



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

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Table of contents

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Table of contents	2
Abstract	5
Administrative information	7
Sponsor	7
Management Committee.....	7
Clinical trial sites	7
Methodological trial sites.....	8
Investigators	8
Independent Data Monitoring and Safety Committee (DMSC)	9
Signatures	9
List of abbreviations	10
1. Introduction and background	11
1.1 The patient population	12
1.2 Current treatment (or current practice).....	13
1.3 Trial interventions	13
1.3.1 Clinical data on the experimental intervention1	13
1.3.2 Clinical data on the escape intervention.....	15
1.4 Risks and benefits	16
1.5 Ethical justification and trial rationale	16
1.6 Trial conduct.....	17
2. Trial objectives and purpose	17
3. Trial design	17
3.1 Trial design.....	17
3.2 Randomization.....	18
3.3 Blinding.....	18
3.3.1 Unblinding.....	18
3.4 Participant timeline	19
3.5 End of trial	19
4. Selection of participants	19
4.1 Inclusion criteria.....	19
4.2 Exclusion criteria	20
4.3 Participant discontinuation and withdrawal	20
4.3.1 Discontinuation and withdrawal at the choice of the participant or the proxy.....	20
4.3.2 Discontinuation and withdrawal at the choice of the investigator.....	21
4.3.3 Discharge to another ICU.....	21

5.	Selection and trial sites and personnel.....	21
5.1	Trial sites and setting.....	21
5.2	Trial personnel.....	21
6.	Trial interventions.....	22
6.1	Experimental intervention	22
6.2	Control intervention	23
6.3	Escape protocol for all randomised patients:.....	23
6.4	Co-interventions for all randomised patients	24
6.5	Concomitant interventions	24
6.6	Criteria for modification of interventions for a given trial participant.....	25
6.7	Assessment of participant compliance	25
7.	Outcomes.....	25
7.1	Primary outcome	25
7.2	Secondary outcomes.....	25
7.3	Process variables	26
8.	Safety.....	26
8.1	Definitions.....	26
8.2	Risk and safety issues in the current trial.....	27
8.3	Assessment of adverse events and reactions.....	28
8.3.1	Timing.....	28
8.3.2	Classification of an event.....	28
8.4	Reporting.....	28
9.	Procedures, assessments and data collection.....	29
9.1	Inclusion procedure	29
9.1.1	Screening.....	29
9.1.2	Procedures for informed consent.....	29
9.2	Data collection.....	29
9.2.1	Methods.....	29
9.2.2	Timing.....	29
9.3	Data management.....	33
9.4	Confidentiality	33
9.5	Collection, handling, storage and transportation of human biological material	33
9.6	Access to data.....	33
10.	Statistical plan and data analysis	33
10.1	Sample size and power.....	33
10.1.1	Sample size estimation.....	33
10.1.2	Power estimations for secondary outcomes.....	35
10.2	Statistical methods.....	35
10.2.1	Pre-planned subgroup analyses.....	36
10.2.2	Significance.....	36
10.2.3	Interim analyses.....	36

10.2.4	Early stopping criteria.....	37
10.2.5	Accountability procedure for missing data/population for analysis.....	37
11.	Quality control and quality assurance	37
11.1	Monitoring	38
11.2	Drug traceability measures	38
12.	Legal and organisational aspects.....	38
12.1	Finance.....	38
12.1.1	Trial funding.....	38
12.1.2	Compensation.....	38
12.2	Insurance.....	39
12.3	Plan for publication, authorship and dissemination.....	39
12.4	Sub-studies.....	39
12.5	Intellectual property rights	40
12.6	Organisational framework	40
12.7	Trial timeline	40
13.	References	41
14.	Appendix	49
14.1	Appendix 1. Research programme organisation	50
14.2	Appendix 2. Trial definitions.....	51
14.3	Appendix 3. Adverse reactions not registered in the GODIF trial and summary of product characteristic.....	59
14.4	Appendix 4. Charter for the independent Data Monitoring and Safety Committee (DMSC)	76
14.5	Appendix 5. Informed consent, Denmark.....	81
14.6	Appendix 6. Simplified Mortality Score for the Intensive Care Unit (SMS-ICU).84	
14.7	Appendix 7. Co-enrolment	855
14.8	Appendix 8. List of proposed sub-studies	888
14.9	Appendix 9. Trial flow chart.....	89
14.10	Appendix 10. International Committee of Medical Journal Editors (ICMJE) form for potential conflict of interest	90
14.11	Appendix 11. Budget	92
14.12	Appendix 12. Mottling score.....	93
14.13	Appendix 13. 5 % Fluid overload – mortality and morbidity	94
14.14	Appendix 14. GODIF algorithm.....	95

