when the criteria for the use of escape are fulfilled. The maximum daily dose of furosemide must not exceed 1500 mg which is the recommended maximum dose (section 6.3).

1.4 Risks and benefits

Rapid resolution of severe fluid overload and restoration of normal fluid status will normalise the structure of organs suffering from interstitial oedema, facilitate oxygen delivery and functionality and potentially improve patient outcomes.

Fluid removal with diuretics may lead to a reduction in total body sodium and chloride. If the rate of fluid removal exceeds the refilling capacity of compensatory fluid movement from the extravascular compartment, the preload can be compromised, and the mean arterial pressure declines. This might lead to progressive loss of renal function due to a reduction in RBF and GFR or other non-renal effects.

Currently, no established guidelines exist to assist clinicians in managing fluid overload in the ICU. Additionally, there is a lack of robust evidence supporting a specific treatment regimen. As a result, treatment practices are left to the discretion of the attending physicians, leading to considerable variation in the use of diuretics across hospitals, regions, and countries. In this trial, both interventions represent common clinical practices, and we do not consider either treatment arm to pose an elevated risk compared to standard of care.

1.5 Ethical justification and trial rationale

Observational studies have indicated that FO is an independent predictor of death in critically ill patients. No trials have been performed to establish whether this correlation is causative or due to confounding and few studies have investigated the outcomes of fluid removal in critically ill patients with FO. We have performed a pilot trial showing that our proposed experimental treatment is effective in treating FO[38]. The present trial will be an important step in the process of improving the care of critically ill patients.

The individual patient will benefit from participating in the trial as it will increase the focus on the patient and the administered treatment. The treating team will be required to assess the patient's fluid status and adjust the treatments given several times a day, with a specific focus on mitigating fluid accumulation. In addition, future patients will benefit from the results of the GODIF trial, regardless of the outcome. The findings will help inform better strategies for fluid removal when necessary and potentially improve overall fluid management in clinical practice.

We find the trial justified since it is believed that it is in the interests of the individual patient, future patients, and society, to establish if goal-directed fluid removal in patients with FO will reduce mortality. If goal-directed fluid removal with furosemide is not superior to placebo, future patients will benefit from this trial by avoiding the potential harm of receiving furosemide.

The trial will be conducted according to the applicable laws in the participating countries for clinical trials conducted in emergency situations (including the European [EU] and Danish legislation). It is important to initiate immediate intervention after FO is diagnosed to investigate if goal-directed fluid removal can improve patient outcomes. Delayed initiation of the intervention might lead to further

fluid accumulation with a potential risk of harm. The trial provides an instant focus on fluid balance which will benefit all participating patients. The patients eligible for enrolment in the GODIF trial cannot consent due to critical illness, organ dysfunctions, need for life support, and administration of strong opioids and /or sedatives (anaesthetic). Therefore, we cannot delay enrolment and need to use the consent procedures for emergency research. Informed consent will be obtained according to the applicable laws in the participating countries with the enrolment and informed consent procedures handled by trained trial staff with thorough insight into the protocol.

The process of informed consent may differ in the participating countries. All applicable regulations in the participating countries will be followed including the European legislation. The Danish consent procedure is described in Appendix 5. In Sweden informed consent must be obtained from the patient before enrolment in the trial and not from next of kin or a legal representative as described in Appendix 17.

1.6 Trial conduct

The GODIF trial will be conducted in compliance with the published trial protocol, the regulation (EU) No 536/2014 of the European Parliament and of the Council, the Helsinki Declaration in its latest version[47], the good clinical practice (ICH-GCP) guidelines[48] General Data Protection Regulation, and national laws in the participating countries. We have written the protocol in accordance with the SPIRIT 2013 Statement[49]. Enrolment will start after approval from the Ethical committees, Medicine Agencies, Data Protection Agencies, and other relevant authorities. The trial was registered at ClinicalTrial.gov (NCT04180397) before the first enrolment. No substantial deviations from the protocol will be implemented without prior review and approval of the regulatory authorities except in case of urgent safety measures where it may be necessary to eliminate an immediate hazard to the trial participants. In such cases, the deviations will be reported to the authorities within 7 days.
In case of serious breaches which are likely to affect safety and the rights of a subject, or the reliability and robustness of the data generated in the clinical trial the Member States will be notified through the EU portal without delay within 7 days.
In case of unexpected events which might affect the benefit-risk balance of the clinical trial (not unexpected serious adverse reactions), the Sponsor will inform all Member States concerned through the EU portal within 15 days.

We will publish the approved protocol at www.cric.nu and submit a manuscript with the main points of the protocol including a description of the design, rationale, and statistical analysis plan to a peer-reviewed medical journal.

2. Trial objectives and purpose

The objective of the GODIF trial is to assess benefits and harms of goal-directed fluid removal with furosemide versus placebo on patient-important outcomes in adult ICU patients with fluid overload.

The experimental intervention will use furosemide infusion to achieve and maintain a neutral cumulative fluid balance.

We hypothesise that goal-directed fluid removal with furosemide will result in an increased number of days alive and out of hospital after 90 days compared to placebo treatment with normal saline.

3. Trial design

3.1 Trial design

The GODIF trial is an investigator-initiated, multi-centre, centrally randomised, blinded, stratified, parallel-group trial of furosemide bolus and infusion versus placebo (0.9 % saline) in adult ICU patients with moderate to severe fluid overload. Participant allocations will be stratified by AKI, simplified mortality score for the intensive care unit (SMS-ICU) score > 25, and trial site.

3.2 Randomisation

Patients fulfilling the inclusion criteria will be randomised if they do not fulfil any exclusion criterion. The 1:1 randomisation will be centralised and web-based according to the computer-generated allocation sequence list, stratification variables (AKI, SMS-ICU score > 25 and by study centre), and varying block size at Copenhagen Trial Unit (CTU). The allocation sequence list will exclusively be known to the data manager at the CTU and will be unknown to the investigators to allow immediate and concealed allocation to one of the two intervention groups. Each participant will be allocated a unique patient-screening number.

3.3 Blinding

Furosemide is contained in liquid form in a vial. The placebo drug will be isotonic saline and will be contained in identical vials. The solution of furosemide 10 mg/ml is colourless and cannot be visually distinguished from isotonic saline. All vials will contain the same volume (50 ml). The trial medication will be labelled with a white label, which is identical for the furosemide and the placebo vials. The label will contain the required information about the trial drugs including the date of expiration. The top of the placebo and furosemide vials will be identical. All vials have a unique identification number. Allocation of medicine is performed through a web-based medicine program and the unique vial numbers. The trial drugs are produced in Denmark at Capital Region Pharmacy in Herlev and distributed to all trial sites in Denmark and one trial site in The Netherlands. Only trial sites in Denmark and the Netherlands have the approval to use the Danish-produced trial drugs.

All other participating countries must use furosemide 10mg/ml and NaCl 0.9% with marketing authorisation available at the participating sites and perform blinding on-site as with a third unblinded party preparing and delivering the trial drug to the participant. This is described further in Appendix 16. After the trial has been transferred to the CTIS portal in 2024, no further countries will have the opportunity to approve and conduct the trial with the Danish-produced trial drug.

The allocated trial medication will be blinded to the clinical staff caring for the patient, relatives, the patient, investigators, and outcome assessors, and only the data manager can unblind the allocated intervention. The statistical analysis of the trial will be blinded with the intervention groups coded as, e.g. X and Y. Based on this blinded analysis, two conclusions will be drawn: one assuming X is the experimental group and Y is the control group, and one conclusion assuming the opposite. Two abstracts will be written and accepted by the author group. After this, the blinding will be demasked.

The members of the independent Data Monitoring Committee (DMC) will remain blinded unless 1) they request otherwise or 2) the interim analysis has provided strong indications of one intervention being beneficial or harmful compared to the other.

3.3.1 Unblinding

Individual patients: The intervention may be unblinded for individual patients if deemed necessary by the clinician or investigator for the treatment and safety of the patient. In case of a suspected unexpected serious adverse reaction (SUSAR) the sponsor (or delegated party) shall break the blinding in order to judge the 'expectedness' and therefore the occurrence of a SUSAR (according to the summary of product characteristics) and report it to the authorities accordingly. See section 8 for more information.

If the intervention for an individual patient needs to be unblinded during the trial, the treating physician must contact the coordinating investigator who will be available around the clock: The coordinating investigator will establish contact with the Copenhagen Trial Unit (CTU) if needed, from where information of allocated trial intervention (furosemide or placebo) is available. This can be done by telephone at all hours, any day of the week.

The entire trial: Unblinding the entire trial will be performed confidentially via the data manager to the steering committee at the end of the statistical analysis and after two approved abstracts are written, one assuming X is the intervention while the other assuming Y is the intervention. The author will be blinded to the allocation until the abstracts are approved by the steering committee. If the interim analysis gives strong indications of one intervention is beneficial or harmful, the trial will be unblinded before planned.

3.4 Participant timeline

All adult patients will be screened daily during their ICU admission. We will strive to enrol patients as soon as they fulfil the inclusion criteria. Patients who develop fluid accumulation of 5 % or more of their ideal body weight and are clinically stable will be eligible for inclusion unless any exclusion criteria are present. Informed consent will be obtained from a trial guardian prior to inclusion in the trial or according to national legislation.

The participants will continue the allocated intervention until they are discharged from the ICU or die in the ICU with a maximum of 90 days after randomisation. If the participant is readmitted to the ICU

within 90 days after randomisation and has fluid accumulation, she/he will continue the allocated intervention.

We will follow the participants for 1 year after randomisation and identify 1-year survivors in hospital registries. We will contact all 1-year survivors approximately 2 weeks after to assess health-related quality of life and cognitive function by telephone interview. The trial sites will be responsible for registration of 90-day mortality, length of stay in the ICU within 90 days, and 1-year follow-up inclusive registration of 1-year mortality.

3.5 End of trial

The trial will end when the last patient enrolled has completed 1-year follow-up (last-patient-last visit). We will contact the last patient approximately 2 weeks after the 1-year follow-up date and allow 3 months of response time for the 1-year follow-up.

4. Selection of participants

All patients admitted or planned to be admitted to an active trial site will be considered for participation. Patients will be eligible if they comply with the inclusion criteria and not any of the exclusion criteria listed below. We aim to include the patients as early as possible.

4.1 Inclusion criteria

All the following criteria must be fulfilled:

- Acute admission to the ICU.
- Age ≥ 18 years of age.
- Fluid accumulation estimated according to the daily fluid charts, the cumulative fluid balance, development in body weight, and clinical examination (oedemas, congestion on X-ray, e.c.t) – see Appendix 15 for more details
  If possible, all fluids administered before admission to the ICU are to be included in the calculation of cumulative fluid balance. The minimum fluid accumulation on inclusion is 5 % of ideal body weight. The following calculation for minimum fluid accumulation must be used:

Height in cm	Male	Female
< 159 cm	+ 3.0 L	+ 2.5 L
160 – 169 cm	+ 3.5 L	+ 3.0 L
170 – 179 cm	+ 4.0 L	+ 3.5 L
180 – 189 cm	+ 4.5 L	+ 4.0 L
> 190 cm	+ 5.0 L	+ 4.5 L

- Clinical stability assessed by the clinicians (minimum criteria: MAP > 50 mmHg and maximum infusion of 0.20 microgram/kg/minute of noradrenaline and lactate < 4.0 mmol/L).

4.2 Exclusion criteria

- Known allergy to furosemide or sulphonamides.
- Known pre-hospitalisation advanced chronic kidney disease (eGFR < 30 mL/minute/1.73 m^2 or chronic RRT).
- Ongoing RRT.
- Anuria for ≥ 6 hours.
- Rhabdomyolysis with indication for forced diuresis
- Ongoing life-threatening bleeding as these patients need specific fluid/blood product strategies.
- Acute burn injury of more than 10 % of the body surface area as these patients need a specific fluid strategy.
- Severe dysnatraemia (p-Na < 120 or > 155 mmol/l) as these patients need a specific fluid strategy.
- Severe hepatic failure as per the clinical team.
- Patients undergoing forced treatment.
- Fertile women (women < 50 years) with positive urine human chorionic gonadotropin (hCG) or plasma-hCG.
- Consent not obtainable as per the model approved for the specific trial site.

We will not exclude patients enrolled in other interventional trials unless the protocols of the two trials collide; we present the rationale for this in Appendix 7. Co-enrolment agreements will be established with the sponsor/investigator to maintain an updated list of trials approved for co-enrolment (Appendix 7).

4.3 Participant discontinuation and withdrawal

The procedure of handling withdrawal of consent from a participant will follow national regulations and will be described for each participating country.

4.3.1 Discontinuation and withdrawal at the choice of the participant or the proxy

The Danish procedure:

A participant, who no longer wishes to participate in the trial, can withdraw his/her's consent at any time without need of further explanation, and without consequences for further treatment. For incompetent participants, consent can be withdrawn at any time by the person(s), who has given the proxy consent. To limit the amount of missing data, we will collect as much data as possible from each participant. Therefore, if possible, the investigator will ask the participant or the proxy to which extent the withdrawal includes:

- Receiving the trial intervention only - allowing for all data registration and follow-up.

OR

- Receiving the trial intervention AND further registration of daily data and/or follow-up.

Only the participant can demand the deletion of already registered data and only if the participant did not consent previously. If so, all data will be deleted, and a new participant will be enrolled to obtain the full sample size.

4.3.2 Discontinuation and withdrawal at the choice of the investigator

A participant may have the intervention stopped by the clinician or investigator at any time, if:

- The participant experiences intolerable adverse reactions or events (including SAR or SUSAR) suspected to be related to the trial intervention.
- The clinicians in conjunction with the coordinating investigator decide it to be in the interest of the participant.
- The participant after inclusion is subject to involuntary hospitalisation, the intervention will stop.

In these participants, the collection of data and the follow-up will continue, and the participant will remain in the intention-to-treat population.

4.3.3 Discharge to another ICU

Participants who are discharged to another ICU will be regarded as discharged from the ICU unless the receiving ICU is an active GODIF trial site. If so, the participant will continue the allocated intervention at the new trial site until discharge from ICU. Participants referred to intermediate or step-up/step-down beds cared for by ICU staff trained in the GODIF trial protocol will continue the allocated intervention.

5. Selection and trial sites and personnel

5.1 Trial sites and setting

Trial sites will be ICUs in Europe and potentially in Canada and Australasia where we explore the possibilities for collaboration.

5.2 Trial personnel

All doctors caring for patients in participating ICUs will be eligible to enrol patients in the trial and all clinicians caring for patients will be eligible to care for and perform the interventions in the trial participants. All participating ICUs will receive written and oral instructions about the trial procedures. A 24-hour hotline will be available for trial-related questions.

6. Trial interventions

The intervention period for both intervention arms is the entire ICU stay to a maximum of 90 days.

6.1 Experimental intervention

Goal-directed fluid removal aimed at neutral fluid status achieved as fast as possible and maintained throughout the entire ICU stay.

Neutral fluid status is achieved by:

- Initially, furosemide bolus of 5 to 40 mg (0.5 to 4 mL) iv. is given according to the physician's discretion. The bolus must be followed by continuous infusion starting with 20 mg/h (2 mL/h) titrated according to the GODIF algorithm to achieve the therapeutic goal with a maximum infusion rate of 40 mg/h (Appendix 14).
- Neutral fluid status or resolution of fluid accumulation must be assessed by the treating clinical team. The assessment must be based on the cumulative fluid balance (if available), daily fluid balance, development in body weight and clinical examination (Appendix 15) and documented in the patient file.

The therapeutic goal of the experimental investigation is guided by an average 8-hour negative fluid balance ≥ 1 ml/kg/h and safety variables indicating inadequate circulation (lactate ≥ 4 mmol/L, MAP < 50 mmHg, or mottling beyond the kneecaps). The ideal body weight (IBW) can be used to calculate the wanted negative fluid balance. This is especially relevant in obese patients where the goal for fluid removal can be unrealistic high if actual body weight is used. A simple formula for the calculation of IBW is height in cm – 100 = IBW for men, and height in cm – 105 = IBW for women.

The following goals for minimum fluid removal per 24 hours according to the participant's height should be used:

Height in cm	**Male**	**Female**
< 159 cm	-1300 mL/24 hours	-1200 mL/24 hours
160 – 169 cm	-1500 mL/24 hours	-1400 mL/24 hours
170 – 179 cm	-1700 mL/24 hours	-1600 mL/24 hours
180 – 189 cm	-1900 mL/24 hours	-1800 mL/24 hours
> 190 cm	-2000 mL/24 hours	-1900 mL/24 hours

The efficacy of fluid removal is evaluated and adjusted according to the therapeutic goal every eight hours (e.g. 06:00, 14:00, and 22:00 or similar), while the safety variables are evaluated continuously.

Resuscitation: During goal-directed fluid removal, physiologic response is monitored with three variables indicating inadequate circulation. These are:

- Plasma lactate ≥ 4.0 mmol/L.

OR

- Hypotension (MAP < 50 mmHg) resistant to inotropes and/or vasopressors.

OR

- Mottling beyond the edge of kneecaps (mottling score > 2).

Mottling and MAP are monitored continuously, and lactate is measured routinely, most often every 4-6 hours.

If one or more signs of inadequate circulation are present the resuscitation algorithm is started:

- Pause fluid removal (pause furosemide/placebo infusion).
- Optional crystalloid fluid bolus of 250-500 ml.
- Re-evaluate circulatory status within 30 minutes.
- Repeat re-evaluation and optional fluid therapy until adequate circulation (lactate < 4 mmol/L, MAP > 50 mmHg and no mottling beyond kneecaps) has been achieved.
- Restart the trial drug at a reduced dose when the patient is assessed stable enough to tolerate fluid removal by the clinical staff.
- Continue titration of the trial drug according to effect and algorithm.

Discontinuation of fluid removal: When neutral fluid status has been achieved, fluid removal with furosemide is paused or adjusted to match the daily fluid input aiming at maintaining neutral fluid status throughout the ICU stay.

6.2 Control intervention

The control intervention will be a placebo in the form of isotonic saline, which will be administered according to the same algorithm described above (Appendix 14). The intervention period will be identical to the intervention period of the experimental intervention.

6.3 Escape protocol for all randomised participants:

Open-label furosemide should only be used in case of:

- Hyperkalaemia (p-K > 6.0 mmol/L).
- Respiratory failure (P/F-ratio < 26 kPa (200 mmHg)) and pulmonary oedema if treating physician has a suspicion of respiratory deterioration is due to fluid overload.

Escape doses must be described in the medical record. The maximum dose of furosemide per 24 hours is 1500 mg and must not be exceeded. The infusion of the trial drug must continue in case of indication of escape open-label furosemide.

RRT may only be started when life-threatening complications in fluid, electrolyte, and acid-base balance occur:

- Hyperkalaemia (p-K > 6.0 mmol/L).
- Respiratory failure (P/F-ratio < 26 kPa (200 mmHg)) and pulmonary oedema if treating physician has a suspicion of respiratory deterioration is due to fluid overload.
- Severe metabolic acidosis attributable to AKI (pH < 7.20 and SBE < -10 mmol/L).

- Persistent AKI > 72 h (defined as: oliguria/anuria or s-creatinine has not declined to 50% from peak value).

If RRT is initiated the trial drug must be paused. When the indication for RRT is not present and RRT is stopped, the trial drug must be restarted and titrated according to the algorithm (See 6.1) if the participant still has FO.

Fluid therapy: Fluid administration at the discretion of the treating clinicians, using haemodynamic goal of choice.

6.4 Co-interventions for all randomised participants

To be used in both intervention groups.

Fluid therapy: standard of care meaning fluid administration as per clinicians' discretion.

Diuretics:

- Loop-diuretics: Patients who normally use loop-diuretics can continue their normal dose of oral diuretic or this can be replaced by an IV dose of furosemide equivalent to 50% of their normal dose.
- Thiazide and aldosterone antagonist diuretics: Can be continued as oral medication but must not be replaced by IV diuretics. Can also be used for the treatment of hypernatraemia as per clinical site.
- Open-label diuretics: If open-label diuretics are required, only furosemide must be used to ensure comparability between intervention arms.

Blood pressure: A target MAP of 65 mmHg using noradrenaline is recommended in both intervention arms during the entire ICU stay.