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 cases fluid accumulate, and patients 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 benefits and harms of goal directed fluid removal with furosemide versus placebo on patient-important outcome measures 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 overload defined as a positive cumulative fluid balance (according to the daily fluid charts) corresponding ≥ 5 % of ideal bodyweight **AND** clinical stable.

Exclusion criteria: Allergy to furosemide or sulphonamides, advanced chronic kidney disease, ongoing renal replacement therapy, anuria ≥ 6 hours, 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 balance achieved as fast as possible and maintained throughout the entire ICU stay. Neutral fluid balance 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.

Control intervention will be matching placebo (saline), which will be administered according to the same goals and algorithm.

Safety variables are monitored continuously and if there is 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, and 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, assuming a 90-day baseline mortality of 27 % ($\alpha = 0.05$, two-

sided and $\beta = 0.1$). 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.

Time Schedule:

- Primo 2020: authority approvals in Denmark .
- August 2020: 1st participant randomised in Denmark.
- Ultimo 2020: 1st interim analysis after 100 randomised patients.
- Medio 2021: 2nd interim analysis after 500 randomised patients.
- Medio 2022: last participant randomised.
- Primo 2023: primary report on 90-day outcomes submitted.
- October 2023: last participant followed for 1 year (last patient, last visit).
- Ultimo 2023: long-term outcome report submitted.

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Other sites are pending. Sites in Denmark, Scandinavia and Europe who are participants of the CRIC network will be contacted for recruitment

Methodological trial sites

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Independent Data Monitoring and Safety Committee (IDMSC)

Pending, IDMSC will consist of a statistician, a trialist, and at least one intensivist. All will have substantial experience in running and interpreting randomised clinical trials. We will aim to have both national and international experts in the IDMSC.

Signatures

Morten H. Bestle, Sponsor

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
DMSC = Data Monitoring and Safety Committee
FB = fluid Balance
FO = fluid overload
FiO₂ = 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
PaCO₂ = partial pressure of arterial carbon dioxide
PaO₂ = 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 treatment of many conditions including hypovolemic shock, sepsis, septic shock, and acute kidney injury (AKI). More and more evidence show that FO is an independent risk factor for mortality in critically ill patients¹⁻³. FO is also a risk factor of 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 stay in the intravascular compartment after 75 minutes⁵. In sepsis the inflammation causes the endothelial glycocalyx to degrade and induce capillary leakage⁶. Aggressive fluid resuscitation can cause release of atrial natriuretic peptide (ANP) which also causes shedding of the endothelial glycocalyx with capillary leak to follow⁷. 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 have shown that infusion of 2 L crystalloid leads to renal swelling⁸. Renal interstitial volume and pressure is correlated in an exponential manner, suggesting that a "renal compartment" exists⁹ 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 AKI¹²⁻¹⁴. 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 % - 57 % in intensive care unit^{3,17-20}. FO is associated with development of AKI^{4,21-24}, and FO in patients with AKI is associated with increased mortality²⁵⁻²⁸. 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 on the basis of the weight on admission to the ICU) is shown to make a difference in outcome on mortality and renal recovery²⁹. It is still not known 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 length of stay in the ICU³⁰, and reduces the mortality in critical illness³¹. There is, however, no evidence for when or how fluid removal should be done.