Types of fluid:

- IV fluids given for circulatory impairment: Only isotonic crystalloids are to be used as per the Scandinavian guideline for fluid resuscitation[50].
- Fluids given to substitute overt loss: isotonic crystalloids are to be used. If large amounts of ascites are tapped, then human albumin may be used.
- Fluids used for dehydration: water or isotonic glucose should be used.
- Fluids used for electrolyte disturbances: fluids should be chosen to substitute the specific deficiency, including water in the case of severe hypernatremia.
- Blood products are only to be used on specific indications including severe bleeding, severe anaemia according to the national guideline [51] (haemoglobin < 4.3 mmol/L, < 4.7 mmol/L in patients with chronic heart disease, or < 5.6 mmol/L in patients with acute coronary syndrome) and prophylactic in case of severe coagulopathy.

6.5 Concomitant interventions

Severe sepsis and septic shock are frequently associated with FO, and the management of sepsis should be performed according to the updated international sepsis guidelines[32]. We recommend the following for trial sites:

- Relevant antibiotics and source control for the infection.
- Noradrenalin as vasopressor.
- Renal replacement therapy as described in 6.3 (escape protocol for all randomised participants).

6.6 Criteria for modification of interventions for a given trial participant

The clinical team may at any time violate the protocol if they find it to be in the best interest of the participant. We will have a GODIF trial hotline to enable discussion around the clock between the clinicians caring for trial participants and the GODIF trial team regarding protocol-related issues.

6.7 Assessment of participant compliance

Protocol violations will be monitored according to the following criteria:

- Participants receiving other diuretics than allowed according to this protocol during their ICU admittance.
- Participants receiving open-label furosemide on other indications than described under escape (section 6.3) during ICU admittance.
- Initiation of RRT, without the presence of RRT escape indications (section 6.3).

7. Outcomes

7.1 Primary outcome

Days alive and out of hospital at day 90 after randomisation.

7.2 Secondary outcomes

1. All-cause mortality at day 90 after randomisation.
2. Days alive at day 90 without life support (vasopressor/inotropic support, invasive mechanical ventilation, or renal replacement therapy).
3. All-cause mortality at 1 year after randomisation.
4. Number of participants with one or more serious adverse events (SAEs) and serious adverse reactions (SARs) to furosemide as described in section 8.1 and 8.2.
5. HRQoL 1-year after randomisation measured using the EuroQoL (EQ)-5D-5L and EQ-VAS scores. Participants who have died will be assigned the lowest possible scores.
6. Participants' subjective assessment of their quality of life since the treatment in the ICU (unacceptable/neutral/acceptable)
7. Cognitive function 1 year after randomisation as assessed by the Montreal Cognitive Assessment (MoCA 5 min) score.

Several of the secondary outcomes above are composite outcomes. The single components of these will also be analysed and presented in a supplement to the primary publication.

7.3 Process variables

- Mean cumulative fluid balance in mL after 3 days censoring at discharge
- Number of days with escape medicine (furosemide) per participant

8. Safety

8.1 Definitions

In the GODIF trial, we will use the definitions bellow[52]

Adverse event (AE): any undesirable medical event occurring to a participant during a clinical trial, which does not necessarily have a causal relationship with the intervention.

Adverse reaction (AR): any undesirable and unintended medical response related to the intervention occurring to a participant during a clinical trial.

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

Serious adverse reaction (SAR): any adverse reaction that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

Suspected unexpected serious adverse reaction (SUSAR): any suspected adverse reaction which is both serious and unexpected (the nature or severity of which is not consistent with the information available to date).

8.2 Risk and safety issues in the current trial

The trial participants will all be ICU patients for whom all adverse events and reactions are documented routinely in the patient health record (i.e. ICU notes, charges and laboratory reports). We will record in the eCRF the occurrence of SAEs and SARs on all trial days in the ICU for all included patients and report SAEs and SARs as outcome measures.

Fluid removal with the use of furosemide is a common intervention in the ICU, and the participants in this trial will not have a significantly different risk profile than other ICU patients. Known adverse events to fluid removal include ischaemic events and/or progression of organ failure. The patients will be in the ICU and closely monitored by clinical staff who can intervene at any time. To assess the frequency and consequence of these events we will register ischaemic events and AKI.

The following are considered SAEs to fluid removal:

At least one episode of either of the following observed in the ICU:

- Ischaemic events are defined as either:
    - Cerebral ischaemia is defined as any form of cerebral ischaemia on a CT- OR MRI scan.
    - Acute myocardial ischaemia is defined as a participant with acute myocardial infarction (ST-elevation myocardial infarction or non-ST elevation myocardial infarction) or unstable angina pectoris according to the criteria in the clinical setting in question (e.g. elevated biomarkers, ischaemic signs on ECG and clinical presentation) AND the participant received treatment as a consequence of this (reperfusion strategies (PCI/thrombolysis) OR initiation/increased antithrombotic treatment).
    - Intestinal ischemia defined as ischaemia verified by endoscopy OR open surgery OR CT-angiography.
    - Limb ischemia defined as clinical signs AND need of open/percutaneous vascular intervention, amputation OR initiation/increased antithrombotic treatment.
- A new episode of severe acute kidney injury defined as modified KDIGO stage 3[53]: A 3 times increase in baseline p-creatinine or increase in p-creatinine to ≥ 354 µmol/L or use of renal replacement therapy (any form).
- New-onset atrial fibrillation in a participant who never has been diagnosed with atrial fibrillation before.

SARs to furosemide:
The experimental group will receive furosemide as part of the protocol. We have identified the SARs to furosemide in the Summary of Product Characteristics (SPCs) as listed below. The adverse reactions to the furosemide not registered in the GODIF trial are listed in Appendix 3 including the reasoning.

- Severe electrolyte disturbance (p-K < 2.5 mmol/L, p-Na < 120 mmol/L, p-Cl < 90 mmol/L).
- Aplastic anaemia.
- Agranulocytosis.
- Pancreatitis.
- Circulatory collapse leading to cardiac arrest.
- Seizures because of furosemide-induced low calcium or magnesium.
- Steven Johnson syndrome.
- Toxic epidermal necrolysis.
- Hearing impairment/loss.
- Anaphylaxis.

SARs to isotonic saline:

The maximum dose of placebo (isotonic saline) in 24 hours is 100 mL. No SARs are likely associated with such a small volume of intravenous isotonic saline.

8.3 Assessment of adverse events and reactions

8.3.1 Timing

In all participants, we will assess the occurrence of SAEs and SARs on all trial days the participants spend in ICU to a maximum of 90 days. All SAEs and SARs must be reported within 24 hours to the Sponsor or his delegate.

8.3.2 Classification of an event

We will register the occurrence of all the SAEs and SARs listed in section 8.2 and report them in the final report. For any other SAR, the investigator and sponsor must assess, if it is related to trial drug according to the summary of product characteristics (Appendix 3). If the SAR/SAE is unexpected and not covered in section 8.2 or appendix 3, the investigators will report them if they are adjudicated to be related to the trial intervention to the Sponsor or his delegate within 24 hours. If such a SAE/SAR is deemed related to the intervention by the Sponsor and the investigator, it will be considered a SUSAR and reported as such (section 8.4). In the case of SUSAR, the trial medication will be demasked. If a SUSAR is still reasonable after demasking, a report will be conducted describing onset and end of event, severity, relation to the intervention, the action taken and the outcome.

8.4 Reporting

Any serious adverse reaction/event not covered in the secondary outcomes (defined in 8.2) adjudicated to be related to the trial intervention by the investigator, will be reported within 24 hours to the Sponsor or his delegate. If deemed a SUSAR by the Sponsor, it will be reported to the EudraVigilance database within 7 days after the report of a life-threatening or fatal SUSAR. No later than 8 days after the reporting, the Sponsor will report on the Sponsor's and the investigator's follow-up action to the life-threatening or fatal SUSAR. Any other SUSARs will be reported to the EudraVigilance database no later than 15 days from when the Sponsor is informed.

Once a year, the Sponsor will submit an annual safety report describing all SARs and the safety of the trial subjects that have occurred at the European sites (sites under CTIS) during the previous year.

Completion of the trial will be notified in CTIS by the Sponsor (no later than 90 days thereafter).
In addition, we will report all SAEs and SARs defined in 8.2 as outcome measures and all SUSARs in the final trial report and the results of the trial. The results of the trial will be reported as soon as possible and no later than one year after the trial has ended, and a summary of the results will be submitted to the CTIS portal.

9. Procedures, assessments, and data collection

9.1 Inclusion procedure

Daily fluid balance is routinely calculated at the end of the 24-hour observation day.

9.1.1 Screening

All clinically stable patients acutely admitted to participating ICUs are eligible for screening. Fluid accumulation is estimated to be ≥ 5 % of ideal body weight according to the daily fluid charts, cumulative fluid balance, weight changes, and clinical examination (Appendix 15). If possible, all fluids administered before admission to the ICU are included in the calculation of cumulative fluid balance. The estimation of fluid accumulation must be documented in the inclusion note in the patient file.

The minimum fluid accumulation on inclusion is listed below according to height:

Height in cm	Male	Female
< 159 cm	+ 3.0 L	+ 2.5 L
160 – 169 cm	+ 3.5 L	+ 3.0 L
170 – 179 cm	+ 4.0 L	+ 3.5 L
180 – 189 cm	+ 4.5 L	+ 4.0 L
> 190 cm	+ 5.0 L	+ 4.5 L

9.1.2 Procedures for informed consent

Participants will be enrolled after consent according to national regulations. The procedure for Danish participants is described in Appendix 5. In Sweden, informed consent must be obtained from the patient prior to enrolment in the trial (Appendix 17).

9.2 Data collection

9.2.1 Methods

Data will be obtained from the participant's hospital files and national/regional/hospital registers (source data as defined per site, region, and country) and by participant survey/interview and entered in the web-based eCRF by trial investigators or their delegates. For participants transferred from a trial ICU to a non-trial ICU, data related to the outcomes will be collected according to national practice e.g. investigator contact to the non-trial ICU or health care registers.

9.2.2 Timing

All variables are defined in Appendix 2.

Screening:

- Patient identification number.
- Sex.
- Inclusion criteria:
    - Age.
    - Admitted or planned to be admitted to the ICU.
    - Is the patient clinical stable?
    - Fluid accumulation in mL.
    - Which measurements are used in assessing the fluid accumulation?
        - Cumulative fluid balance Y/N
        - Daily fluid balance Y/N
        - Weight Y/N
        - Clinical examination Y/N
    - Actual body weight (kg).
    - Height (meters).
- Exclusion criteria:
    - Allergy towards furosemide or sulphonamides.
    - Advanced chronic kidney disease.
    - Ongoing renal replacement therapy.
    - Anuria for > 6 hours.
    - Rhabdomyolysis with indication for forced diuresis
    - Life-threatening bleeding.
    - Acute burn injury of more than 10 % of the body surface.
    - Severe dysnatremia.
    - Severe hepatic failure.
    - Forced treatment.
    - Pregnancy for women aged 50 years old or younger. Documentation with u-hCG or p-hCG.
    - Consent unobtainable according to national regulations.

Patient information and stratification variables:

- Name.
- Site.
- Acute kidney injury:
    - Habitual plasma creatinine prior to current hospitalisation (if unobtainable, it will be back calculated with the MDRD formula. Race must be documented).
    - Highest plasma creatinine within 24 hours prior to randomisation.
    - Diuresis the last 24 hours prior to randomisation.
- SMS-score:
    - Lowest systolic blood pressure 24 hours prior to randomisation.
    - Use of vasopressors/inotrope agent.
    - Acute surgery during current hospital admission.

    - Respiratory support within the last 24 hours prior to randomisation.
    - Metastatic cancer or haematological malignancy.

Baseline variables:

- Date of admission to hospital.
- Date and time of admission to ICU.
- From where the patient was admitted to the ICU:
    - Emergency department or directly from the pre-hospital setting.
    - Hospital ward.
    - Operating or recovery room.
    - Another ICU.
- Elective surgery during current hospital admission prior to randomisation.
- Septic shock according to Sepsis-3 criteria:
    - Suspected or confirmed site of infection.
    - Infusion of vasopressor/inotropic agent.
    - Lactate ≥ 2 mmol/L within the last 3-hours.
- Co-morbidities:
    - Ischemic heart disease (IHD) or heart failure.
    - Chronic obstructive pulmonary disease (COPD).
    - Diabetes.
    - Stroke or neurodegenerative illness.
- Is the participant in treatment with diuretics from before admittance to hospital?
    - Is the participant receiving habitual diuretics during the ICU stay?
    - Which group of habitual diuretics is the patient receiving during the ICU stay:
        - Loop-diuretics.
        - Thiazides.
        - Potassium sparing diuretics.
        - Carbon anhydrase inhibitors.
- Is the participant COVID-19 (SARS-CoV-2) positive on admission.
- P-sodium on inclusion (must be maximum 24 hours old).
- P-potassium on inclusion (must be maximum 24 hours old).
- P-chloride on inclusion (must be maximum 24 hours old).

Daily during entire ICU stay

- 24 hours diuresis (measured at 06:00 am).
- Daily fluid balance in mL (calculated at 06:00 am).
- Weight in kg (measured).
- Cumulative dose of trial drug.
- P-creatinine (highest), P-sodium (highest), P-potassium (lowest), P-chloride (lowest).

- Has the patient fluid accumulation on this day assessed by treating clinician? Y/N/not described
- Major protocol violations
    - Administration of extra furosemide without presence of an escape criterion.
    - Administration of other diuretics not allowed according to protocol.
    - Initiation of renal replacement therapy without the presence of escape indications.
- Co-interventions
    - Infusion of vasopressor/inotrope agents.
    - Mechanical ventilation.
    - Use of escape renal replacement therapy on this day, If yes – on which criteria.
    - Use of escape open-label furosemide on this day. If yes – dose in mg.
    - Use of resuscitation algorithm on this day.
- Serious adverse events (defined in section 8.2).
- Serious adverse reactions (defined in section 8.2).

<u>On discharge</u>

- Date and time for discharge.
- Where is the participant discharged to?
- Enrolment in other interventional trials during the ICU admission.
- Readmissions time and date.
- COVID 19 positive during the admission.

<u>Withdrawal</u>

- Date and time of withdrawal.
- Reason of withdrawal.
- Who is not giving consent or withdrawing consent?
- Permission to collection daily data for the rest of the trial? Y/N

<u>Day 90 follow-up:</u>

- Date of 90-day follow-up.
- Did the patient die within 90 days after randomisation? If yes – date of death.
- Discharge from the hospital within 90 days after randomisation.
- Date of hospital discharge (index admission)
- Additional admissions within 90 days after randomisation. Date and time.

<u>One year follow up:</u>

- Date of follow-up.
- Is the patient dead? If yes – date of death.
- <u>HRQoL</u> measured using the EuroQoL (EQ)-5D-5L questionnaires and EQ-VAS scores by telephone interview. Registration of all the questions.

- Cognitive function assessed by the Montreal Cognitive Assessment (MoCA Mini) score by telephone interview. Registration of all the questions.
- The participants subjective experience of health related to quality of life since the ICU admittance: unacceptable / neutral / acceptable – asked during telephone interview.

Consent form:

- All consent forms must be up-loaded in the eCRF.
- The date where information about the trial has been given to the second trial guardian, the next of kin and the participant.

9.3 Data management

The data manager at CTU or his/her delegate will construct and oversee the eCRF. He/she will, as the only person, have access to the randomisation list during trial. The eCRF and the trial database will be hosted at the server of CTU with appropriate back-up and security as per the GCP regulative.

9.4 Confidentiality

Each participant will receive a unique trial identification number. Trial investigators will receive a personal username and password to access the randomisation system and the eCRF. Each site will only have access to site specific participant data. Data will be handled according to the National Data Protection Agency and protected by the Danish national laws ‘Loven om behandling af personoplysninger’ and ‘Sundhedsloven’.

9.5 Collection, handling, storage, and transportation of human biological material

No additional sampling of human material will be done in the main trial as data entry will rely on routine testing done in the clinical setting. In sub-studies, blood tests will likely be taken in addition to the routine clinical tests. If so, specific protocols will be submitted for approval, as described in section 12.4.

9.6 Access to data

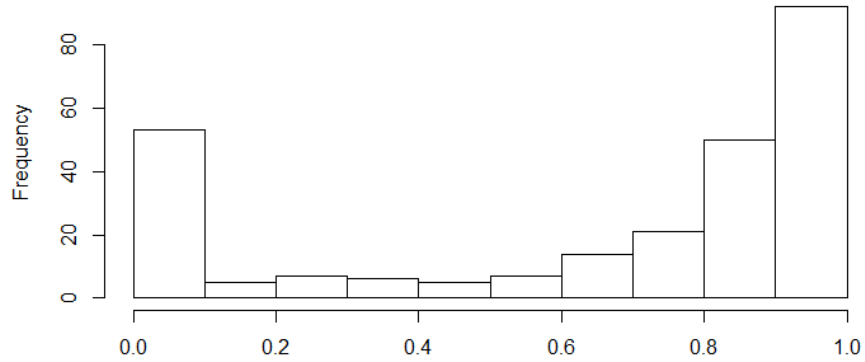
All original records (incl. consent forms, eCRFs, and relevant correspondences) will be archived for 25 years. De-identified data will be made publicly available 9 months after the publication of the outcome data according to the recent ICMJE recommendations (Appendix 10). As it is for all CRIC trials, all trial-related documents will be publicly available at www.CRIC.nu including those of the site master file, the eCRF template, instructions, educational material etc.

10. Statistical plan and data analysis

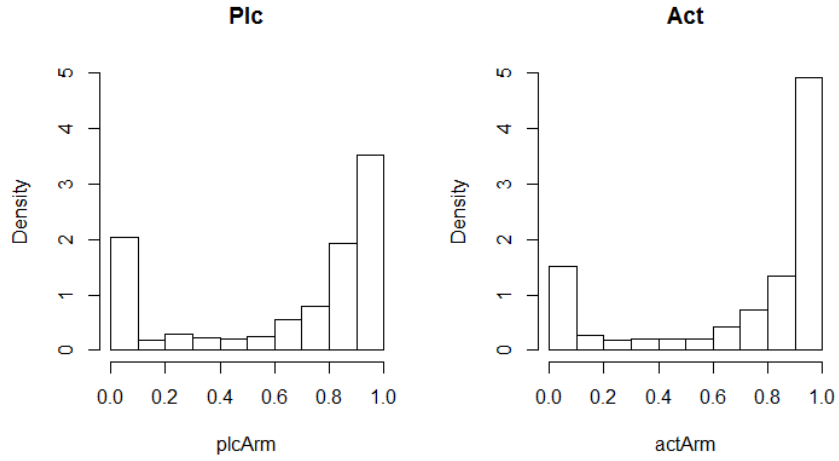
10.1 Sample size and power

10.1.1 Sample size estimation

The primary outcome is days alive and out of hospital within 90 days. For technical reasons we will divide this number by 90 to produce an outcome in the range 0 to 1 where high is good. Based on observational data the distribution of this outcome is expected to look like the histogram below.



The peak at zero corresponds to in-hospital mortality. It is evident that the distribution is highly non-normal and regular power calculations based on t-test will not be applicable. Accordingly, the following calculations are based on employing a Wilcox rank sum test. We will assume a minimal clinically relevant difference of a) lower in-hospital mortality by 15 % and b) shift the distribution for the rest to the right by an amount such that the combined effect on the mean is an improvement of 8 %. Under these assumptions, we will have 90 % power to detect such an improvement at the 5 % significance level by including 500 patients in each arm. To illustrate the hypothesized intervention-effect the two histograms below present the placebo and active arm distributions of the outcome with the differences as the described for the minimal clinically relevant.



As the hypothesized effect size is unconventional, we also compute a standard t-distribution based power assessment. Here we maintain an improvement in mean of 8 % and get an estimated power

of 60 %. While this seems low, it is to be expected as the standard deviation computed from the observed data is vastly overstating the true variation in the data because of the non-normality.
We also compute the power from a 500 patient-in-each-arm design on 90-day mortality. Here the observational data yields a current mortality of 27 %. Using standard formulas, we conclude that we will have 90 % power to detect a drop of 8.5 %-point corresponding to a risk ratio of 0.68 on 90-day mortality.

10.1.2 Power estimations for secondary outcomes

1. Assuming a control group risk of 30 % for all-cause mortality at day 90 after randomisation we have about 60 % power to detect a relative risk reduction of 15 %.
2. Assuming the same in-hospital mortality as described in the primary outcome and in addition that days alive at day 90 without life support (vasopressor/inotropic support, invasive mechanical ventilation, or renal replacement therapy) is increased by 10 % then we have about 80 % power.
3. Assuming a control group risk of 37 % for all-cause mortality at 1 year after randomisation we have about 75 % power to detect a relative risk reduction of 15 %.
4. Assuming a control group proportion of participants with one or more serious adverse events (SAEs) or/and serious adverse reactions (SARs) of 30 %, we have about 60 % power to detect a relative reduction of 15 %.