1.2 Current treatment (or current practice)

Over the last 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 campaign³² 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 which randomised fluid therapy in patients with septic shock in a restrictive group and a standard of care group 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 group³³. This is a relatively small difference after 5 days and might indicate that FO will happen in most critical 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.

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) vs. 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 a significantly faster weaning from mechanical ventilation in the restrictive therapy group³⁴. 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 FO³⁵.

A small trial of 10 mechanically ventilated patients with AKI, has been performed to test a protocol of goal directed fluid removal³⁶. 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 μ mol/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 36-72 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 hemodynamic evaluation using three readily available and minimally invasive methods: lactate ≥ 4 mmol/L, mottling beyond 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 guidelines³². Mottling of the lower extremities have been shown to be an easy-to-use, accurate and highly reproducible method to evaluate hemodynamic adequacy in patients with septic shock³⁷ (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 care³⁸. The rate of fluid removal in that trial was similar to the cut off for beneficial outcome identified by Murugan et al. in an observational study of ultrafiltration rates in critically ill patients with AKI and fluid overload above 5 % bodyweight³⁹. This observational study showed that patients with a fluid removal rate > 25 ml/kg/day had a better survival than patients receiving fluid removal at a rate < 25 ml/kg/day.

Taken together 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 intermittent bolus or continuous infusion. Several trials have examined efficacy and safety of bolus therapy versus 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 made⁴⁰. 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 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 infusion⁴¹. Similar results have been shown in smaller trials of critically ill patients^{42,43}.

A new 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 on the requirement for renal replacement therapy (RRT)⁴⁴.

The Danish summary of product characteristic (SPC) provides no guidelines for continuous infusion dose. However, recommendations are available at www.uptodate.com⁴⁵. These suggest that treatment of patients with severe kidney injury (eGFR < 30 mL/min) is initiated with a loading dose of 40-80 mg followed by an infusion rate of 20-40 mg/h.

The treatment regime for furosemide in the present trial, consist of an initial bolus of 40 mg 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). This regime is well within the safety limits described in the SPC (Starting dose 20-40 mg, maximum infusion rate = 4 mg/min and maximum daily dose = 1500 mg). The adverse effects and complications to 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 (SAR's) is described in 8.2.

1.3.2 Clinical data on the escape intervention

Initiation of RRT

The optimal time for initiation of RRT remains controversial. A new systematic review with meta-analysis of randomised clinical trials suggests that early initiation of RRT compared with standard initiation of RRT in critical ill patients with AKI provide no advantage⁴⁶. Large multicentre randomised clinical trials need to clarify the optimal time for starting RRT.

The Kidney Disease Improving Global Outcome (KDIGO) guidelines states that "RRT should be initiated emergently when life-threatening changes in fluid, electrolyte, and acid-base balance exists" (not graded), and that "... 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 neither early nor late RRT and we find it reasonable to perform a trial in which 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 is 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 normo-volaemia will normalise the structure of organs suffering from interstitial oedema and facilitate oxygen delivery and functionality. Furthermore, fluid removal with diuretics will lead to a reduction in total body sodium and chloride. However, if the rate of fluid removal exceeds the refilling capacity of compensatory fluid movement from the extravascular compartment, the preload will be compromised, and the mean arterial pressure will decline. This might lead to progressive loss of renal function due to a reduction in RBF and GFR or other non-renal effects.

1.5 Ethical justification and trial rationale

Observational studies have indicated that FO is an independent predictor of death in critically ill patients. At present, no trials have been performed to establish whether this correlation is causative or due to confounding. We have recently performed a pilot trial showing that our proposed experimental treatment is effective in treating FO³⁸. The present trial will be an important step in the process of improving the care of critically ill patients.

The individual patient may benefit from participating in the trial as this will lead to increased focus on the patient. Future patients will benefit from the GODIF trial results, regardless of the direction of the effect, as the results will enable better strategies for fluid removal when needed and maybe also better fluid therapy.

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 found superior to placebo, future patients will benefit from this trial by avoiding the potential harm of receiving furosemide.