The estimates of the control event rates originate from data from previous ICU multicentre trials and epidemiological studies[19,54–59].

10.2 Statistical methods

Our primary analyses will be based on the intention-to-treat population being all randomised patients consenting to use their data. Secondary analyses will be performed on a per protocol population defined as all patients randomised and consenting to use their data except for patients having a major protocol violation during the intervention period. We will consider the following violations of the protocol to be major:

1) Participants receiving other diuretics than allowed according to this protocol during their ICU admittance.
2) Participants receiving open-label furosemide on other indications than described under escape (section 6.3) during ICU admittance.
3) Initiation of RRT, without the presence of RRT escape indications (section 6.3).

The primary analyses will be adjusted for the stratification variables including site. Secondary analyses will be adjusted for the stratification variables and for other known prognostic co-variates:

1) Ischaemic heart disease
2) Septic shock

3) Chronic obstructive pulmonary disease
4) Diabetes
5) Stroke or neurodegenerative illness

To obtain maximal statistical power the primary outcome will be compared between treatment groups using a likelihood ratio test building on a logistic model for mortality and a linear regression for days alive outside hospital within 90 days for patient who are discharged alive within 90 days. Both models will be adjusted for stratification variables as described above. The likelihood ratio test will produce a single p-value. The size of the treatment effect will be quantified using raw means in the two groups along with confidence intervals for each mean and for the difference derived from the likelihood function underpinning the likelihood ratio test. As a robustness check a linear regression including stratification variables will also be conducted, but power is expected to be lower because of the non-normality of the outcome variable.

Secondary outcomes no. 2 will be analysed using the same methods as the primary outcome.

Secondary outcomes no. 1, 3, and 4 will be analysed using logistic regressions. All analyses of secondary outcomes will be adjusted for the covariates as described in the previous section.

10.2.1 Pre-planned subgroup analyses

We will compare the primary outcome measure in pre-specified subgroups defined according to:

1) SMS-score > 25 (Y/N). We expect the participants with SMS-score > 25 to have better effect of the intervention.
2) AKI (Y/N). We expect the participants with AKI stage 2 and 3 to have better effect of the intervention compared to participants with no AKI.
3) COVID-19 (SARS-CoV-2) infection: Y/N. We expect the participants with COVID-19 infection to have better effect of the intervention.
4) Patients included in GODIF post septic shock: Y/N. We expect the participants with post septic shock will benefit more from the intervention.

10.2.2 Significance

A two-sided P-value of less than 0.05 or a 95 % confidence interval not including 0.0 for the primary outcome will be considered statistically significant. The secondary outcomes will be analysed using 99 % and 95 % confidence intervals, corresponding to Bonferroni adjustment and no adjustment of significance for statistical multiplicity. P-values will also be provided, but 99 % confidence intervals not including 1.0 (for RR) or 0.0 (for MD) will be considered as definitely statistically significant, while 95 % confidence intervals not including 1.0 (for RR) or 0.0 (for MD) will be considered only possibly statistically significant.

10.2.3 Interim analyses

Interim analyses will be conducted when patients number 100 and number 500 have been followed for 90 days. The first interim analysis after 100 participants will be on the process variables to

ensure separation between groups. The second interim analysis will be on our primary outcome and the number of patients with one or more SAEs/SARs will be conducted. The independent Data Monitoring Committee (DMC) will recommend pausing or stopping the trial if group-difference in the primary outcome measure, mortality or SAEs/SARs are found at the interim analyses with statistical significance levels adjusted according to the Lan-DeMets group sequential monitoring boundaries based on O'Brien Fleming α spending function. If an analysis of the interim data from 500 patients fulfils the Lan-DeMets stopping criterion the inclusion of further patients will be paused and an analysis including patients randomised during the analysis period will be performed. If this second analysis also fulfils the Lan-DeMets stopping criterion according to the group sequential monitoring boundaries the DMC will recommend stopping the trial. Furthermore, the DMC can recommend pausing or stopping the trial if continued conduct of the trial clearly compromises patient safety.

Further details are specified in the charter for the DMC (Appendix 4)

10.2.4 Early stopping criteria

See previous section.

10.2.5 Accountability procedure for missing data/population for analysis

If less than 5 % of data are missing on any primary or secondary outcome, a complete case analysis without imputation of missing values will be performed[60]. If missing data are more than 5 % multiple imputations using chained equations will be performed by creating 25 input data sets under the assumption that the data are missing data at random (MAR criterion). We will use outcomes and the most important baseline characteristics in the multiple imputation. The exact variables to be used to estimate the missing values will be outlined in the detailed statistical analysis plan. If multiple imputation is used, then the primary result of the trial will be based on these data. The unadjusted, non-imputed analysis will also be made available. If multiple imputation is used, we will use a best-worst, worst-best case scenario as a sensitivity analysis to assess the potential impact of any pattern of missingness including that the data are missing not at random (MNAR criterion) for the trial results. In the 'best worst-case' scenario it is assumed that all patients lost to follow-up in the experimental group have had a beneficial outcome (e.g. have survived, had no serious adverse reactions etc.); and all those with missing outcomes in the control group have had a harmful outcome (e.g. have not survived; have had a serious adverse reaction etc.). Conversely, in the 'worst-best-case' scenario, it is assumed that all patients who were lost to follow-up in the experimental group have had a harmful outcome; and that all those lost to follow-up in the control group have had a beneficial outcome. When continuous outcomes are used, a 'beneficial outcome' will be defined as the group mean plus two standard deviations (SD) of the group mean or highest possible value whichever is smallest, and a 'harmful outcome' will be defined as the group mean minus two SD of the group mean or lowest possible value whichever is highest.

11. Quality control and quality assurance

The Sponsor and the coordinating investigator will be responsible for organizing the trial sites including education of local investigators, research nurses, and other trial site personnel before the initiation of the trial. This education will be continuously documented in the site master file. An annual investigator meeting will be planned.
After initiation, trial site investigators will be responsible for all trial-related procedures at their site, including education of staff in trial-related procedures, recruitment and follow-up of participants and entry of data. Clinical staff at the trial sites will be responsible for the treatment of trial participants.

11.1 Monitoring

The trial will be externally monitored according to the GCP directive and the monitoring and data verification plan including the documentation of informed consent of trial participants. The monitoring and data verification plan will be developed together with the GCP unit of Copenhagen University Hospital and adhered to by the staff monitoring trial sites in all countries. In addition, we will use central monitoring of site through the eCRF including adherence to the protocol.

11.2 Drug traceability measures

The dosage of furosemide administered will be registered in the eCRF for every day the participant is in the ICU to a maximum of 90 days. The registration of the batch numbers and the expiry dates of furosemide and the identity of the clinician administering the drug will be registered as per standard practice at the sites. These data will not be registered in the trial documents but can be obtained by the Sponsor or the authorities if needed. We believe that this is a safe procedure because furosemide has been in clinical use for many years and the safety of single doses and infusion cannot be questioned. The same procedure was approved by the Danish Medicines Agency in the CLASSIC pilot trial (EudraCT no. 2014-000902-37).

12. Legal and organisational aspects

12.1 Finance

12.1.1 Trial funding

The trial is funded by grants from the Novo Nordisk Foundation (DKK 5.082.180),Jakob Madsens and wife Hustru Olga Madsens Foundation (DKK 100.000), Jakob Ehrenreich and wife Grete Ehrenreich's Foundation (DKK 200.000), Svend Andersen's Foundation (DKK 840.000), and Sygeforsikringen Danmark (DKK 5.156.965). None of the funding organisations have been or will be involved in the design, conduct, analyses, or reporting of the trial nor will they have ownership of the data. Further funding will be sought from independent and governmental sources. When additional funding is granted The Institutional Review Board/Independent Ethics Committee of the Capital Region will be informed and the patient information document will be updated. When the participants are contacted by telephone for the 1-year follow-up, the participants will be informed if further funding is granted after they signed the consent form.

12.1.2 Compensation

All trial sites will be paid DKK 3000 (EUR 400) for each participant with completed 1-year follow-up status to partly compensate for the increased workload regarding screening, consent, inclusion, data entry, and follow-up. If a participant is admitted to two ICU sites participating in the GODIF trial during the 90-day trial, the first site will receive EUR 200, the second site must perform 1-year follow-up and will also receive EUR 200. Trial sites providing their own trial drug will be paid 475 EUR for each patient.

12.2 Insurance

In Denmark, the Patient Insurance Association insures all trial participants. Patient insurance will be ensured before initiating the trial in each participating country. We will use external funding for the costs of insurance.

12.3 Plan for publication, authorship, and dissemination

All trial results whether positive, negative, or neutral will be published in a peer-reviewed medical journal. Furthermore, the results will be published on the CRIC home page (www.cric.nu). We will adhere to the CONSORT statement including the accountability of all patients screened (Appendix 10).

Authorship will be granted according to the guidelines from the International Committee for Medical Journal Editors (ICMJE; http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html).

The order of authorships will be in agreement with Vancouver guidelines and in agreement with the steering committee.

The listing of authors will be as follows on the primary publication: the first author: Sine Wichmann, the second: to be decided, the third: to be decided, the next authors will be the national investigators according to the number of included participants per country, then the other members of the Management Committee, the trial statistician and trial site investigators dependent on the number of included participants per site. Morten Bestle will be the last and corresponding author.

The Management Committee will grant authorship depending on personal input as per the Vancouver definitions. If a trial site investigator is to gain authorship on the primary publication, the site has to include 25 participants or more. If a site includes 50 participants, 2 authorships may be granted, at 75 participants 3 authorships and so on. Investigators on sites including less than 25 participants may be granted authorship on the long-term outcome publication if they contribute significantly as per the Vancouver definitions.

The DMC and investigators not qualifying for authorship will be acknowledged with their names under ‘the GODIF Trial investigators’ in an appendix to the final manuscript.

The funding sources will be acknowledged, but they will not influence the data handling or analyses, the writing of the manuscript or the decision to publish.

12.4 Sub-studies

Sub-studies will be planned at selected sites and more will be encouraged if they do not hamper the completion of the main protocol and can be conducted after approval of the specific protocol by the Management Committee and the authorities. Thus, specific protocols for any sub-studies will be submitted to and approved by the relevant authorities and ethics committees before the commencement of such studies. In Appendix 8, the presently proposed sub-studies are listed.

12.5 Intellectual property rights

The GODIF trial group owns the trial data. The Contract between the Sponsor and an investigator will be reviewed and approved by the Unit for Research and Innovation (Law and Contracts) of the Capital Region (https://www.regionh.dk/english/research-and-innovation/Pages/default.aspx) and by the Medical Director of Nordsjællands Hospital.

12.6 Organisational framework

The GODIF trial will be managed by the Management Committee (Appendix 1). The day-to-day conduct of the trial will be done by the Sponsor and the Coordinating Investigator.

12.7 Trial timeline

- Primo 2020: authority approvals in DK
- August 2020: 1st participant randomised in DK
- October 2022: 1st interim analysis after 100 randomised patients
- October 2024: 2nd interim analysis after 500 randomised patients.
- Ultimo 2026: the last participant randomised.
- Primo 2028: the last participant followed for 1 year (last patient, last visit).

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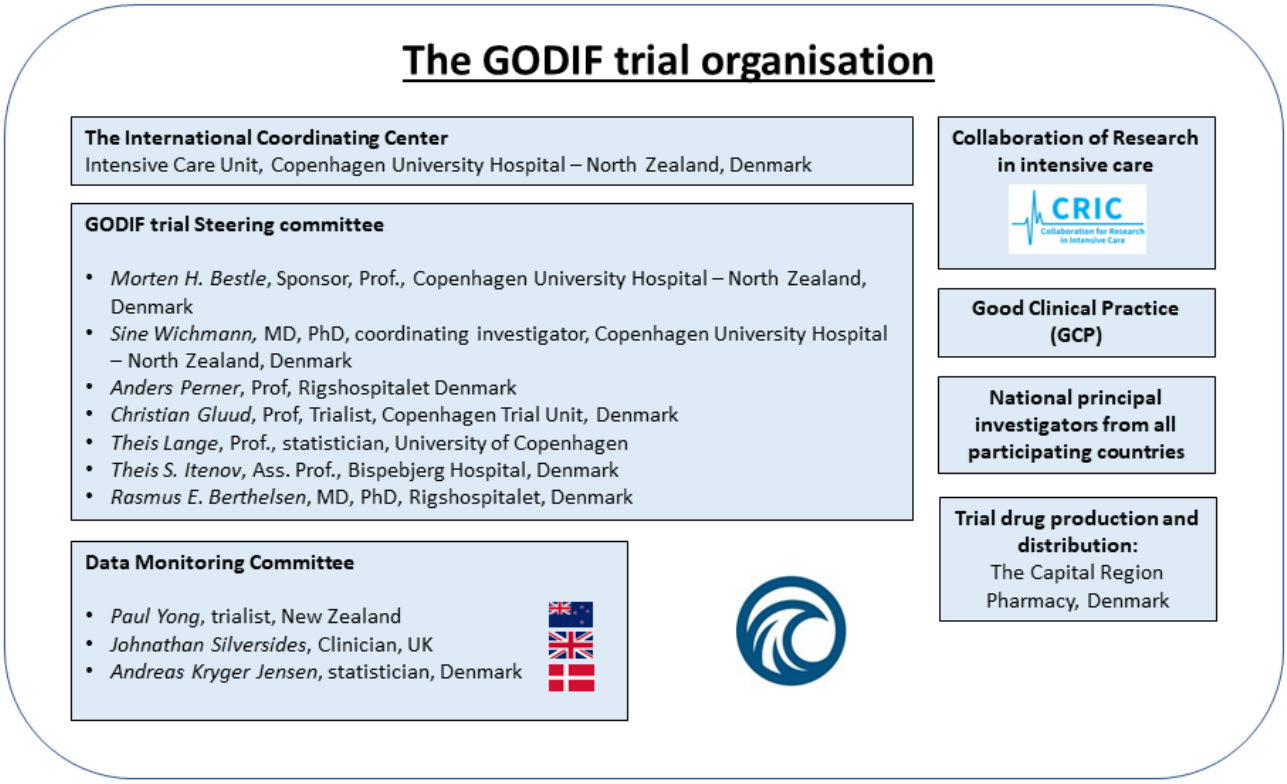
14. Appendix

Appendix 1: Research program organisation
Appendix 2: Trial definitions
Appendix 3: Adverse reactions not registered in the GODIF trial and summary of product characteristics
Appendix 4: Charter for the independent Data Monitoring and Safety Committee
Appendix 5: Informed consent procedure in Denmark
Appendix 6: Simplified Mortality Score
Appendix 7: Co-enrolment agreement form
Appendix 8: List of proposed sub-studies
Appendix 9: Trial participant flow chart
Appendix 10: International Committee of Medical Journal Editors (ICMJE) form for potential conflict of interest.
Appendix 11: Budget
Appendix 12: Mottling score
Appendix 13: 5 % Fluid overload - Mortality and morbidity
Appendix 14: GODIF algorithm
Appendix 15: Estimation of the fluid balance
Appendix 16: Amendment to Protocol V2.7, version V1.0 14.04.2023
Appendix 17: Swedish regulations and informed consent procedures for the GODIF trial

14.1 Appendix 1. Research programme organisation



14.2 Appendix 2. Trial definitions

Definition of stratification variables

- Site: all participating intensive care units (ICUs) will be assigned a number identifying the unit.
- Simplified Mortality Score for the intensive care unit (SMS-ICU)[61] is a score developed to predict 90 days mortality in adults upon acute admission to the ICU. The score uses 7 variables obtained in the first 24 hours of admission to the ICU: (see Appendix 6 for further details)
- Acute kidney injury (AKI) defined according to KDIGO[62]: as any of the following:
    - Increase in serum creatinine by ≥ 0.3 mg/dl (≥ 26.5 µmol/l) within 48 hours; or
    - Increase in serum creatinine to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or
    - Urine volume < 0.5 ml/kg/h for 6 hours

Definition of the inclusion criteria:

All the points below must be met:

- Acute admitted to the ICU or acute admittance is planed to the ICU: We will only recruit sites that have the status as an ICU. These may oversee beds defined as high-dependency, step-up or step-down beds. We will consider these as being part of the trial site ICU if staff trained in the protocol looks after the patients in these beds. The medical doctors at the site may enrol patients from other locations in the hospital (e.g. emergency departments, general wards or the recovery room) if the patient for clinical reasons is planned to be admitted to the ICU.
- Age ≥ 18 years of age. The age of the participant in whole years at the time of randomisation. The age will be calculated from date of birth.
- Fluid accumulation in the body estimated according to the cumulative fluid balance (if available), daily fluid charts, changes in body weight, and clinical examination (oedemas, congestion on x-ray e.c.t. see Appendix 15 for more explanation). If possible, cumulative fluid balance from before admission to the ICU are to be included in the calculation of cumulative fluid balance during the ICU admission. The minimum fluid accumulation on inclusion is 5 % of ideal body weight. The following calculation of minimum fluid accumulation according to height must be used:

Height in cm	Male	Female
< 159 cm	+ 3.0 L	+ 2.5 L
160 – 169 cm	+ 3.5 L	+ 3.0 L
170 – 179 cm	+ 4.0 L	+ 3.5 L
180 – 189 cm	+ 4.5 L	+ 4.0 L
> 190 cm	+ 5.0 L	+ 4.5 L

The assessment of fluid accumulation must be documented in the inclusion note for the trial.

- Clinical stable is assessed by the clinicians. Minimum criteria are MAP > 50 mmHg and maximum infusion of 0.20 microgram/kg/minute of noradrenaline and lactate < 4.0 mmol/L.

Definition of the exclusion criteria

- Know allergy to furosemide or sulphonamides.
- Known pre-hospitalisation advanced chronic kidney disease with eGFR < 30 mL/minute/1.73 m^2 or chronic RRT as furosemide might not have the expected effect in this patient group.
- Acute renal replacement therapy or anuria for ≥ 6 hours. Administration of furosemide will often be a contraindication in this situation.
- Rhabdomyolysis with indication for forced diuresis.
- Ongoing life-threatening bleeding as these patients need specific fluid/blood product strategies.
- Acute burn injury of more than 10 % of the body surface area: burn injury leading to the present ICU admission as these patients need a specific fluid strategy. Patients with burn injury who are re-admitted to the ICU or were initially cared for in a general ward and admitted to the ICU for infection may be screened to enrolment. The latest documented estimate of the burn area will be used as these may be downgraded after the initial assessments.
- Severe dysnatraemia (p-Na < 120 mmol/L or > 155 mmol/L) as these patients may need a specific fluid or diuretic therapy.
- Severe hepatic failure or coma (liver coma grade 3 and 4).
- Patients undergoing forced treatment.
- Pregnancy (non-pregnancy confirmed by patient having a negative urine- or plasma hCG or being postmenopausal defined as females at 50 years old or beyond or at the investigators discretion). The hCG test must be documented in the patient file.
- Lack of commitment for on-going life support in the form of RRT.
- Consent not obtainable according to national regulations: patients where the clinician or investigator is unable to obtain the necessary consent before inclusion of the patient according to the national regulations.

We will not exclude patients enrolled in other interventional trials unless the protocols of the two trials collide; we present the rational for this in Appendix 7. Co-enrolment agreements will be established with the sponsor/investigator to maintain an updated list of trials approved for co-enrolment (Appendix 7).

Definition of collected variables:

Screening:

- Patient identification number.
- Sex (the genotypic sex of the participant).
- Inclusion criteria:
    - Age.
    - Admitted or planned to be admitted to the ICU.
    - Is the patient clinical stable? Y/N. Definition of clinical stable (minimum criteria are MAP > 50 mmHg and maximum infusion of 20 microgram/kg/minute of noradrenaline and lactate < 4.0 mmol/L).
- Fluid accumulation in mL. The fluid accumulation is assessed by the treating clinical team according to the cumulative fluid balance, daily fluid balance, changes in weight and clinical

examination (oedemas, congestion on x-ray e.c.t.) (Appendix 15). It must be documented in the inclusion note for GODIF trial in the patient file. Fluid balance is defined by the balance of all fluid in- and outputs. This includes all types of IV fluids, blood products, medicines, nutrition products AND oral fluids, nutrition products, and medicine. Output as urine, drainage, perspiration, aspirates, stools, bleeding.
    - Which measurements are used in assessing the fluid accumulation?
        - Cumulative fluid balance Y/N
        - Daily fluid balance Y/N
        - Weight Y/N
        - Clinical examination Y/N
    - Actual body weight in kg.
    - Height in cm.
- Exclusion criteria:
    - Allergy towards furosemide or sulphonamides.
    - Advanced chronic kidney disease.
    - Ongoing renal replacement therapy.
    - Anuria for > 6 hours.
    - Rhabdomyolysis with indication for forced diuresis.
    - Life-threatening bleeding.
    - Acute burn injury of more than 10 % of the body surface.
    - Severe dysnatraemia.
    - Severe hepatic failure.
    - Forced treatment.
    - Pregnancy for women aged 50 years old or younger. Documentation with u-hCG or p-hCG.
    - Consent unobtainable according to national regulations.