ICU patients are regarded as temporarily incompetent because of the severe illness, the medications they receive (opioids/anaesthetics) and they are often sedated and unconscious. FO is prevalent and associated with a high degree of morbidity and mortality and for that reason fluid removal is time dependent. The intervention cannot be withheld for them to regain competence so that informed consent can be obtained.

In Denmark, we will use the consent procedures for temporarily incompetent patients for all patients (<https://www.retsinformation.dk/Forms/R0710.aspx?id=192671>). Patients will be enrolled after informed consent from a doctor, who is independent of the trial, who has knowledge of the clinical condition, and who is familiar with the trial protocol to such extent that he or she can judge for each patient if it will be reasonable to enrol the patient in the trial (the first trial guardian). As soon as possible after enrolment, consent will be obtained from the patient's next of kin and a second doctor (the second trial guardian). The second trial guardian must be different from the first trial guardian, but also independent of the trial. Patients, who regain competence, will be asked for informed consent as soon as possible. The process leading to informed consent will follow all applicable

regulations. The consenting subjects will be provided with written and oral information about the trial allowing them to make an informed decision about participation in the trial. Written information and the consent form will be subject to review and approval by the ethical committee system according to national law in all participating countries. The consenting party can at any time, without further explanation, withdraw consent. The process leading to informed consent may differ in the participating countries but will be described and follow all applicable regulations in the country (Appendix 5).

1.6 Trial conduct

The GODIF trial will be conducted in compliance with the published trial protocol, the Helsinki Declaration in its latest version ⁴⁷, the good clinical practice (GCP) guidelines ⁴⁸, 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 by the ethical committee, Danish Medicines Agency, Danish Data Protection Agency and trial registration at www.clinicaltrials.gov and European Union Drug Regulating Authorities Clinical Trials (EudraCT).

No substantial deviation from the protocol will be implemented without prior review and approval of the regulatory authorities except where it may be necessary to eliminate an immediate hazard to the trial participants. In such case, the deviation will be reported to the authorities as soon as possible. We will publish the approved protocol at www.cric.nu and submit a manuscript with main points of the protocol including description of 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 outcome measures 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 increased number of days alive and out of hospital after 90 days as compared with 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 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 an ampule. The placebo drug will be isotonic saline and will be contained in an identical ampule. The solution of furosemide is colourless and cannot be visually distinguished from isotonic saline. Each vial will contain the same volume with furosemide 10 mg/mL in the experimental intervention group. The trial medication will be labelled with a white label, which is identical on placebo and active drug. The label will contain the required information of the trial drugs including date of expire. The top of the placebo ampule will be identical with the ampule of the active drug.

The allocated trial medication will be blinded to the clinical staff caring for the patient, to the patient, investigators, outcome assessors, and only the data manager has the possibility to 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 and Safety Committee (DMSC) 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 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 a cumulative fluid balance of 5 % or more of their ideal bodyweight 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.

The participants will continue the allocated intervention until they are discharged from the ICU or death 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 becomes fluid overloaded, 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 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 \geq 18 years of age.

- FO defined as a positive cumulative fluid balance (according to the daily fluid charts) corresponding ≥ 5 % of ideal body weight (calculated as: $22 \times (\text{height in meters})^2$). If possible, all fluids administered before admission to the ICU are to be included in the calculation of cumulative fluid balance.
- Clinical stable defined as 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 m² or chronic RRT).
- Ongoing RRT.
- Anuria for ≥ 6 hours.
- 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 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. Trial sites are listed in the section Administrative information. This section will be updated during the trial.

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 balance achieved as fast as possible and maintained throughout the entire ICU stay.

Neutral fluid balance is achieved by:

- Furosemide at a bolus dose of 40 mg (4 mL) i.v. followed by continuous infusion at 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 balance is defined by a cumulative fluid balance of - 750 mL to + 750 mL. In case the participant is still considered to be significantly fluid overloaded or dehydrated when the cumulative fluid balance is neutral according to fluid charts (e.g. peripheral oedema, reduced skin turgor, or the body weight is higher or lower than known from pre-admittance which cannot be attributed to loss to other body compartments, or other signs) the clinician must estimate a more accurate neutral fluid balance. This must be documented in the participant file and the eCRF. The goal for the further treatment will be this modified neutral fluid balance.