Patient information and stratification variables:

- Name.
- Site.
- Acute kidney injury:
    - Habitual plasma creatinine prior to current hospitalisation. Defined by previous creatinine value measured in the last 6 months prior to this hospital admittance. If habitual creatinine is unobtainable, it will be back calculated with the MDRD formula. Race must be documented.
    - Highest plasma creatinine within 24 hours prior to randomisation.
    - Diuresis the last 24 hours prior to randomisation.
- SMS-score:
    - Lowest systolic blood pressure 24 hours prior to randomisation (either invasive or non-invasive). In case of cardiac arrest within the 24-h period ‘0’ must be registered.
    - Use of continuous infusion of vasopressor or inotrope (noradrenaline, adrenaline, phenylephrine, vasopressin analogues, angiotensin, dopamine, dobutamine, milrinone or levosemindan).

- Acute surgery during current hospital admission.
- Respiratory support within the last 24 hours prior to randomisation. Use of invasive or non-invasive mechanical ventilation including continuous mask CPAP or CPAP via tracheostomy within the last 24 hours prior to randomisation. Intermittent CPAP and high flow nasal cannula oxygen therapy are NOT considered as respiratory support
- Metastatic cancer or haematological malignancy.
  - Metastatic cancer: proven metastasis by surgery, CT scan or any other method.
  - Haematological malignancy includes any of the following:
    - Leukaemia: Acute lymphoblastic leukaemia (ALL), acute myelogenous leukaemia (AML), chronic myelogenous leukaemia (CML), chronic lymphocytic leukaemia (CLL).
    - Lymphoma: Hodgkin's disease, and Non-Hodgkin lymphoma (e.g. small lymphocytic lymphoma (SLL), diffuse large B-cell lymphoma, follicular lymphoma and mantle cell lymphoma).
    - Hairy cell leukaemia (HCL), marginal zone lymphoma, Burkitt's lymphoma, post-transplant lymphoproliferative disorder (PTLD), T-cell prolymphocytic leukaemia (T-PLL), B-cell prolymphocytic leukaemia (B-PLL), Waldenström's macroglobulinemia and other NK- or T-cell lymphomas.
    - Multiple myeloma/plasma cell myeloma.

<u>Baseline variables:</u>

- Date of admission to hospital.
- Date and time of admission to ICU.
- From where was the patient admitted to the ICU?
  - Emergency department or directly from the pre-hospital setting.
  - Hospital ward.
  - Operating or recovery room.
  - Another ICU.
- Elective surgery during current hospital admission prior to randomisation.
- Septic shock according to Sepsis-3 criteria?
  - Suspected or confirmed site of infection.
  - Infusion of vasopressor/inotropic agent (noradrenaline, epinephrine, phenylephrine, vasopressin analogues, angiotensin, dopamine, dobutamine, milrinone or levosemindan) to maintain a mean arterial blood pressure of 65 mmHg or above.
  - Lactate ≥ 2 mmol/L within the last 3-hours.
- Co-morbidities:
  - Ischemic heart disease (IHD) or heart failure.
  - Chronic obstructive pulmonary disease (COPD).
  - Diabetes.
  - Stroke or neurodegenerative illness.
- Is the participant in treatment with diuretics from before admittance to hospital? Y/N
  - Is the participant receiving habitual diuretics during the ICU stay? Y/N

    - Which group of habitual diuretics is the patient receiving during the ICU stay?
        - Loop-diuretics.
        - Thiazides.
        - Potassium sparing diuretics.
        - Carbon anhydrase inhibitors.
- Is the participant COVID-19 (SARS-CoV-2) positive on admission?
- The P-sodium on inclusion (the value closest to inclusion time maximum 24 hours before inclusion)
- The P-potassium on inclusion (the value closest to inclusion time – maximum 24 hours before inclusion)
- The P-chloride on inclusion (the value closest to inclusion time – maximum 24 hours before inclusion)

<u>Daily during entire ICU stay:</u>

- 24 hours diuresis (measured at 06:00 am).
- Daily fluid balance in mL (calculated at 06:00 am). This includes all fluid input and output in mL cumulated during the last 24 hours. This includes all types of IV fluids, blood products, medicines, nutrition products AND oral fluids, nutrition products, and medicine. Daily output as urine, drainage, perspiration, aspirates, stools, bleeding. In case of escape renal replacement therapy also fluid removal with dialysis.
- Weight in kg (measured).
- Cumulative dose of trial drug on this day registered in mL.
- P-creatine measured on this day.
- The highest P-sodium on this day.
- The lowest P-potassium on this day.
- The lowest P-chloride on this day.
- Has the patient fluid accumulation on this day assessed by treating clinician? Y/N/not described (assessed according to the cumulative fluid balance, daily fluid balance, changes in weight and clinical examination (oedemas, congestion on x-ray ect. see Appendix 15 for further description)
- Major protocol violations on this day.
    - Administration of open label furosemide without presence of escape criteria (section 6.3).
    - Administration of other diuretics not allowed according to protocol.
    - Initiation of renal replacement therapy without the presence of escape indications (section 6.3).
- Co-interventions
    - Infusion of vasopressor/inotrope agents on this day.
    - Mechanical ventilation on this day (use of invasive or non-invasive mechanical ventilation including continuous mask CPAP or CPAP via tracheostomy within the last 24 hours. Intermittent CPAP and high flow nasal cannula oxygen therapy are NOT considered as mechanical ventilation).

    - Use of escape renal replacement therapy on this day, if yes – the criteria must be documented.
    - Use of escape open-label furosemide on this day. If yes – dose in mg.
    - Use of resuscitation algorithm on this day: Y/N
- Serious adverse events (defined in section 8.2 or below): Y/N
- Serious adverse reactions (defined in section 8.2 or below) Y/N

On discharge

- Date and time for discharge.
- Where the participant discharged to.
- Enrolment in other interventional trials during the ICU admission.
- Readmissions time and date.
- COVID-19 positive during hospital admission: Y/N

Withdrawal

- Date and time of withdrawal.
- Reason of withdrawal.
- Who is not giving consent or withdrawing consent?
- Permission to collect daily data for the rest of the trial. Y/N

Day 90 follow-up:

- Date of 90-day follow-up.
- Did the patient die within 90 days after randomisation? If yes – date of death.
- Discharge from the hospital within 90 days after randomisation.
- Date of hospital discharge (index admission).
- Additional admissions within 90 days after randomisation. Date and time.

One year follow up:

- Date of follow-up.
- Was the patient dead? If yes – date of death.
- HRQoL measured using the EuroQoL (EQ)-5D-5L questionnaires and EQ-VAS scores by telephone interview. Registration of all the questions.
- Cognitive function assessed by the Montreal Cognitive Assessment (MoCA Mini) score by telephone interview. Registration of all the questions.

The participants subjective experience of health related to quality of life since the ICU admittance: unacceptable / neutral / acceptable – asked during telephone interview.
Consent form:

- All consent forms must be up-loaded in the eCRF.
- The date where information about the trial has been given to the second trial guardian, the next of kin and the participant.

Definition of variables for one-year follow-up

- Is the patient death on follow-up: Y/N
- Date of death (if dead)
- MoCA mini test, EQ-5D-5L questionnaires and EQ-VAS scores.
- Subjective assessment of the participant's current quality of life after treatment in the ICU: unacceptable, neutral, acceptable.

Definition of outcome measures

Primary outcome:

- Days alive and out of hospital day 90 after randomisation. It will be assessed from the discharge date from the index hospitalisation, the number of days readmitted to hospital (if any) and date of death, if relevant, within the 90-day period.

Secondary outcomes:

1. All-cause mortality at day 90 after randomisation.
2. Days alive without life support at day 90: will be assessed from the use of life support including vasopressor/inotrope, mechanical ventilation and renal replacement therapy as defined above. Total number of days alive without all the 3 life supporting interventions within 90 days after randomisation.
3. All-cause mortality at 1-year after randomisation. If the participant has deceased, date of death will be registered.
4. Number of participants with one or more adverse events (SAEs) and serious adverse reactions (SARs) to furosemide as described in section 8.

Explorative outcomes:

1. HRQoL at 1-year (+/- 2 weeks): EQ-5D-5L and EQ-VAS scores (https://euroqol.org/) obtained by survey by mail or phone as chosen by the participant. If the participant is incapable of answering the questionnaire (e.g. due to cognitive impairment or coma) we will ask proxies to assess HRQoL for the trial participant (proxy point of view) using the questionnaire aimed for proxies. Non-survivors will be given the worst possible score. EQ-5D-5L will be converted to an index value in combination with the EQ-VAS quantitative measure (0-100 points) quantifying self-rated health.
2. Participants subjective assessment of their quality of life since the treatment in the ICU (unacceptable/neutral/acceptable) compared to (EQ)-5D-5L and EQ-VAS scores. They will be asked during the phone interview or by mail on the 1-year follow-up.
   Cognitive function at 1-year (+/- 2 weeks): the Montreal Cognitive assessment (MoCA) Mini score (or MoCA 5-minute test) (http://www.mocatest.org/). The score will be obtained in all survivors by interview as this was recommended to be the test of cognition in a core outcome set for patients with acute respiratory failure following a modified Delphi process involving patients, researchers and clinicians from multiple continents (http://www.improvelto.com/). Non-survivors will be given the worst possible score. The cognitive function score will be conducted before HRQoL to ensure an equal procedure and avoid that patients are disturbed or tired from the HRQoL score.

Definition of Serious Adverse Reactions:
A serious adverse reaction (SAR) is defined as any adverse reaction that results in death, is life threatening, requires hospitalisation or prolongation for existing hospitalisation, or results in persistent or significant disability or incapacity.
Participants will be monitored for onset of SARs occurring between the first dose of trial medication and until discharge from the ICU. If the participant is readmitted to the ICU and trial intervention is reintroduced, data collection for SARs will be resumed. If a participant experiences a SAR, the participant will be withdrawn from the trial intervention, but data collection and follow-up will be continued.

SARs to be registered daily in the CRF:
General tonic-clonic seizures due to low calcium or magnesium in the blood. The seizures are defined as stiffening and/or jerking movements of all 4 extremities in a participant who becomes or is unconscious in the ICU after randomisation.

- Anaphylactic reactions defined as urticarial skin reaction AND at least one of the following observed in the ICU after randomisation
    - Worsened circulation (> 20 % decrease in blood pressure or > 20 % increase in vasopressor dose)
    - Increased airway resistance (> 20 % increase in the peak pressure on the ventilation)
    - Clinical stridor or bronchospasm
    - Subsequent treatment with bronchodilators
- Severe electrolyte disturbance of p-K < 2.5, p-Na < 120, p-Cl < 90 on any plasma sample, including point-of-care testing, done in the ICU after randomisation.
- Agranulocytosis is defined as any new drop in granulocytes to < 0.5 x 10^9/L.
- Aplastic anaemia defined as a syndrome of bone marrow failure characterised by peripheral pancytopenia and marrow hypoplasia. Drop in haemoglobin < 5.0 mmol/l, neutrophil leucocytes < 0.5 x 10^9/l, thrombocytes < 20 x 10^9/l, reticulocytes < 1 %.
- Pancreatitis
- Circulatory collapse leading to cardiac arrest.
- Steven Johnsons syndrome
- Toxic epidermal necrolysis
- Hearing impairment/loss

<u>SAE to be registered daily in the CRF:</u>

- Ischaemic events defined as either
    - Cerebral ischaemia defined as any form of cerebral ischemia on a CT- OR MRI scan
    - Acute myocardial ischaemia defined as participant with acute myocardial infarction (ST-elevation myocardial infarction or non-ST elevation myocardial infarction) or unstable angina pectoris according to the criteria in the clinical setting in question (e.g. elevated biomarkers, ischemic signs on ECG and clinical presentation) AND the participant received treatment as a consequence of this (reperfusion strategies (PCI/thrombolysis) OR initiation/increased antithrombotic treatment).

    - Intestinal ischaemia defined as ischaemia verified by endoscopy OR open surgery OR CT-angiography.
    - Limb ischemia defined as clinical signs AND need of open/percutaneous vascular intervention, amputation OR initiation/increased antithrombotic treatment.
- A new episode of severe acute kidney injury defined as modified KDIGO 3: 3.0 times increase in baseline p-creatinine or increase in p-creatinine to ≥ 354 µmol/L or use of renal replacement therapy (any form).
- New onset atrial fibrillation after randomisation in a participant who never have been diagnosed with atrial fibrillation before.

14.3 Appendix 3. Adverse reactions not registered in GODIF trial and summary of product characteristics

These adverse reactions to furosemide will not be registered in the eCRF but in the patient files:

- Dehydration will not be registered directly, as fluid removal and a negative daily fluid balance is part of the intervention.
- Hypovolaemia will not be registered as an SAR since it is expected in some of the participants, because the intervention and the goal for the study is to remove excess fluid form the body. Hypovolaemia will be closely monitored and intervened according to the algorithm in appendix 14.
- Thrombocytopenia will not be registered as an SAR. Thrombocytopenia is a common condition in ICU patients and the reasons can be multiple. Thrombocytopenia is not regarded as a SAR in the ICU setting.
- Syncope is not registered, since most patients will be sedated and intubated during the trial, and thus the incidence of syncope is un-assessable. Furthermore, syncope is not considered a serious adverse reaction in ICU patients.
- Arrythmias as sinus tachycardia and premature ventricular or supraventricular contractions are very often seen in critical ill patients and are not considered a serious adverse reaction in the ICU setting.
- Elevation of s-creatinine, proteinuria, and acute nephropathy are not registered since acute kidney injury is part of outcome.
- Hyperglycaemia, impaired glucose tolerance, diabetes mellitus is not registered since change in glucose metabolism is frequently associated with critical illness and it is not regarded as a serious adverse reaction in the ICU setting.
- Headache, paraesthesia, dizziness, nausea, diarrhoea, constipation, tinnitus, confusion, visual disturbances, orthostatic hypotension, hypertriglyceridemia, hyperlipidaemia, pruritus, urticaria, purpura, exfoliative dermatitis, erythema multiforme, photosensitivity, cholestasis, jaundice, fever, porphyria and attacks of gout are not registered, because they are not regarded as serious adverse reactions in the ICU setting.
- Thrombophlebitis is often seen in critical ill patients receiving multiple drugs and fluids iv; thus, this is not regarded as a serious adverse reaction in the ICU setting.
- Eosinophilia is not registered, as transient eosinophilia is not regarded as a serious adverse reaction in the ICU setting.
- Arrythmias are a very common condition in the ICU population. About 27 %[63] will experience atrial fibrillation during their ICU stay. Other arrythmias are also seen regularly because of the patients' severe illness and co-morbidities. For that reason, we will not register arrythmias as a serious adverse reaction in the ICU setting.

Summary of product characteristics:

LÆGEMIDDELSTYRELSEN
DANISH MEDICINES AGENCY

20. februar 2017

PRODUKTRESUMÉ

for

Furosemid "Accord", injektions-/infusionsvæske, opløsning

0. D.SP.NR.

29573

1. LÆGEMIDLETS NAVN

Furosemid "Accord"

2. KVALITATIV OG KVANTITATIV SAMMENSÆTNING

Hver 1 ml opløsning indeholder 10 mg furosemid.
Hver 2 ml ampul indeholder 20 mg furosemid (20 mg/2 ml).
Hver 4 ml ampul indeholder 40 mg furosemid (40mg/4ml).

Hver 5 ml ampul indeholder 50 mg furosemid (50mg/5ml).

Hver 25 ml hætteglas indeholder 250 mg furosemid (250mg/25ml).

Hjælpestoffer, som behandleren skal være opmærksom på:
Hver 2 ml steril opløsning indeholder ca. 7 mg natrium.
Hver 4 ml steril opløsning indeholder ca. 15 mg natrium.

Hver 5 ml steril opløsning indeholder ca. 19 mg natrium.

Hver 25 ml steril opløsning indeholder ca. 93 mg natrium.

Alle hjælpestoffer er anført under pkt. 6.1.

3. LÆGEMIDDELFORM

Injektions-/infusionsvæske, opløsning

Klar, farveløs eller næsten farveløs opløsning (pH: 8,0 til 9,3).

4. KLINISKE OPLYSNINGER

4.1 Terapeutiske indikationer

Fremkaldelse af forceret diurese. Anvendes i nødstilfælde, eller når peroral behandling er udelukket.

Indikationer omfatter:

- Ødem og/eller ascites forårsaget af hjerte- eller leversygdomme
- Ødem forårsaget af nyresygdomme (i tilfælde af nefrotisk syndrom er behandling af den underliggende sygdom afgørende)
- Lungeødem (fx. i tilfælde af akut hjertesvigt)
- Hypertensiv krise (i tillæg til andre terapeutiske foranstaltninger)

4.2 Dosering og indgivelsesmåde

Administrationsvej: intravenøs eller (i særlige tilfælde) intramuskulær

<u>Generelt:</u>

Den parenterale administration af furosemid er indiceret i tilfælde, hvor peroral administration ikke er mulig eller ikke effektiv (fx. i tilfælde af nedsat intestinal absorption),

eller når en hurtig virkning er påkrævet. For at opnå optimal effekt og undertrykke modregulation er en kontinuerlig furosemid-infusion generelt at foretrække frem for gentagne bolusinjektioner.

Gældende kliniske retningslinjer bør overvejes, hvor de er tilgængelige.

Hvor kontinuerlig furosemid-infusion ikke er muligt til opfølgende behandling efter en eller flere akutte bolusdoser, foretrækkes et opfølgende regime med lave doser givet med korte intervaller (ca. 4 timer) frem for et regime med højere bolusdoser over længere intervaller.

Behandling bør individualiseres i henhold til patientens respons for at opnå maksimal terapeutisk respons og for at bestemme den minimale dosis, der er nødvendig for at opretholde dette respons.

Intravenøs furosemid skal injiceres eller infunderes langsomt; en hastighed på 4 mg pr. minut må ikke overskrides, og det bør aldrig gives sammen med andre lægemidler i samme sprøjte.

Generelt bør Furosemid Accord administreres intravenøst. Intramuskulær administration skal begrænses til særlige tilfælde, hvor hverken peroral eller intravenøs administration er mulig. Det skal bemærkes, at intramuskulær injektion er ikke egnet til behandling af akutte tilstande, såsom lungeødem.

Voksne:

I mangel af tilstande, der kræver en reduceret dosis (se nedenfor) er den anbefalede indledende dosis, til voksne og unge over 15 år, på 20 mg til 40 mg furosemid ved intravenøs (eller i særlige tilfælde intramuskulær) administration. Den maksimale dosis varierer alt efter individuel respons.

Hvis der er behov for større doser, bør de gives med en stigning på 20 mg og ikke indgives oftere end hver anden time.

Hos voksne er den anbefalede maksimale daglige dosis furosemidadministration på 1500 mg.

Når det indgives som en infusion, kan Furosemid Accord administreres ufortyndet ved brug af en infusionspumpe med konstant hastighed, eller opløsningen kan yderligere fortyndes med en forligelig væske, såsom natriumchloridinjektion B.P. eller Ringeropløsning til injektion. I begge tilfælde bør infusionshastigheden ikke overstige 4 mg/minut.

Den parenterale administration af furosemid er indiceret i tilfælde, hvor peroral administration ikke er mulig eller ikke effektiv (fx. i tilfælde af nedsat intestinal absorption), eller når en hurtig virkning er påkrævet. I tilfælde hvor der anvendes parenteral indgivelse, anbefales det, at skifte til peroral indgivelse så hurtigt som det er muligt.

Børn og unge (op til 18 år):

Der er begrænset erfaring hos børn og unge. Intravenøs administration af furosemid til børn og unge under 15 år anbefales kun i særlige tilfælde.

Doseringen vil blive tilpasset legemsvægt og den anbefalede dosis varierer fra 0,5 til 1 mg/kg legemsvægt dagligt op til en maksimal samlet daglig dosis på 20 mg.

Der bør ske et skift til peroral behandling så hurtigt som muligt.

Nedsat nyrefunktion:

Hos patienter med alvorlig nedsat nyrefunktion (serumkreatinin > 5 mg/dl) anbefales det, at en infusionshastighed på 2,5 mg furosemid pr. minut ikke overskrides.

Ældre:

Den anbefalede startdosis er 20 mg/dag, stigende gradvist indtil der opnås den ønskede respons.

Særlige dosisanbefalinger:

Hos voksne er dosis baseret på følgende betingelser:

- Ødem forbundet til kronisk og akut kongestiv hjertesvigt

Den anbefalede startdosis er 20 til 40 mg dagligt. Denne dosis kan tilpasses patientens respons efter behov. Dosis bør gives i to eller tre individuelle doser pr. dag ved kronisk kongestiv hjerteinsufficiens og som en bolus for akut kongestiv hjertesvigt.

- Ødem associeret med nyresygdom

Den anbefalede startdosis er 20 til 40 mg dagligt. Denne dosis kan tilpasses respons efter behov. Den samlede daglige dosis kan indgives som en enkelt dosis eller som flere doser i løbet af dagen.

Hvis dette ikke fører til en optimal stigning i væskeudskillelse, skal furosemid administreres i kontinuerlig intravenøs infusion, med en initial hastighed på 50 mg til 100 mg pr. time.

Inden påbegyndelse af administrationen af furosemid skal hypovolæmi, hypotension og syre-base og elektrolytiske ubalancer korrigeres.

I dialyserede patienter varierer den sædvanlige vedligeholdelsesdosis fra 250 mg til 1500 mg dagligt.

Hos patienter med nefrotisk syndrom skal dosis bestemmes med forsigtighed på grund af risikoen for en højere forekomst af bivirkninger.

- Ødem associeret med leversygdom

Når intravenøs behandling er absolut nødvendigt, bør den initiale dosis variere fra 20 mg til 40 mg. Denne dosis kan tilpasses respons efter behov. Den samlede daglige dosis kan indgives som en enkelt dosis eller som flere doser.

Furosemid kan anvendes i kombination med aldosteronantagonister i tilfælde, hvor disse midler ikke er tilstrækkelige i monoterapi. For at undgå komplikationer såsom ortostatisk intolerance eller syre-base og elektrolytiske ubalancer eller hepatisk encephalopati skal dosis justeres omhyggeligt for at opnå et gradvis væsketab. Dosis kan frembringe et dagligt vægttab på ca. 0,5 kg hos voksne.

I tilfælde af ascites med ødem bør vægttab induceret af forøget diurese ikke overstige 1 kg/dag.

- Lungeødem (ved akut hjertesvigt)

Initialdosis til indgivelse er 40 mg furosemid ved intravenøs anvendelse. Hvis det patientens tilstand kræver det, gives endnu en injektion på 20 til 40 mg furosemid efter 30 - 60 minutter.

Furosemid bør anvendes som supplement til andre terapeutiske foranstaltninger.

- Hypertensiv krise (i tillæg til andre terapeutiske foranstaltninger)

Den anbefalede initialdosis ved hypertensiv krise er 20 mg til 40 mg administreret i bolus ved intravenøs injektion. Denne dosis kan tilpasses respons efter behov.

4.3 Kontraindikationer

- Overfølsomhed over for det aktive stof eller over for et eller flere af hjælpestofferne
- Patienter med anuri eller nyresvigt med oligoanuria, der ikke reagerer på furosemid
- Nyresvigt som følge af forgiftning med nefrotoksiske eller hepatotoksiske stoffer
- Nyresvigt i forbindelse med hepatisk koma
- Patienter med svær hypokaliæmi eller svær hyponatriæmi
- Patienter med hypovolæmi (med eller uden hypotension) eller dehydrering
- Patienter i prækomatøse eller komatøse tilstande, der er forbundet med hepatisk encefalopati

- Patienter med overfølsomhed over for sulfonamider (fx. Sulfonyureas eller antibiotika af sulfonamidgruppen) kan udvise krydsallergi over for furosemid
- Amning (se pkt. 4.6)

4.4 Særlige advarsler og forsigtighedsregler vedrørende brugen

Omhyggelig kontrol er påkrævet i tilfælde af:
- Patienter med partiel obstruktion af urinvejene (fx. prostatahypertrofi, hydronefrose, ureterostenosis). Diuresen må sikres opretholdt.
- Patienter med hypotension eller med øget risiko for udtalt blodtryksfald (patienter med stenoser i koronararterierne eller hjernens forsyningskar)
- Patienter med manifest eller latent diabetes mellitus eller variation af glykæmi (regelmæssig kontrol af blodsukkeret er påkrævet)
- Patienter med gigt og hyperurikæmi (regelmæssig overvågning af urinsyreniveauer i serum er påkrævet)
- Patienter med leversygdom eller hepatorenalt syndrom (nedsat nyrefunktion associeret til svær leversygdom)
- Hypoproteinæmi (forbundet til nefrotisk syndrom, furosemids virkning kan reduceres, og dets ototoksicitet øges)
- Samtidig administration med lithiumsalte (overvågning af lithiumniveauer er påkrævet, se pkt. 4.5)
- Akut porfyri (brugen af diuretika anses for at være usikker ved akut porfyri og der bør udvises forsigtighed)
- I tilfælde af ascites med ødem bør vægttab induceret af forøget diurese ikke overstige 1 kg/dag
- For kraftig diurese kan forårsage ortostatisk hypotension eller akutte hypotensive episoder.
- NSAID'er kan modvirke den diuretiske virkning af furosemid og andre diuretika. Anvendelse af NSAID'er med diuretika kan øge risikoen for nefrotoksicitet.
- Hvor det angives, skal der tages skridt til at korrigere hypotension eller hypovolæmi, før behandling påbegyndes.

Forsigtig dosistitrering er påkrævet:
- Elektrolytvariationer (fx. hypokaliæmi, hyponatriæmi). Kaliumtilskud og/eller kostforanstaltninger kan være nødvendige for at kontrollere eller undgå hypokaliæmi
- Væskevariationer, dehydrering, reduktion i blodvolumen med kredsløbskollaps og mulighed for trombose og emboli, navnlig hos ældre, ved overdreven anvendelse
- Ototoksicitet (hvis det administreres hurtigere end 4 mg/min) - andre ototoksiske forbindelser administreret samtidigt kan øge denne risiko, se pkt. 4.5
- Administration af høje doser
- Administration ved progressiv og alvorlig nyresygdom
- Administration med sorbitol. Samtidig administration af begge stoffer kan føre til øget dehydrering (sorbitol kan medføre yderligere væsketab ved at inducere diarré)
- Administration ved lupus erythematosus
- Lægemidler, der forlænger QT-intervallet

Symptomatisk hypotension, der fører til svimmelhed, besvimelse eller tab af bevidsthed, kan forekomme hos patienter, der behandles med furosemid, især hos de ældre, patienter på andre medikamenter, som kan forårsage hypotension og patienter med andre medicinske tilstande, hvor der er risiko for hypotension.

Præmature spædbørn (mulig udvikling af nefrocalcinose/nyresten. Nyrefunktionen skal overvåges, og der skal foretages ultralydsscanning af nyrerne). Hos præmature spædbørn med respiratory distress syndrome kan vanddrivende behandling med furosemid i de første uger øge risikoen for vedvarende ductus arteriosus Botalli.

Der skal udvises forsigtighed hos patienter med risiko for elektrolytmangel.

Det anbefales sædvanligvis at foretage en regelmæssig overvågning af serumnatrium, kalium og kreatinin under furosemidbehandling. Der kræves især nøje monitorering af patienter med høj risiko for at udvikle elektrolytforstyrrelser eller i tilfælde af signifikant, yderligere væsketab. (Fx. på grund af opkastning eller diarré).
Hypovolæmi eller dehydrering samt alle udtalte elektrolytforstyrrelser eller syre-base-forstyrrelser skal korrigeres. I sådanne tilfælde kan det være nødvendigt at seponere furosemid midlertidigt.

Hos patienter, der har høj risiko for røntgenkontrastinduceret nefropati, anbefales furosemid ikke til brug for diurese som en del af de forebyggende foranstaltninger mod røntgenkontrastinduceret nefropati.

Samtidig brug af risperidon

I placebokontrollerede forsøg med risperidon hos ældre patienter med demens blev der set en højere forekomst af mortalitet hos de patienter, der blev behandlet med furosemid og risperidon (7,3 %; gennemsnitlig alder 89 år; aldersområde 75-97 år), end hos de patienter, der blev behandlet med risperidon alene (3,1 %; gennemsnitlig alder 84 år; aldersområde 70-96 år) eller med furosemid alene (4,1 %; gennemsnitlig alder 80 år; aldersområde 67-90 år). Samtidig brug af risperidon og andre diuretika (især thiaziddiuretika i lave doser) var ikke forbundet med lignende observationer.

Der er ikke blevet identificeret nogen patofysiologisk mekanisme, der kan forklare denne observation, og der blev ikke set noget konsekvent dødsårsagsmønster. Ikke desto mindre skal der udvises forsigtighed, og risiciene og fordelene ved denne kombination eller samtidig behandling med andre potente diuretika skal overvejes, før der tages en beslutning om eventuel brug. Der var ingen øget forekomst af mortalitet blandt de patienter, der tog andre diuretika samtidig med risperidon. Uanset behandling var dehydrering en generel risikofaktor for mortalitet. Dehydrering skal derfor undgås hos ældre patienter med demens (se pkt. 4.3 Kontraindikationer).

Lysfølsomhed: Tilfælde af lysfølsomhedsreaktioner er blevet rapporteret. Hvis der opstår lysfølsomhedsreaktioner under behandlingen, anbefales det at stoppe behandlingen. Hvis en re-administration skønnes nødvendig, anbefales det at beskytte udsatte områder mod sol og kunstig UVA.

<u>Furosemid Accord 10 mg/ml Injektions-/infusionsvæske (2 ml, 4 ml og 5 ml)</u>

Dette lægemiddel indeholder mindre end 1 mmol (23 mg) natrium pr. ampul, dvs. det er i det væsentlige ”natriumfrit”.

Furosemid Accord 10 mg/ml Injektions-/infusionsvæske (25 ml)

Dette lægemiddel indeholder ca. 93 mg natrium pr. hætteglas. Dette skal tages i betragtning hos patienter på en natrium-kontrolleret diæt.

4.5 Interaktion med andre lægemidler og andre former for interaktion

Ikke anbefalede kombinationer

Lithium:

Lithiumudskillelseniveauer kan reduceres af furosemid, hvilket resulterer i øget kardiotoksisk effekt og lithiumtoksicitet. Denne kombination kan derfor ikke tilrådes (se pkt. 4.4). Hvis denne kombination skønnes nødvendig, bør lithiumniveauerne overvåges nøje og lithiumdosis bør justeres.

Risperidon:

Der skal udvises forsigtighed, og der skal tages højde for risiciene og fordelene ved kombinationen eller samtidig behandling med furosemid eller andre potente diuretika, før der tages en beslutning om eventuel brug. Se pkt. 4.4 vedrørende øget mortalitet hos ældre demenspatienter, der får samtidig behandling med risperidon.

Kombinationer, der kræver en advarsel vedr. brug

Ototoksiske lægemidler (fx. aminoglycosider, cisplatin):

Furosemid kan intensivere visse lægemidlers ototoksicitet, for eksempel cisplatin eller aminoglycosidantibiotika såsom kanamycin, gentamicin og tobramycin, især hos patienter med nedsat nyrefunktion. Da dette kan føre til uoprettelige skader, må disse lægemidler kun bruges med furosemid, hvis der er tvingende medicinske årsager.

Chloralhydrat:

I enkeltstående tilfælde kan der opstå varmefornemmelse, svedudbrud, angst, kvalme, blodtryksstigning og takykardi efter intravenøs administration af furosemid inden for 24 timer efter indtagelse af chloralhydrat. Samtidig administration af furosemid og chloralhydrat skal derfor undgås.

Carbamazepin og aminoglutethimid:

Samtidig administration af carbamazepin eller aminoglutethimid kan øge risikoen for hyponatriæmi.

Andre antihypertensive midler:

Effekten af andre visse antihypertensiva (diuretika og andre lægemidler med blodtrykssænkende potentiale) kan forstærkes af samtidig administration af furosemid.

Hæmmere af angiotensin-konverterende enzym (ACE) og angiotensin II-receptorantagonister:

Virkningerne af andre antihypertensiva kan forstærkes ved samtidig administration af furosemid. Der er set svære blodtryksfald, der i ekstreme tilfælde har været ledsaget af shock og forværring af nyrefunktionen (akut nyresvigt i enkeltstående tilfælde), særligt når der er blevet administreret en ACE-hæmmer for første gang eller for første gang ved høj dosering (first dose hypotension). Hvis det er muligt, bør furosemidbehandlingen afbrydes midlertidigt (eller i det mindste reduceres dosis) i tre dage før behandling med en ACE-hæmmer eller en angiotensin II-receptorantagonister indledes eller dosis af en ACE-hæmmer eller angiotensin II-receptorantagonister øges.

Patienter, der tager diuretika kan risikere forøget hypotension og forringelse af nyrefunktionen. Nedsat nyrefunktion kan også forekomme under den første samtidige administration, eller med den første administration af høje doser af ACE eller en antagonist af angiotensin II-receptoren.

Thiazider:

Der kan opstå en synergistisk effekt af diurese som følge af interaktion mellem furosemid og thiazider.

Diabeteslægemidler:

Der kan forekomme et fald i glukosetolerance, da furosemid kan reducere disse lægemidlers virkning.

Metformin:

Blodets indhold af metformin kan øges af furosemid. Omvendt kan metformin reducere furosemidkoncentration. Risikoen er forbundet med en øget forekomst af laktatacidose ved funktionel nyreinsufficiens.

Hjerteglykosider (fx. digoxin) og andre lægemidler, der kan forårsage forlængelse af QT-intervallet:

Et fald i kaliumniveauer kan øge digitalis-toksicitet; kaliumniveauer skal derfor overvåges.

Nogle elektrolytforstyrrelser kan øge toksiciteten af visse samtidigt administrerede lægemidler, der kan forårsage forlængelse af QT-intervallet (fx. klasse Ia antiarytmika og klasse III antiarytmika såsom amiodaron, sotalol, dofetilid, ibutilid og quinoloner). Kalium-plasma niveauer og EKG skal overvåges.

Fibrater:

Blodets indhold af furosemid og fibrinsyrederivater (fx. clofibrat og fenofibrat) kan øges ved samtidig administration (især i tilfælde af hypoalbuminæmi). Forøgelsen af dets virkning/toksicitet skal overvåges.

Non-steroide anti-inflammatoriske midler og høje doser salicylater:

Non-steroide anti-inflammatoriske midler (herunder coxiber) kan fremkalde akut nyresvigt i tilfælde af allerede eksisterende hypovolæmi og reducere den diuretiske, natriuretiske og antihypertensive virkning. Ved samtidig administration af høje doser af salicylater kan dispositionen for salicylsyretoksicitet øges på grund af en reduceret renaludskillelse eller en modificeret nyrefunktion.

Nefrotoksiske lægemidler (fx. polymyxiner, aminoglycosider, cephalosporiner organoplatiner, immunosuppressiver, jodholdige kontrastmidler, foscarnet, pentamidin):

Furosemid kan forstærke de nefrotoksiske virkninger af nefrotoksiske lægemidler.

Antibiotika såsom cephalosporiner: patienter, der får behandling med furosemid og høje doser af visse cephalosporiner kan udvikle nedsat nyrefunktion.

Der er risiko for cytotoksiske virkninger, hvis cisplatin og furosemid gives samtidig.

Derudover kan cisplatins nefrotoksicitet muligvis øges, hvis furosemid ikke administreres i lave doser (f.eks. 40 mg hos patienter med normal nyrefunktion) og med positive væskebalancer, når det bruges til at opnå tvungen diurese under behandlingen med cisplatin.

Lægemidler, som undergår betydelig renaltubulær sekretion:

Probenecid, methotrexat og andre lægemidler, der, på samme måde som furosemid, gennemgår en udtalt renal tubulær sekretion, reducerer muligvis furosemids effekt. Omvendt nedsætter furosemid muligvis disse produkters renale elimination. Højdosisbehandling (især af både furosemid og de andre lægemidler) kan medføre forhøjede serumniveauer og en større risiko for bivirkninger på grund af furosemid eller det lægemiddel, der administreres samtidigt.

Perifere adrenerge hæmmere:

Disse stoffers virkninger kan forstærkes ved samtidig administration af furosemid.

Phenobarbital og phenytoin:

Efter samtidig administration af disse lægemidler kan der forekomme svækkelse af furosemids virkning.

Tubokurarin, kurarinderivater og succinylcholin:

Disse stoffers muskelafslappende virkning kan forøges eller forlænges af furosemid.

Glukokortikoider, carbenoxolon, amphotericin B, Penicillin G, ACTH, laksantia og lakrids:

Samtidig administration af furosemid med glukokortikoider, carbenoxolon, større mængde lakrids eller langvarig brug af afføringsmidler kan øge kaliumtab. I forbindelse med glukokortikoider bør hypokaliæmi overvejes og dens forværring med overforbrug af afføringsmidler. Da dette kan føre til irreversible høreskader, må denne kombination kun bruges, hvis der er tvingende medicinske årsager.

Kaliumniveau bør overvåges.

Sukralfat:

Samtidig administration af sukralfat og furosemid kan reducere furosemids natriuretiske og antihypertensive effekt. Patienter, der får begge lægemidler, bør observeres nøje for at afgøre, om der er opnået den ønskede diuretiske og/eller antihypertensive effekt af furosemid. Indtaget af furosemid og sukralfat skal adskilles af mindst to timer.

Orale antikoagulantia:

Furosemid øger virkningen af orale antikoagulantia.

Teophyllin:

Virkningerne af theophyllin og kurare-lignende muskelrelaksantia kan forstærkes.

Pressoraminer (fx. adrenalin (epinephrin), noradrenalin (noradrenalin)):

Samtidig brug af furosemid kan svække effekten af pressoraminer.

Andre interaktioner:

Samtidig brug af ciclosporin og furosemid er forbundet med en øget risiko for urinsyregigt.

4.6 Graviditet og amning

Brug under graviditet
Furosemid må ikke anvendes under graviditet, med mindre der er tvingende medicinske årsager. Furosemid passerer placentabarrieren og kan derfor forårsage øget diurese hos fosteret. Behandling under graviditet kræver overvågning af fostrets vækst.

Diuretikabehandling af ødemer og hypertension, forårsaget af graviditet, anbefales generelt ikke, eftersom den fysiologiske hypovolæmi kan forværres og den placentale perfusion muligvis reduceres.
Hvis brugen af furosemid er nødvendig til behandling af hjerte- eller nyreinsufficiens under graviditet, skal der foretages nøje overvågning af elektrolyt-, hæmatokritværdier og fostrets vækst. Mulig fortrængning af bilirubin fra albuminbindingen og dermed øget risiko for icterus nuclearis i hyperbilirubinæmi drøftes for furosemid. Furosemid kan prædisponere fosteret til hypercalcuri, nephrocalcinose, og sekundær hyperparathyroidisme.

Furosemid når 100 % af den maternelle serumkoncentration i navlestrengsblod. Hidtil er der ikke rapporteret om misdannelser hos mennesker, som kan være forbundet med eksponeringen af furosemid. Der foreligger imidlertid utilstrækkelig dokumentation, som kan give en endelig vurdering af en mulig skadelig effekt på embryonet/fostret.

Brug under amning
Furosemid passerer over i modermælken og kan hæmme amning. Kvinder må ikke amme, hvis de behandles med furosemid (se pkt. 4.3).

4.7 Virkninger på evnen til at føre motorkøretøj eller betjene maskiner

Furosemid påvirker i ubetydelig grad evnen til at føre motorkøretøj eller betjene maskiner.

Patienter reagerer individuelt på Furosemid Accord.

Evnen til at føre motorkøretøj eller betjene maskiner kan forbigående blive reduceret på grund af behandling med furosemid, især i starten af behandlingen, ændring af medicinering eller i kombination med alkohol.

4.8 Bivirkninger

Bivirkningernes hyppighed er klassificeret i henhold til følgende konvention:
Meget almindelig (≥1/10)
Almindelig (≥1/100 til <1/10)

Ikke almindelig (≥1/1.000 til <1/100)
Sjælden (1/10.000 til </1.000)
Meget sjælden (<1/10.000). Ikke kendt (kan ikke estimeres ud fra forhåndenværende data).