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 efficacy of fluid removal is evaluated and adjusted according to the therapeutic goal every eighth hour (e.g. 06:00, 14:00, and 22:00), 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) have been maintained for minimum 1 hour.
- Restart trial drug at 25 % reduced dose for minimum 4 hours before evaluation of effect.
- Continue titration of the trial drug according to effect and algorithm.

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

6.2 Control intervention

The control intervention will be 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 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 i.v. 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 by used for 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 resuscitation⁵⁰.
- 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 guideline⁵¹ (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 guidelines³². We recommend the following to 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 following criteria:

- Participants not receiving the intervention (trial drug) for two days despite persisting fluid overload at these days (cumulative fluid balance > + 750 ml).
- Participants receiving the intervention (trial drug) for two days despite fulfilling pausing criteria at these days resulting in a negative cumulative fluid balance (< - 750 ml).
- 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).
- Participants withdrawing or withdrawn from the allocated intervention despite having FO. This includes patients discontinued from the trial by choice of the patient or the clinician for other reasons than SAR/SAEs or SUSARs.

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.

Explorative outcomes:

1. 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.
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.
3. Cognitive function 1-year after randomisation as assessed by the Montreal Cognitive Assessment (MoCa) 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

- Cumulative fluid balance at day 5 (or until discharge) after randomisation (calculated as the sum of daily intake – daily output, as registered on the daily fluid chart).
- Mean daily fluid balance during ICU stay.
- Cumulative fluid balance during the entire ICU stay.
- Time to resolution of fluid overload (neutral cumulative fluid balance) with censoring at discharge.
- Number of participants needing one or more doses of escape medicine (furosemide) and the dosages of escape medicine per participant in the furosemide group compared to the placebo group.
- Number of participants needing escape RRT in the two groups.

8. Safety

8.1 Definitions

In the GODIF trial, we will use the definitions below: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 ICU for all included patients and report SAEs and SARs as outcomes 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 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 the following observed in the ICU:

- Ischaemic events defined as either:
 - Cerebral ischaemia defined as any form of cerebral ischaemia 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, 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 3⁵³: A 3 times increase in baseline p-creatinine or increase in p-creatinine to $\geq 354 \mu\text{mol/L}$ or use of renal replacement therapy (any form).
- New onset atrial fibrillation in a participant who never have 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 Danish 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 Johnsons 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 every SAR, the investigator and sponsor must assess, if it is related to trial drug according to the summary of product characteristic (Appendix 3). As for any other unexpected SAE/SAR 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 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, he will report it to the Danish Medicine Agency within 7 days after the report of a life-threatening or fatal SUSAR. No later than 8 days after the reporting, the Sponsor will inform the Danish Medicines Agency of relevant information 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 Danish Medicines Agency no later than 15 days from the time when the Sponsor is informed.

Once a year, the Sponsor will submit a list of all SARs that have occurred at all sites during the trial period and a report on safety of the trial subjects to the Danish Medicines Agency as well as to the regional ethics committee.

The Sponsor will notify the Danish Medicines Agency when the trial has been completed (no later than 90 days thereafter) and if earlier than planned, the reasons for stopping the trial.

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 will be reported on EudraCT.

9. Procedures, assessments, and data collection

9.1 Inclusion procedure

Daily fluid balance is routinely calculated at the end of the 24 hours observation day (06:00).

9.1.1 Screening

All patients admitted to participating ICU's are eligible for screening. FO is defined as accumulation of fluids according to the daily fluid charts corresponding to $\geq 5\%$ of ideal bodyweight calculated as: $22 \times (\text{height in meters})^2$ (squared).

If possible, all fluids administered before admission to the ICU are included in the calculation of cumulative fluid balance.

9.1.2 Procedures for informed consent

Participants will be enrolled after consent by proxy is obtained according to national regulations. The procedure for each participating country will be described. The procedure for Danish participants is described in Appendix 5.