Blod- og lymfesystem
Ikke almindelig: trombocytopeni. Trombocytopeni kan blive manifest, især med en stigning i blødningstendens.
Sjælden: eosinofili, leukopeni, knoglemarvsdepression. Forekomst af dette symptom nødvendiggør seponering af behandling.
Meget sjælden: hæmolytisk anæmi, aplastisk anæmi, agranulocytose.
Alvorlig dehydrering kan føre til hæmokoncentration med en tendens til at thromboser udvikles især hos ældre patienter.

Immunsystemet
Sjælden: svære anafylaktiske og anafylaktoide reaktioner såsom anafylaktisk chok (behandling se pkt. 4.9).

Det endokrine system
Glucosetolerance kan nedsættes med furosemid. Hos patienter med diabetes mellitus kan dette føre til en forværring af den metaboliske kontrol. Latent diabetes mellitus kan blive manifest.

Metabolisme og ernæring
Hypokaliæmi, hyponatriæmi og metabolisk alkalose kan forekomme, især efter længere tids behandling, eller når der administreres høje doser. Regelmæssig monitorering af serumelektrolytter (især kalium, natrium og calcium) er derfor påkrævet.
Kaliumdepletering kan forekomme, især på grund af dårlig kaliumdiæt. Især ved samtidigt nedsat kalium-tilførsel og/eller øgede ekstrarenale kaliumtab, f.eks. i tilfælde af opkastning eller kronisk diarré). Hypokaliæmi kan forekomme som et resultat af øget renal kaliumtab. Underliggende lidelser (fx. sygdom eller hjertesvigt), samtidig medicin (se pkt. 4.5) og ernæring kan medføre disposition til kaliummangel. I sådanne tilfælde er det nødvendigt med passende overvågning samt substitutionsbehandling.

Som følge af øget renalt natriumtab kan der opstå hyponatriæmi med tilsvarende symptomer, især hvis tilførslen af natriumchlorid er begrænset.

Øget renalt calciumtab kan føre til hypocalcæmi, som kan fremkalde tetania i sjældne tilfælde.
1
Hos patienter med øget renalt magnesiumtab blev der i sjældne tilfælde observeret tetania eller hjertearytmi som følge af hypomagnesiæmi.

Urinsyreniveauer kan stige og der kan forekomme gigtanfald.

Der kan udvikles metabolisk alkalose, eller eksisterende metabolisk alkalose (fx. dekompenseret levercirrose) kan blive mere alvorligt med furosemid.

Nervesystemet
Sjælden: paræstesi, vertigo, svimmelhed, søvnighed, forvirring, fornemmelser af tryk i hovedet.

Ikke kendt: Svimmelhed, besvimelse og bevidstløshed (forårsaget af symptomatisk hypotension)

Øjne
Sjælden: forværring af nærsynethed, sløret syn; synsforstyrrelser med hypovolæmi-symptomer.

Øre og labyrint
Sjælden: dysakusis og/eller syrigmus (tinnitus aurium) på grund af furosemid er sjældent og som regel forbigående. Forekomsten er højere ved hurtig intravenøs administration, især hos patienter med nyresvigt eller hypoproteinæmi (fx. ved nefrotisk syndrom).
Ikke almindelig: døvhed (undertiden irreversibel)

Hjerte
Især i den indledende del af behandlingen og hos ældre kan en meget intens diurese medføre en reduktion i blodtrykket, som, hvis den er udtalt, kan forårsage tegn og symptomer som ortostatisk hypotension, akut hypotension, fornemmelser af tryk i hovedet, svimmelhed, kredsløbskollaps, tromboflebitis eller pludselig død (ved IM- eller IV-administration).

Mave-tarmkanalen
Sjælden: kvalme, opkastning, diarré, anoreksi, gastrisk gene, forstoppelse, mundtørhed.

Lever og galdeveje
Meget sjælden: akut pancreatitis, intrahepatisk kolestase, kolestasisk gulsot, hepatisk iskæmi, stigninger i levertransaminaser.

Hud og subkutane væv
Ikke almindelig: pruritus, dermal- og slimhindereaktioner (fx. bulløs eksantem, udslæt, nældefeber, purpura, erythema multiforme, eksfoliativ dermatitis, lysfølsomhed)
Sjælden: vasculitis, lupus erythematosus forværring eller aktivering.
Ikke kendt: akut generaliseret eksantematøs pustulose (AGEP)

Knogler, led, muskler og bindevæv
Sjælden: muskelkramper i ben, asteni, kronisk arthritis.

Nyrer og urinveje
Diuretika kan forværre eller afsløre symptomer på akut urinretention (blæretømningslidelser, prostatahyperplasi eller forsnævring af urinrøret), vaskulitis, glukosuri, forbigående stigning af blodkreatinin og urinstofniveauer.
Sjælden: interstitiel nefritis.

Graviditet, puerperium og perinatale tilstande

Præmature børn behandlet med furosemid kan udvikle nefrocalcinose og/eller nefrolithiasis pga. calciumdepot i nyrevæv.

Hos præmature spædbørn med respiratory distress syndrome kan vanddrivende behandling med furosemid i de første uger øge risikoen for vedvarende ductus arteriosus Botalli.

Almene symptomer og reaktioner på administrationsstedet
Sjælden: febrile tilstande. Efter IM-injektion kan der forekomme lokale reaktioner såsom smerte.

Undersøgelser
Sjælden: serumkolesterol og triglycerider kan stige under furosemidbehandling.

Indberetning af formodede bivirkninger

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

Lægemiddelstyrelsen

Axel Heides Gade 1

DK-2300 København S

Websted: www.meldenbivirkning.dk

E-mail: dkma@dkma.dk

4.9 Overdosering

Det kliniske billede ved akut eller kronisk overdosering afhænger primært af omfanget og konsekvenserne af elektrolyt- og væsketab (fx. hypovolæmi, dehydrering, hæmokoncentration, hjertearytmi - herunder AV-blokering og ventrikelflimren) på grund af overdreven diurese.

Symptomer:
Symptomer på disse forstyrrelser omfatter svær hypotension (forløber til chok), akut nyresvigt, trombose, deliriske tilstande, paralyse, apati og forvirring.

Behandling:
Ved de første tegn på chok (hypotension, sudorese, kvalme, cyanose) bør injektionen straks afbrydes, patienten placeres med hovedet nedad og sikring af frie luftveje. Væskesubstitution og korrektion af elektrolytforstyrrelser; overvågning af metaboliske funktioner og vedligeholdelse af urinproduktion.

Medicinsk behandling i tilfælde af anafylaktisk chok: fortynd 1 ml 1:1000 adrenalinopløsning i 10 ml og injicér langsomt 1 ml af opløsningen (svarende til 0,1 mg adrenalin). Kontrollér puls og blodtryk og overvåg eventuelle arytmier. Adrenalinadministration kan gentages, hvis det er nødvendigt. Efterfølgende IV-injiceres et glukokotikoid (fx. 250 mg methylprednisolon), hvilket gentages om nødvendigt.

Tilpas de ovennævnte doseringer til børn, i henhold til legemsvægt.

Korrigér hypovolæmi med tilgængelige midler og supplér med kunstig ventilation, ilt og i tilfælde af anafylaktisk chok med antihistaminer.

Der kendes ingen specifik antidot mod furosemid. Hvis overdosering har fundet sted under parenteral behandling består behandlingen i princippet i opfølgning og understøttende behandling. Hæmodialyse accelererer ikke furosemids elimination.

4.10 Udlevering

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5. FARMAKOLOGISKE EGENSKABER

5.0 Terapeutisk klassifikation

Farmakoterapeutisk gruppe: Diuretikum, sulfonamider, usammensatte
ATC-kode: CO3C A01

5.1 Farmakodynamiske egenskaber

Furosemid er et stærkt diuretisk hurtigvirkende middel. Fra et farmakologisk synspunkt hæmmer furosemid reabsorptionen af følgende elektrolytter Na^+, K^+ og $2CL^-$, som ligger på den luminale cellemembran i den ascenderende gren af Henles slynge. Som følge heraf afhænger furosemids effektivitet af, at lægemidlet når frem til det tubulære lumen via en anion-transportmekanisme. Den diuretiske virkning skyldes hæmning af natriumchlorids reabsorption i denne del af Henles slynge. Herved kan natriumudskillelsen udgøre op mod 35 % af den glomerulært udfiltrerede natriummængde. De sekundære virkninger af øget eliminering af natrium er: Øget diurese og øget distal tubulær kaliumsekretion. Udskillelsen af calcium, magnesium, ammonium og bikarbonat øges også.

Furosemid hæmmer feedback-mekanismen ved macula densa og inducerer dosisafhængig stimulering af renin-angiotensin-aldosteron-systemet.

Ved hjerteinsufficiens reducerer furosemid akut hjertets fyldningstryk (gennem dilatation af de venøse kapacitanskar). Denne tidlige vaskulære effekt synes at være prostaglandinmedieret og forudsætter adækvat nyrefunktion med aktivering af renin-angiotensin-aldosteron-systemet og intakt prostaglandinsyntese. Som følge af den natriuretiske virkning sænker furosemid yderligere den vaskulære følsomhed for katekolaminer, der er forhøjet hos hypertonikere.

Furosemids diuretiske virkning indtræder inden for 15 minutter efter intravenøs indgift.

Hos raske forsøgspersoner er påvist en dosisafhængig stigning i diurese og natriurese efter doser på 10-100 mg furosemid. Virkningsvarigheden hos raske forsøgspersoner er ca. 3 timer efter intravenøs indgift af 20 mg samt 3-6 timer efter oral indgift af 40 mg.

Hos patienter er der en S-formet sammenhæng mellem den intratubulære koncentration af ubundet (frit) furosemid (estimeret ved hjælp af furosemids udskillelseshastighed med urinen) og den natriuretiske virkning. Furosemids minimale effektive udskillelseshastighed er ca. 10 mcg/min. Derfor er kontinuerlig infusion mere effektiv end intermitterende bolusinjektioner. Desuden stiger effekten ikke yderligere over en vis bolusdosis. Furosemids virkning reduceres, hvis den tubulære sekretion nedsættes eller stoffet intratubulært bindes til albumin.

5.2 Farmakokinetiske egenskaber

Fordeling
Furosemids fordelingsvolumen er 0,1-0,2 l/kg legemsvægt. Fordelingsvolumen kan øges afhængigt af samtidig sygdom.
Over 98 % er bundet til plasmaproteiner, overvejende albumin.

Elimination
Furosemid elimineres overvejende uomdannet, primært ved sekretion til proksimale nyretubuli. Efter intravenøs administration udskilles 60-70 % furosemid ad denne vej. Furosemid glukuronidmetabolit udgør 10-20 % i urinen. Resten udskilles i fæces, formentlig via galden. Terminal halveringstid efter intravenøs administration er 1-1,5 time. Furosemid udskilles i modermælk. Furosemid passerer placentabarrieren og overføres langsomt til fosteret. Furosemid genfindes i samme koncentrationer hos moderen, fosteret og den nyfødte.

Nedsat nyrefunktion
I tilfælde af nedsat nyrefunktion er furosemids eliminering langsommere og halveringstiden øges. Hos patienter med terminal nyresygdom er den gennemsnitlige halveringstid 9,7 timer. Ved multiorgansvigt kan halveringstiden variere fra 20-24 timer.
Ved nefrotisk syndrom medfører den nedsatte plasmaproteinkoncentration en øget koncentration af ubundet (frit) furosemid. På den anden side nedsættes effekten af furosemid hos disse patienter pga. nedsat sekretion samt binding til intratubulært albumin. Furosemid er dårligt dialyserbart hos patienter i hæmodialyse, peritonealdialyse og CAPD (kontinuerlig ambulant peritonealdialyse).

Nedsat leverfunktion
Ved leverinsufficiens er halveringstiden øget 30-90 %, primært som følge af et større fordelingsvolumen. Biliær elimination kan blive reduceret (op til 50 %). Desuden udviser alle farmakokinetiske parametre en bred variation i denne patientgruppe.

Kongestiv hjerteinsufficiens, svær hypertension, ældre
Furosemids eliminationen er mindsket pga. nedsat nyrefunktion hos patienter med kongestiv hjerte-insufficiens eller svær hypertension samt hos ældre.

Præmature og nyfødte

Afhængig af nyrernes modning kan eliminationen være nedsat. Metaboliseringen reduceres, hvis spædbarnets kapacitet til glukuronering er forringet. Terminal halveringstid er mindre end 12 timer hos nyfødte.

5.3 Prækliniske sikkerhedsdata

Studier af kronisk toksicitet hos rotter og hunde medførte nyreforandringer (bl.a. fiberdegeneration og nefrocalcirose). Furosemid viste ikke genotoksisk eller karcinogent potentiale.

I forsøg med reproduktiv toksikologi hos rottefostre forekom der et begrænset antal differentierede glomeruli, knoglemisdannelser af scapula, humerus og ribben (induceret af hypokaliæmi) samt hydronefrose i muse- og kaninfostre efter administration af høje doser. Resultaterne af en undersøgelse med mus og en ud af tre undersøgelser med kaniner viste en øget forekomst og sværhedsgrad af hydronefrose (udspilning af nyrebækkenet og, i nogle tilfælde, af urinlederne) hos fostre fra de behandlede moderdyr i forhold til dem fra kontrolgruppe.

Præmature kaniner, der fik furosemid, havde en højere forekomst af intraventrikulær blødning end saltvandsbehandlede i samme kuld, muligvis på grund furosemid-induceret intrakraniel hypotension.

6. FARMACEUTISKE OPLYSNINGER

6.1 Hjælpestoffer

Natriumchlorid
Natriumhydroxid
Vand til injektionsvæsker

6.2 Uforligeligheder

Furosemid kan præcipitere ud af opløsning i væsker med lav pH. Dette lægemiddel må ikke anvendes samtidig med andre lægemidler, med undtagelse af de, der er nævnt i pkt. 6.6.

6.3 Opbevaringstid

Uåbnet: 3 år
Efter første åbning: Efter åbning bør produktet straks anvendes.
Efter fortynding Der er påvist kemisk og fysisk stabilitet under brug i 24 timer ved 25 °C, beskyttet mod lys.

Af mikrobiologiske hensyn skal produktet anvendes straks. Hvis præparatet ikke anvendes straks, er brugsopbevaringstider og -forhold før anvendelse brugerens ansvar. Det bør sædvanligvis ikke opbevares længere end 24 timer ved 2-8 °C, med mindre fortynding har fundet sted under kontrollerede og validerede aseptiske forhold.

6.4 Særlige opbevaringsforhold

Må ikke opbevares over 25 °C.
Må ikke opbevares i køleskab.
Opbevar ampuller/hætteglas i den ydre karton for at beskytte mod lys.
Opbevaringsforhold for det fortyndede lægemiddel, se pkt. 6.3.

6.5 Emballagetyper og pakningsstørrelser

20 mg i 2 ml: ravfarvet ampul med to hvide ringe og hvid OPC-prik med 2 ml opløsning.
40 mg i 4 ml: ravfarvet 5 ml ampul med hvid afbrækning og blå ring med 4 ml opløsning.
50 mg i 5 ml: ravfarvet 5 ml ampul med hvid afbrækning og hvid ring med 5 ml opløsning.
250 mg i 25 ml: Type I ravfarvet hætteglas forseglet med en chlorbutylgummiprop og aluminiumsforsegling og en rød afbrækningshætte indeholdende 25 ml opløsning.

Pakningsstørrelser:

5,10 x 2 ml ampuller

1, 5, 10 x 4ml ampuller

5,10 x 5ml ampuller

1, 5, 10 x 25 ml hætteglas

Ikke alle pakningsstørrelser er nødvendigvis markedsført.

6.6 Regler for destruktion og anden håndtering

Furosemid-injektion fortyndet til 1 mg/ml er kompatibel med 0,90 % NaCl-infusionsvæske, og sammensat natriumlactat-injektionsvæske i 24 timer. Fortyndingen af opløsning til injektion skal foretages under aseptiske forhold.

Opløsningen skal inspiceres visuelt for partikler og misfarvning før administration. Opløsningen bør kun anvendes, hvis opløsningen er klar og fri for partikler. Ikke anvendt lægemiddel samt affald heraf skal bortskaffes i henhold til lokale retningslinier. Kun til engangsbrug, resterende indhold kasseres efter brug.

Furosemid Accord 10 mg/ml Injektions-/infusionsvæske, opløsning må ikke blandes med andre lægemidler i indsprøjtningsflasken.

7. INDEHAVER AF MARKEDSFØRINGSTILLADELSEN

Accord Healthcare Limited
Sage House, 319, Pinner Road
North Harrow, Middlesex, HA1 4HF
Storbritannien

8. MARKEDSFØRINGSTILLADELSESNUMMER (NUMRE)

55263

9. DATO FOR FØRSTE MARKEDSFØRINGSTILLADELSE

8. september 2015

10. DATO FOR ÆNDRING AF TEKSTEN

20. februar 2017

14.4 Appendix 4. Charter for the independent Data Monitoring Committee (DMC)

Introduction
This charter will define the minimum of obligations and responsibilities of the DMC as perceived by the GODIF Management Committee. The charter will outline the procedures for ensuring confidentiality, proper communication, implementation of the statistical monitoring guidelines, and describe the content of open and closed reports which will be provided to the DMC.

Primary responsibilities of the DMC
The DMC will be responsible for monitoring the overall conduct of the trial, safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial. DMC may provide recommendations relating to the recruitment/selection/retention of participants, about management of the participants, improving adherence to protocol, and procedures for data management and quality control. The DMC will provide recommendations about stopping or continuing the trial to the Management Committee of the GODIF trial.

The DMC will be advisory to the GODIF Management Committee, which will be responsible for reviewing the DMC recommendations promptly, to decide whether to continue or stop the trial, and to assess if amendments to the protocol or changes in trial conduct are required.

The DMC plan their own monitoring meetings to evaluate the planned interim analyses of the GODIF trial or other aspects of safety for trial participants. The interim analyses will be performed by an independent statistician. The sponsor will report the overall number of SARs annually to the DMC. The DMC can, at any time during the trial, request information about distribution of the events, outcome measures, and serious adverse reactions (SARs) according to intervention group. The DMC may also request unblinding of the intervention (see section on ‘closed sessions’) if deemed necessary by the data. The recommendations regarding stopping, continuing, or changing the design of the trial should be communicated without delay to the Management Committee of the GODIF trial. Within 48 hours the Management Committee has the responsibility to inform all investigators and sites participating in the trial, about the recommendation from the DMC and the Management Committee’s decision hereof.

Members of the DMC
The DMC is an independent group consisting of two clinicians and a biostatistician. They have experience in the management of ICU patients and in the conduct, monitoring, and analysis of randomised clinical trials.

<u>DMC Clinician</u>
Jonathan Silversides, MD, consultant, Queen’s University Belfast, UK

<u>DMC Trialist</u>
Paul Young, MD, specialist, medical Research Institute of New Zealand

DMC Biostatistician
Andreas Kryger Jensen, ass. professor, Department of Biostatistics, University of Copenhagen, Denmark.

Conflicts of interest
DMC members will sign a declaration of conflicts of interests and the members must be without any conflicts of interest. The conflicts may be financial, scientific, or regulatory in nature. Trial investigators or individuals employed by the sponsor, or individuals with regulatory responsibilities for the trial products cannot be members of the DMC. The DMC members do not own stocks in companies having products investigated by the GODIF trial.
The DMC members will disclose any consulting agreements or financial interests they have with the sponsor of the GODIF trial, with the contract research organisation (CRO) for the trial (if any), or with other sponsors having products that are being evaluated or having products that are competitive with those being evaluated in the GODIF trial. The DMC is responsible for deciding whether these consulting agreements or financial interests impact their objectivity in relation to the GODIF trial.

The DMC members must advice fellow members of any changes in these consulting agreements and financial interests that occur during the trial. If a DMC member develops significant conflicts of interest during the trial, the member should resign from the DMC.
DMC membership is for the duration of the clinical trial. If any members leave the DMC during the trial, the Management Committee will appoint the replacement.

Formal interim analysis meetings
Two formal interim analysis meetings will be held to review data relating to protocol adherence, treatment efficacy, and safety of the participants. The three members of the DMC will meet when 90-day follow-up data of 100 participants (10% of sample size) and 500 participants (50% of sample size) have been obtained.

Proper communication
Procedures will be implemented to ensure the DMC has sole access to evolving information from the clinical trial regarding comparative results of efficacy and safety data, aggregated by treatment group. An exception will be made to permit access to an independent statistician who will be responsible for serving as a link between the database and the DMC.
Open and closed sessions will be held to provide a forum for exchange of information among the parties who share the responsibility for successful conduct of the trial. The intent is to enable the DMC to preserve confidentiality of the comparative efficacy results and provide an opportunity for interaction between the DMC and others who have valuable insights into trial-related issues.

Closed sessions
Sessions involving only DMC members who generate the closed reports (called closed sessions) will be held to allow discussion of confidential data from the clinical trial, including information about the protocol adherence, and the relative safety and efficacy of interventions. To ensure that the

DMC's primary mission of safeguarding the interest of participants, the DMC will be blinded in its assessment of safety and efficacy data. However, the DMC can request unblinding from the Management Committee.

Closed reports will contain analysis of the primary outcome measure. These closed reports will be prepared by an independent biostatistician (a member of the DMC), with assistance from the trial data manager, in a way that allow them to remain blinded. The closed reports should provide information that is precise, with follow-up on mortality that is completed within two months from the date of the DMC meeting.

Open reports
On the DMC meetings, open reports will be available to all who attend the meeting. The reports will include data on recruitment and baseline characteristics, data on eligibility violations, completeness of follow-up, and compliance. The independent statistician (member of the DMC) will prepare these open reports in co-operation with the trial data manager.

Minutes of the DMC Meetings
The DMC will write minutes of their meetings with a description of the proceedings from all sessions, including the listing of recommendations by the committee. The minutes will be closed because they might contain unblinded information and must not reach individuals outside DMC.

Recommendations to the Management Committee
The planned interim analyses will be conducted after participant no. 100 and no. 500 has been followed for 90 days. The first interim analysis after 100 participants will only be on the process variables to ensure separation between the groups. The second interim analysis after 500 participants will be on primary outcome and SAE/SAR.
After the interim analysis meetings, the DMC will make a recommendation to the MC to continue, hold or terminate the trial.
The DMC will conduct a qualitative assessment of the results from the interim analysis of process variables to make recommendations for the trial. For the interim analysis after 500 participants of primary outcome measure and SAR/SAR - the DMC will recommend pausing or stopping the trial if group-difference is found with statistical significance levels adjusted according to the Lan DeMets group sequential monitoring boundaries based on O'Brien Fleming alfa-spending function[3].

If the recommendation is to stop the trial, the DMC will discuss whether the final decision to stop the trial will be made after the analysis of all participants included at the time (including participants randomised after this interim analysis) or whether the trial should be set on hold during these extra analyses. If further analyses are recommended after the interim analysis the rules for finally recommending stopping of the trial should obey the Lan DeMets stopping boundary[3]. Furthermore, the DMC can recommend pausing or stopping the trial if continued conduct of the trial clearly compromises participant safety. However, stopping for futility to show an intervention effect of 15% RRR (or RRI) for in-hospital mortality and improvement of 8% for 'days alive outside hospital at day 90' will not be an option. An intervention effect less than these may be clinically relevant as well.

The recommendation will be based primarily on safety and efficacy considerations and will be guided by statistical monitoring guidelines defined in trial protocol and this charter.

The Management Committee and the DMC are responsible for safeguarding the interests of participants and for the conduct of the trial. Recommendations to amend the protocol or on conduct of the trial made by the DMC will be considered and decided upon by the Management Committee. The Management Committee will be responsible for deciding whether to continue, hold or stop the trial based on the DMC recommendations. The DMC will be notified of all changes to the trial protocol or conduct.

Statistical monitoring guidelines
The outcome parameters are defined in the GODIF trial protocol. The DMC will evaluate data on:

Interim analysis of process variables after 100 participants have completed 90-days follow-up
Process variables:
- Mean cumulative fluid balance in mL after 3 days or censoring at discharge for participants in the two groups
- Number of days with escape medicine per participant

Interim analysis of process variables after 500 participants have completed 90-days follow-up
Primary outcome and SAE/SAR:
The primary outcome measure: Days alive and out of hospital day 90 after randomisation.
Number of participants with one or more SAEs/SARs at day 90.

The DMC will be provided with these data from the coordinating centre as:
- Number of participants randomised
- Number of participants randomised per intervention group
- Number of participants stratified per stratification variable per intervention group
- Number of events, according to the outcomes, in the two groups

Based on evaluations of these outcomes, the DMC will decide if they want further data from the coordinating centre for analysis and when to do the analyses. The data will be provided in one file as described below.

The DMC can be asked to ensure that procedures are properly implemented, to adjust trial sample size or duration of follow-up to restore power, if protocol specified event rates are inaccurate. If so, the algorithm for this should be clearly described.

Conditions for transfer of data from the Coordinating Centre to the DMC
The DMC will be provided with a CSV file containing the data defined as follows:

- Row 1 contains the names of the variables (to be defined below).
- Row 2 to N (where N-1 is the number of participants in the trial) each contains the data of one participant.

- Column 1 to p (where p is the number of variables to be defined below) each contains in row 1 the name of a variable and in the next N rows the values of this variable.

The values of the following variables should be included in the database for the first interim analysis:

1. screening_id: a number that uniquely identifies the participant
2. rand_code: The randomisation code (group 0 or 1). The DMSC will be blinded for group-intervention.
3. Mean cumulative fluid balance for the first 3 days or censoring at discharge.
4. Number of days with escape medicine per participant

The values of the following variables should be included in the database for the second interim analysis:

1. screening_id: a number that uniquely identifies the participant
2. rand_code: The randomisation code (group 0 or 1). The DMSC will be blinded for group intervention.
3. days alive outside hospital during the 90 days observation period for each patient.
4. day_90_indic: 90 day-mortality indicators (2 = censored, 1 = dead, 0 = alive at day 90)
5. SAE/SAR_indic: SAE/SAR indicator (1 = one or more SAES/SARs, 0 = no SAE/SAR)

14.5 Appendix 5. Informed consent, Denmark

In emergency research in Denmark where patients are temporarily incompetent due to critical illness and need immediate initiation of treatment, they will be enrolled in the trial followed by informed consent from a trial guardian and next of kin as soon as possible after enrolment. Participants, who regain competence, will be asked for informed consent as soon as possible. The process leading to the achievement of informed consent will follow all applicable regulations. The consenting party will be provided with written and oral information about the trial, so he/she can make an informed decision about participation in the trial. The information will be given in a separate room, and the consenting party has the right to bring a companion.
Written information and consent forms will be subjected to review and approval by the relevant ethics committees.

Trial guardian: a doctor independent of the interests of the principal investigator and any other interests in the trial project. The trial guardian must have professional knowledge of the research area. All attempts of collecting the written consent must be documented in the medical chart or in a log. Before the guardian signs the consent form, written information about the GODIF trial will be handed out.

Next of kin: After enrolment in the trial consent from next of kin must be obtained as fast as possible without undue delay and must be obtained within a few days. If the relatives are not present at the ICU at the time of randomisation, the clinical staff must inform them when they arrive at the ICU. In cases where the next of kin do not visit the ICU daily, they must be contacted by telephone to arrange a meeting for trial information. This ensures that the information is provided without delay. Information should always be adjusted to the situation. Oral and written information about the trial must be provided. The relatives must have time to read the material, think about it and ask questions about the trial before they give their written consent. If the next of kin does not give consent, the trial intervention must be stopped. The next of kin will be asked for permission to continue data collection. All contacts to the next of kin concerning the consent must be documented in the patient file.

Specific situations.

- If the next of kin seems to be in a state or condition where they are not able to understand or relate to the information about the trial, it must be documented in the patient files and reviewed daily.
- If the next of kin does not come to the ICU in the first couple of days – they should be contacted by phone and informed about the trial. The call must be documented in the patient files. Also, if the next of kin is not reached.
- If information about the participant's next of kin is not available after inclusion, the investigator will seek information from e.g. the participant's general practitioner, the police, nursing homes etc. In this situation, it may take 1-2 weeks to conclude that no next of kin can be identified. If no one is identified and the participant remains incompetent the trial

intervention will be discontinued. All initiatives to identify the participant's next of kin will be documented in patient files, logs or similar.
- The next of kin does not have to be family but can be a friend, neighbour, a contact person from a home or another relevant facility.

The patient: when the patient regains competence, he/she will receive written and oral information about the trial. Most patients are regarded as competent when their treatment in the ICU is ended and they are referred to another department. Most informed consents are expected to be obtained at that time or before they are discharged from the hospital. In case, it is not possible the patient must be contacted by phone and the written information about the trial and consent form mailed or sent by post. A few participants are expected to regain competence within a few days from randomisation. If that happens before consent from relatives can be obtained, the patient can sign the consent and no further consent from the relatives is required.

Specific situations:

- If a competent patient has difficulties in reading and writing because of acute/chronic disease a witness can be used to document the patient's consent. The witness can be a nurse or other staff. The witness must write his/her name in capital letters, signature, date and that they witness the patient's consent.
- If a patient at the time of referral to another department or home is not competent because of delirium/psychosis or other conditions of the kind. Informed consent must be obtained later. Consent can only be obtained from a competent patient. The patients must regularly be contacted and re-evaluated if he/she has regained competence. These contacts must be documented in a file or log.
- If the patient has a legal guardian. The guardian can give consent on behalf of the patient (if the guardian has the authorisation to do so).
- If the patient dies before it is possible to obtain informed consent (from the patient), data can be collected during the trial and used if consent by the trial guardian is documented in patient files/log or other.
- If the patient dies before informed consent has been obtained (due to rapid progression of critical illness or because the participant's next of kin is not yet identified) and the participant has been correctly included in the trial, the collected data will be kept for analysis.

Deviation from the standard informed consent

According to the standard informed consent form from the National Ethics Committee regarding competent participants, the participant can choose not to receive information about the data collected during the trial. However, the purpose of this trial is not to generate new knowledge about the specific participant, so we find that this question is redundant, and have omitted the question from the consent form to spare the participant from making unnecessary decisions.

Trial personnel

Screening will be performed by medical doctors, research nurses, or medical students working under the responsibility of a trained medical doctor. Collection of informed consent will be performed by doctors only. If questions arise during informed consent, responsible study personnel can be reached through a 24-hour hotline. All personnel with functions in the GOODIF trial will be trained and approved according to GCP guidelines before engaging in the trial.

14.6 Appendix 6. Simplified Mortality Score for the Intensive Care Unit (SMS-ICU)

In trial settings, the variables are measured in the 24-h period before randomisation; further details are presented in appendix 2 and in reference [61].

SMS-ICU	
Age	
≤ 39 years → **0**	
40-59 years → **5**	
60-79 years → **10**	
≥ 80 years → **13**	
Lowest systolic blood pressure	
≤ 49 mmHg → **6**	
50-69 mmHg → **5**	
70-89 mmHg → **3**	
≥ 90 mmHg → **0**	
Acute surgical admission	
No → **3**	Yes → **0**
Hematologic malignancy or metastatic cancer	
No → **0**	Yes → **7**
Vasopressors/inotropes	
No → **0**	Yes → **4**
Respiratory support	
No → **0**	Yes → **5**
Renal replacement therapy	
No → **0**	Yes → **4**
Total score: 0-42 points	

Total score and predicted 90-day mortality risk			
0	3.3 %	22	40.1 %
3	4.8 %	23	43.4 %
4	5.5 %	24	46.7 %
5	6.2 %	25	50.1 %
6	7.1 %	26	53.5 %
7	8.0 %	27	56.9 %
8	9.1 %	28	60.2 %
9	10.3 %	29	63.4 %
10	11.6 %	30	66.4 %
11	13.1 %	31	69.4 %
12	14.7 %	32	72.2 %
13	16.5 %	33	74.8 %
14	18.4 %	34	77.3 %
15	20.5 %	35	79.6 %
16	22.8 %	36	81.7 %
17	25.3 %	37	83.7 %
18	28.0 %	38	85.4 %
19	30.8 %	39	87.0 %
20	33.8 %	41	89.8 %
21	36.9 %	42	91.0 %
Use the worst values recorded during the first 24 hours in the ICU.			

14.7 Appendix 7. Co-enrolment

Based upon an updated critical appraisal of the literature, the GODIF Management Committee endorses and encourages co-enrolment in the GODIF trial. The following issues have been considered.

Ethical considerations
Preventing eligible patients from co-enrolment in trials, which they would authentically value participating in, and whose material risks and benefits they understand, violates their autonomy - and thus contravenes a fundamental principle of research ethics[64].
Permitting co-enrolment is in accordance with existing recommendations for the conduct of trustworthy clinical practice guidelines, considering benefits and harms, quality of evidence, values and preferences (of patients or their proxies) and cost considerations, as outlined by the Institute of Medicine, the Guideline International Network, and according to the GRADE methodology[65–67].
Patient relatives have limited concerns about co-enrolment[68].

General considerations
Critically ill patients receive many different interventions in addition to the trial intervention because of acute and chronic illness. Consequently, the potential for interactions is a prerequisite in clinical trials in critically ill patients, and co-enrolment is thus little different from what occurs in single-enrolment trials[64].
In large pragmatic trials, like the GODIF trial, other interventions will be given at random and are therefore difficult to control for. If interaction in fact is an issue, it may be better controlled for if patients are co-enrolled and randomised to more than one intervention.
Factorial design trials allow detailed assessment of interactions between interventions, and are considered cost-efficient, as two or more treatments are assessed for the price of one[69]. Co-enrolment trials and factorial design trials share many similarities[64].

A pre-planned sub-study will assess the impact of co-enrolment in the GODIF trial, and thus generate valuable knowledge on the topic of co-enrolment.
Clinical research with a potential to inform and improve clinical practice is valuable and should be supported. More high-quality clinical research can be conducted in a timely fashion and more information can be generated to guide clinical practice, if co-enrolment is permitted[70].

Scientific and statistical considerations
Pragmatic clinical trials allowing inclusion of a broad range of trial participants and options for drug treatments and other therapies (co-enrolment) have higher external validity/generalisability than non-pragmatic trials with restrictions regarding trial participants and co-enrolment[71].
Non-pragmatic trials with restrictions regarding study participants and co-enrolment are exposed to drugs and other treatments in a less clinically relevant setting where interactions are largely

uncontrolled and poorly evaluated. Co-enrolment in pragmatic trials facilitates evaluation of clinically relevant patient-important interactions[64].

Co-enrolment into two or more trials does not invalidate the original randomisation of the individual trials. Separate analysis of each individual trial, ignoring the issue of co-enrolment into the other trial, will retain the balance of patient characteristics expected by standard random assignment within each trial[64].

The National Institute of Health supports co-enrolment[66], so does the Canadian Critical Care Trials group (http://www.ccctg.ca/Home.aspx) and the Australian New Zealand Intensive Care Society's Clinical Trial Group (http://www.anzics.com.au/Pages/CTG/CTG-home.aspx).
Co-enrolment into two or more trials does not seem to affect the natural course of the disease of the other condition being studied[64].

Co-enrolment does not appear to influence patient safety or trial results[72,73].

Empirically, co-enrolment has a small effect on study power[64]. In conclusion, we highly support and encourage co-enrolment because of overall benefit, including ethical, practical and scientific benefit, and no evidence of harm.

14.7.1 Co-enrolment agreement form

In general, we will encourage engagement in research projects other than the GODIF trial.
Please, fill in the information of the trial to be evaluated as counterpart for co-enrolment with GODIF, and send it by e-mail to contact@cric.nu.

Once we have received the information below, we will contact the principal/coordinating investigator of the trial and facilitate exchange of protocols and other relevant documents between the Management Committees. You will find a list of titles already considered for co-enrolment by clicking http://www.cric.nu/co-enrolment-list/

We have prepared the form for only one trial, but please feel free to copy as many forms as you need.

a. Official full/short title of the project and clinicaltrials.gov no.:

b. Contact information of principal/coordinating investigator of the trial:

Name:

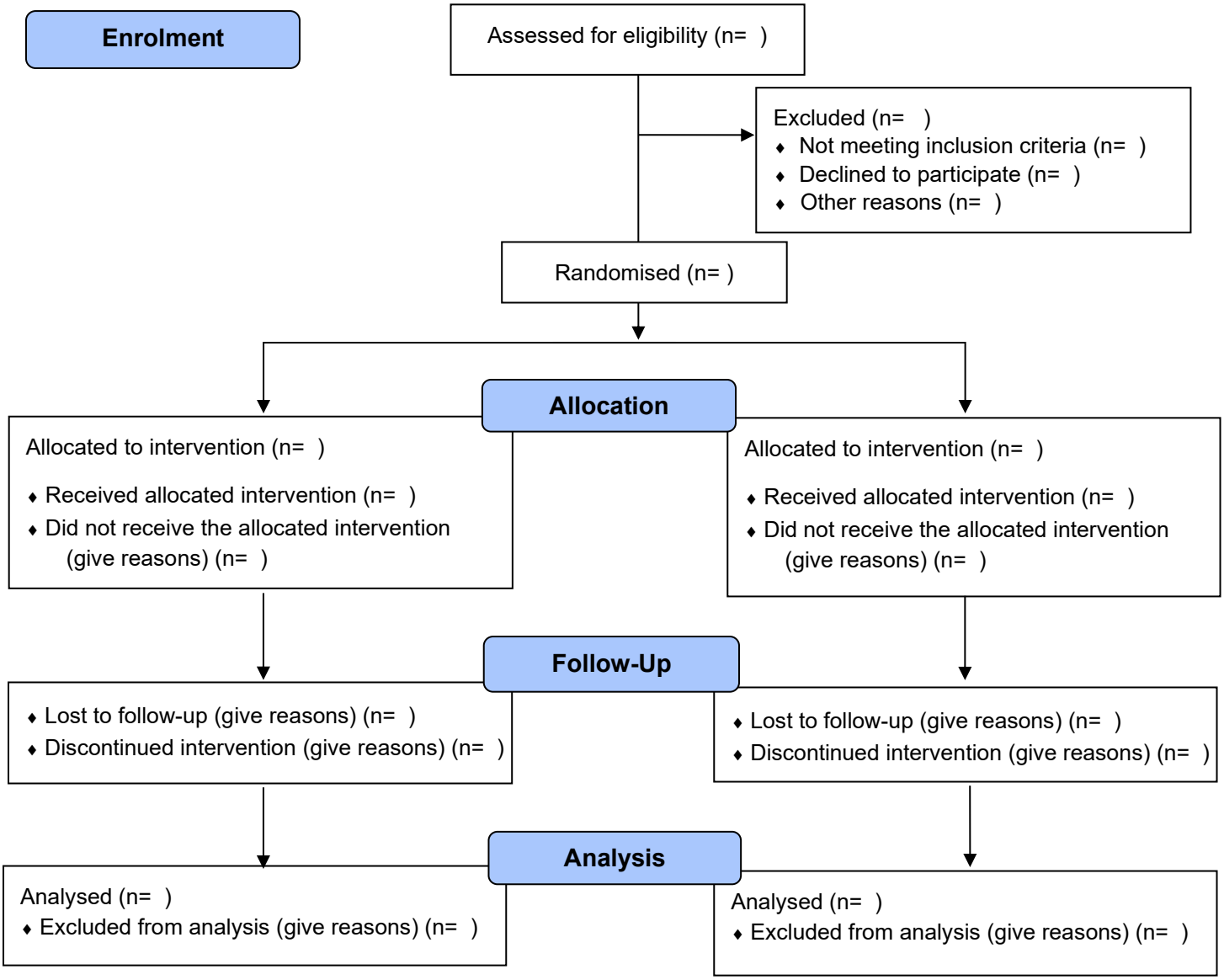
E-mail:

14.8 Appendix 8. List of proposed sub-studies

FO is a risk factor for AKI and for this reason, we want to make a sub-study of this group of participants. We will look at:

- Number of participants with AKI at randomisation
- Number of participants developing AKI during the trial in the two groups
- Number of recoveries from AKI during the trial.
- KDIGO grading will be used to describe the severity of AKI.
- Electrolyte disturbances in the two groups

14.9 Appendix 9. Trial flow chart



14.10 Appendix 10. International Committee of Medical Journal Editors (ICMJE) form for potential conflict of interest

ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

SAVE

ICMJE Form for Disclosure of Potential Conflicts of Interest

Instructions

The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. The form is designed to be completed electronically and stored electronically. It contains programming that allows appropriate data display. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in six parts.

1. Identifying information.

2. The work under consideration for publication.

This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking "No" means that you did the work without receiving any financial support from any third party -- that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check "Yes".

3. Relevant financial activities outside the submitted work.

This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. You should disclose interactions with ANY entity that could be considered broadly relevant to the work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

4. Intellectual Property.

This section asks about patents and copyrights, whether pending, issued, licensed and/or receiving royalties.

5. Relationships not covered above.

Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.

Definitions.

Entity: government agency, foundation, commercial sponsor, academic institution, etc.
Grant: A grant from an entity, generally [but not always] paid to your organization
Personal Fees: Monies paid to you for services rendered, generally honoraria, royalties, or fees for consulting , lectures, speakers bureaus, expert testimony, employment, or other affiliations
Non-Financial Support: Examples include drugs/equipment supplied by the entity, travel paid by the entity, writing assistance, administrative support, etc.
Other: Anything not covered under the previous three boxes
Pending: The patent has been filed but not issued
Issued: The patent has been issued by the agency
Licensed: The patent has been licensed to an entity, whether earning royalties or not
Royalties: Funds are coming in to you or your institution due to your patent

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name) | 2. Surname (Last Name) | 3. Date

4. Are you the corresponding author? ☐ Yes ☐ No

5. Manuscript Title

6. Manuscript Identifying Number (if you know it)

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☐ No

ADD

Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were **present during the 36 months prior to publication.**

Are there any relevant conflicts of interest? ☐ Yes ☐ No

ADD

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☐ No

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14.11 Appendix 11. Budget for 2020-2023

Budget	DKK
Statistician/trial manager/Copenhagen Trial Unit/IT (eCRF)	1.300.000
Salary to project nurse	350.000
Salary to PhD-students	2.428.596
Case money	3.000.000
GCP-monitoring	650.000
Patient insurance	300.000
Fees (publications, MoCA certification, Ph.D. fee to university, conferences e.c.t.)	280.000
Meetings/visits/initiation of sites, travel to sites in DK and Europe	120.000
Trial drug (production and distribution)	900.000
Budget in total	9.328.596

14.12 Appendix 12. Mottling score

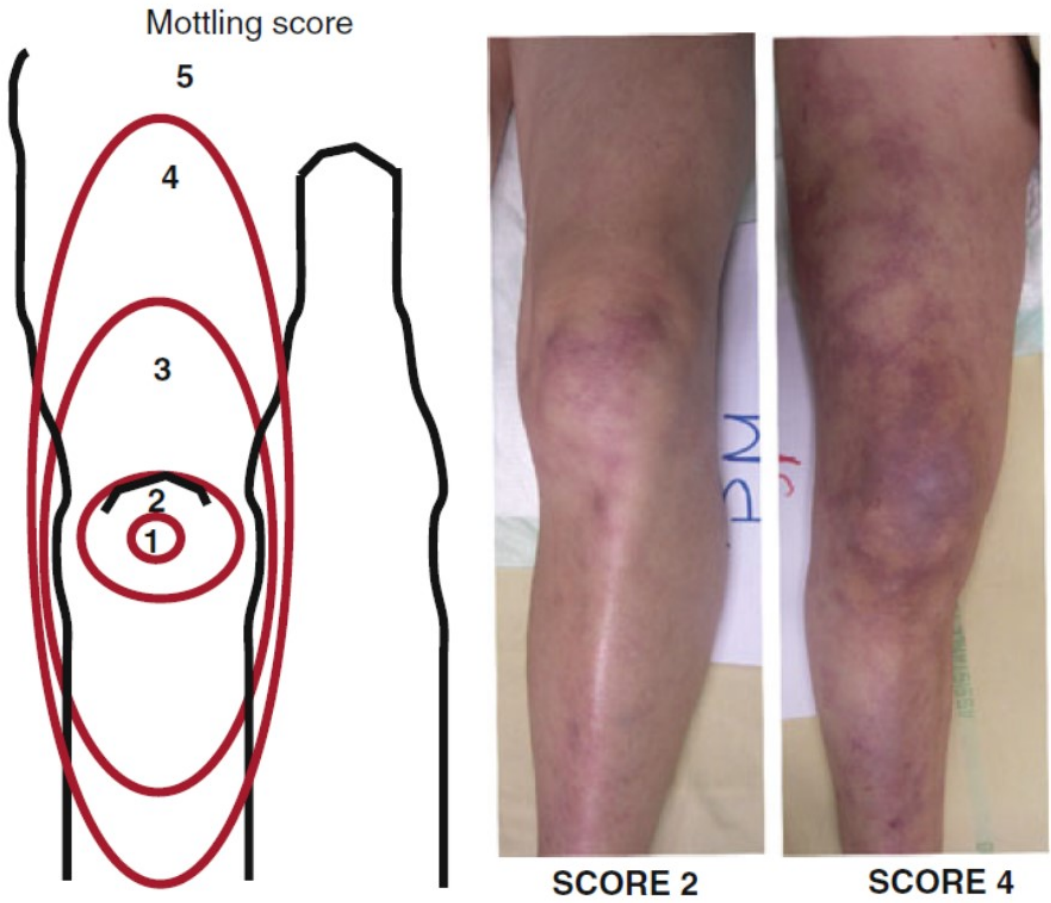

Fig. 1 *Left*: the mottling score is based on a mottling area extension on the legs. Score 0 indicates no mottling; score 1, a modest mottling area (coin size) localized to the center of the knee; score 2, a moderate mottling area that does not exceed the superior edge of the kneecap; score 3, a mild mottling area that does not exceed the middle thigh; score 4, a severe mottling area that does not go beyond the fold of the groin; score 5, an extremely severe mottling area that goes beyond the fold of the groin. *Right*: Examples of the mottling score

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14.13 Appendix 13. 5 % Fluid overload - Mortality and morbidity

Baseline and outcome data stratified for 5% FO			
	FB < 5% BW	**FB > 5% BW**	***p***
Total*,n	367	460	
Demographic			
Age, years, mean (sd)	66 (15)	66 (14)	0.63
Male gender, n(%)	**237 (65%)**	**266 (58%)**	0.05
Weight, kg, mean (sd)	**83(22)**	**74 (17)**	< 0.01
Admission type, n(%)			
Medical	199 (54%)	246 (54%)	0.83
Elective surgery	**25 (7%)**	**13 (3%)**	< 0.01
Acute Surgery	143 (39%)	201 (44%)	0.18
Disease severity			
SAPS II, mean (sd)	**49 (17)**	**55 (17)**	< 0.01
Missing, n	1		
KDIGO-grade at admission, n(%)			
I	**212 (58%)**	**223 (49%)**	< 0.01
II	**62 (17%)**	**116 (25%)**	< 0.01
III	93 (25%)	121 (26%)	0.81
Severe sepsis or septic shock	**109 (30%)**	**237 (52%)**	< 0.01
Oliguria, n(%)	**73 (22%)**	**154 (34%)**	< 0.01
Need for mechanical Ventilation, n(%)	**300 (82%)**	**401 (87%)**	0.03
Need for norepinephrine, n(%)	**232 (63%)**	**347 (75%)**	< 0.01
Need for renal replacement therapy, n(%)	**97 (26%)**	**171 (37%)**	< 0.01
Outcome			
Length of Stay, days, median (IQR)	**4 (2 to 7)**	**7 (3 to 14)**	< 0.01
Recovery status at day 28, n(%)			
Recovery	**246 (70%)**	**247 (54%)**	< 0.01
Non-recovery	52 (15%)	56 (12%)	0.35
Death prior to recovery	**55 (16%)**	**152 (33%)**	< 0.01
Missing, n(%)	14 (4%)	5 (1%)	
Mortality at day 28, n(%)	**85 (23%)**	**192 (42%)**	< 0.01

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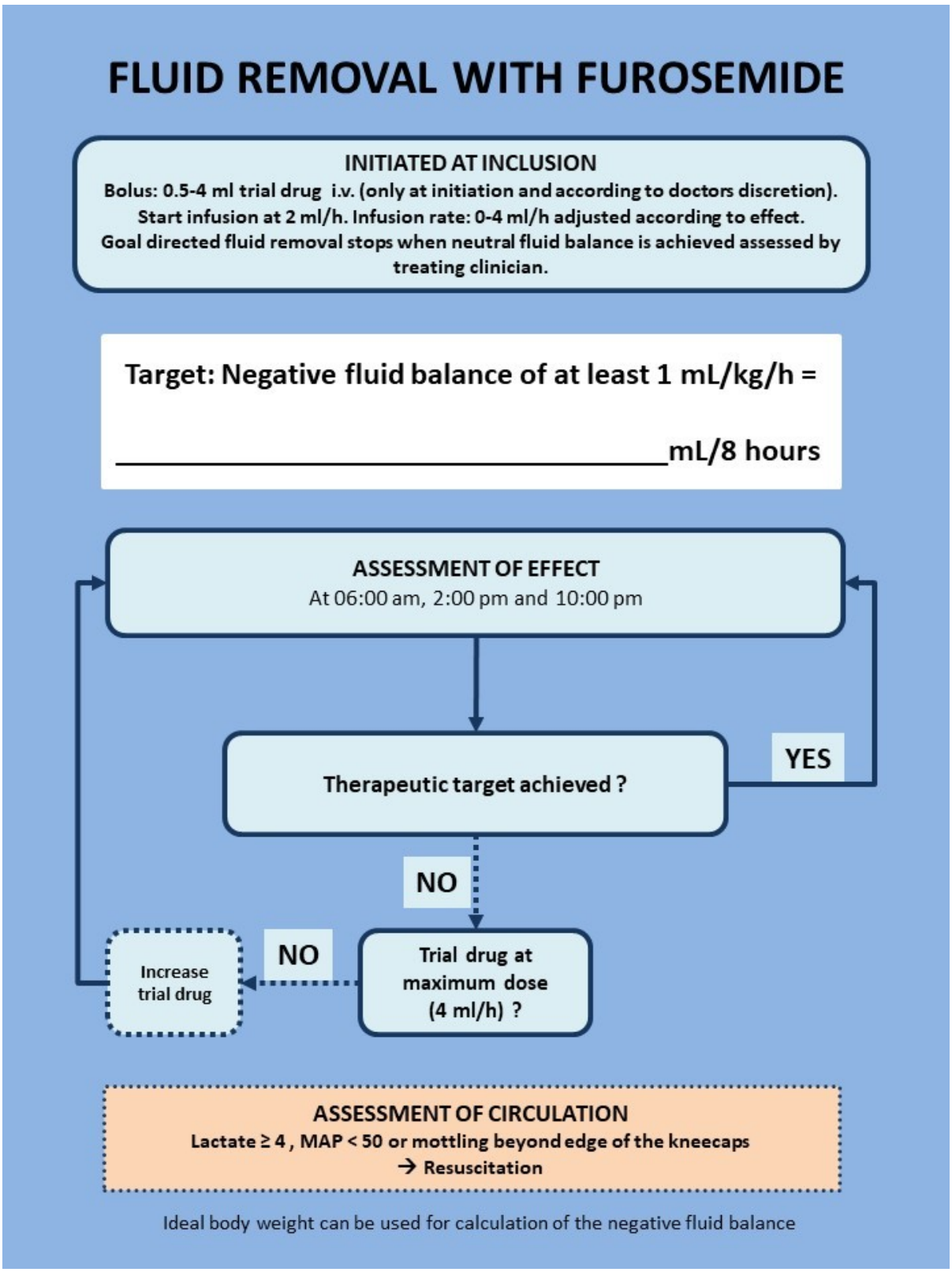
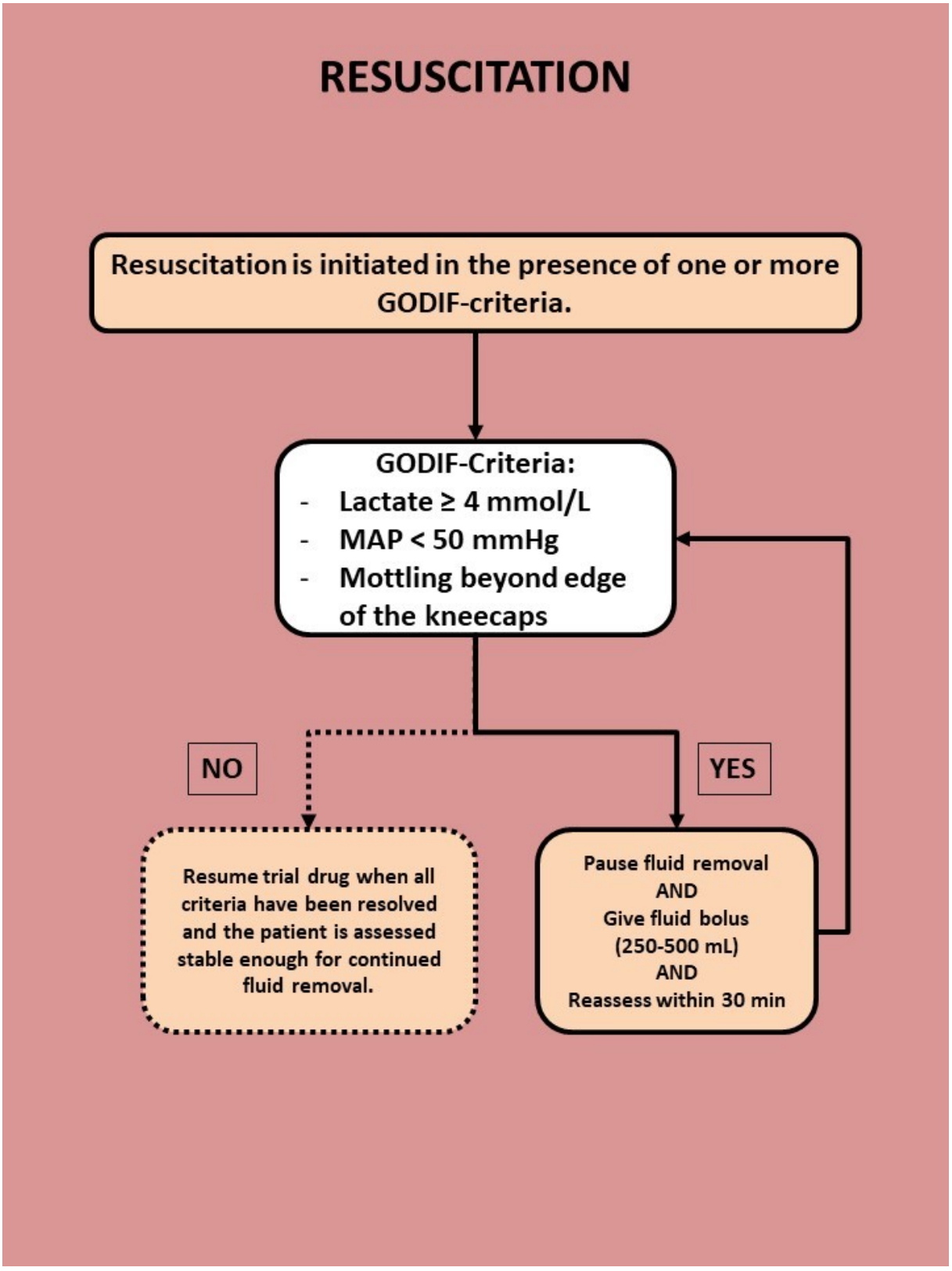
14.14 Appendix 14. GODIF algorithm




RESUSCITATION
Resuscitation is initiated in the presence of one or more GODIF-criteria.
GODIF-Criteria:
- Lactate ≥ 4 mmol/L
- MAP < 50 mmHg
- Mottling beyond edge of the kneecaps
NO
YES
Resume trial drug when all criteria have been resolved and the patient is assessed stable enough for continued fluid removal.
Pause fluid removal
AND
Give fluid bolus
(250-500 mL)
AND
Reassess within 30 min

14.15 Appendix 15. Estimation of the fluid overload

Estimation of a patient's fluid balance is often difficult, and no exact measures exists to be used bedside. The listed fluid balance is often incorrect because inputs and outputs are not registered in detail on general wards which often precede admittance to ICU. If the fluid balance only is recorded in the ICU, it will be flawed too – because of missing data for the time before referral to the ICU.

Patients can also be dehydrated or with fluid accumulation already on admission to hospital because of their medical or surgical condition.

The habitual weight is often not known, and the actual weight might not represent the habitual weight. This makes the weight unpredictable in estimating the fluid balance alone, but the trend in daily weight can be helpful. If the habitual weight is known at admission, this can be helpful during the first days to estimate fluid balance. However, during critical illness patients quickly lose muscle mass and after some time changes in the body weight will not precisely reflect changes in fluid balance. This is of great importance in the later stage when estimating when to stop the trial intervention. Neutral body weight in this stage will usually indicate a positive fluid balance.

To estimate the fluid overload in a patient. The clinical team treating the patient must evaluate the fluid status according the following 4 points to achieve the best and most correct assessment of the patient's fluid status:

- The cumulative fluid balance since admittance (if such one is available)
- Daily fluid balances
- The habitual body weight (if known), body weight on admission (or close after), and weight changes during admission
- Clinical examination (peripheral oedemas, congestion on chest X-ray, lung ultrasound ect.)

The treating team must estimate the actual fluid overload/accumulation and state it in the inclusion note for the GODIF trial in the patient file. This estimated fluid overload is used to calculate the percentage of fluid overload on inclusion in the study.

The same procedure must be used to assess neutral fluid balance. It must be documented in the patient file that neutral fluid balance is achieved, and the trial drug can be paused. If the

patient later accumulate fluid again during the admittance in ICU (maximum 90 days) the trial drug must be restarted.

The fluid status must be assessed according to the 4 points and documented in the patient file daily.

14.16 Appendix 16. Amendment to Protocol V2.7, version V1.0 14.04.2023

Date 14.04.2023_version 1

Amendment to protocol

Trial drug and blinding for the GODIF trial

The trial drug for the GODIF trial is currently produced by The Capital Region Pharmacy in Herlev, Denmark. The pharmacy has a license to produce and distribute medicine for clinical trials from the Danish Medicine Agency.

The trial drug furosemide is produced at a concentration of 10 mg/ml, identical to the furosemide on the commercial market. The trial drug placebo is isotonic saline (NaCl 0.9%) identical to NaCl 0.9% for intravenous infusions on the commercial market.

The trial drug is produced in identical vials of 50 ml to ensure blinding and easy handling (section 3.3 of the protocol). The trial drug is distributed from The Capital Region Pharmacy to the sites at Sponsor's expense.

The GODIF trial is currently approved in Denmark, Norway, Finland, Iceland, and The Netherlands. More countries are expected to seek approval.

In case the trial drug from The Capital Region Pharmacy cannot be approved by legal authorities in other countries, the management committee will allow participation with the use of shelf medication.

In this case, the blinding will be maintained by the following procedure: a dedicated team of unblinded trial site staff. They will have a personal login to the GODIF database with only access to the allocated treatment. The unblinded team will be responsible for preparing the trial drug from furosemide 10 mg/ml or NaCl 0.9% from shelf medication. The trial drug must be prepared in 50 ml syringes for an infusion pump or similar device according to the common practice at the site. The preparation must look identical for both furosemide and placebo to maintain blinding and it must be delivered to the participant ready to infuse. The unblinded team cannot be involved in the treatment or care of the participant, entry of outcome data in the database, statistical analyses, or other aspects of the trial. The Sponsor will not provide the drugs but pay an extra fee of 75 euros in compensation for the medicine for every included participant.

The method with an unblinded third party to prepare and deliver the trial drug in a blinded form to the participants is widely used and we consider it appropriate for the GODIF trial too. The aim to allow this change is to be able to include more countries and sites in the trial which will deliver data from a broader population of critically ill patients and results with a broader relevance.

It can be speculated that the change in the blinding procedure can affect the outcome of the trial. For that reason, we will perform a subgroup analysis of the primary outcome to assess heterogeneity between countries. It will be made clear which blinding procedure the countries have been using. It will be published in the primary paper of the trial.

14.17 Appendix 17. Swedish regulations and informed consent procedures for the GODIF trial

Informed consent

Patients eligible for inclusion in GODIF will receive written and oral information about the trial and will be asked by the treating physician to give written consent before enrollment. Patients will only be asked for consent if they have Glasgow Coma Scale ≥14. Informed consent must be obtained from the patient and cannot be obtained from next of kin or a legal representative. According to the Swedish Medicinal Products Act [Läkemedelslagen (2015:315, 7 kap.3§)].

Definition of postmenopausal Women

A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.
A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

Monitoring

The monitoring and data verification plan are developed by Copenhagen University Hospital GCP Unit, Denmark. National investigators will ensure local monitoring in adherence to the monitoring plan and national regulations. The sponsor local investigators will ensure that the monitors and the regulatory personnel will have access to patient records/ source data for monitoring and inspections. The sponsor local investigators will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection, providing direct access to source data/documents.

Insurance
All patients will be covered by the Patientförsäkringen. Substantial changes in the protocol (or in other documentation included in the trial application) will be submitted for approval by the MPA before implementation.