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?
 - Cumulative fluid balance in ml.
 - 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.
 - 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.

Daily during entire ICU stay

- 24 hours diuresis (measured at 06:00 am).
- Cumulative fluid balance in mL (calculated at 06:00 am).
- Weight in kg (measured).
- Cumulative dose of trial drug.
- P-creatinine.
- Indication for new estimation of neutral fluid balance? If Yes reasons why and a new estimate.
- Major protocol violations
 - Discontinuation of fluid removal with trial drug for 2 days before neutral cumulative fluid balance has been achieved.
 - Continuation of administration of trial drug for 2 days despite fulfilling pausing criteria.
 - Administration of extra furosemide without presence of escape criteria.
 - 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).

On discharge

- 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.

Withdrawal

- 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

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) 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 randomization 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

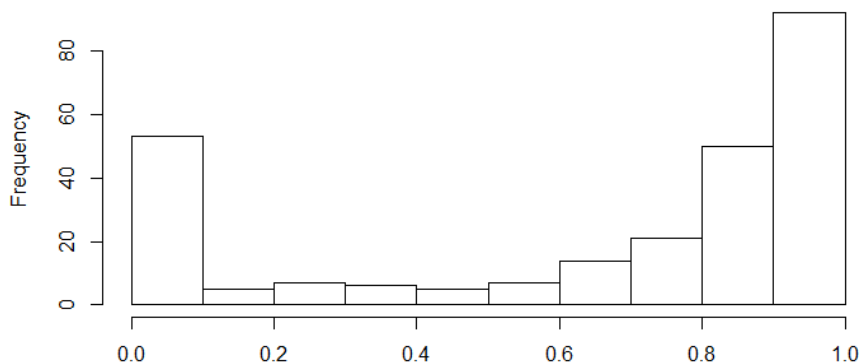
All original records (incl. consent forms, eCRFs, and relevant correspondences) will be archived for 15 years. De-identified data will be made publicly available 9 months after the publication of the outcome data according to the recent ICMJE recommendations (Appendix 10). As it is for all CRIC trials, 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

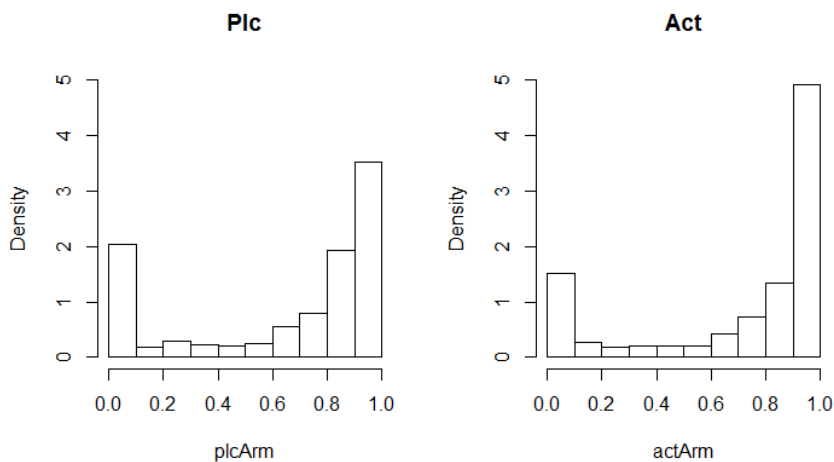
10.1 Sample size and power

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 Wilcoxon 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 randomized 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 not receiving the intervention (trial drug) for two days despite persisting FO at these days (cumulative fluid balance > + 750 ml).
- 2) Participants receiving the intervention (trial drug) for two days despite fulfilling pausing criteria resulting in a negative cumulative fluid balance (< - 750 ml).
- 3) Participants receiving other diuretics than allowed according to this protocol during their ICU admittance.
- 4) Participants receiving open-label furosemide on other indications than described under escape (section 6.3) during ICU admittance.
- 5) Initiation of RRT, without the presence of RRT escape indications (section 6.3).
- 6) Participants withdrawing or withdrawn from the allocated intervention despite having FO. This includes patients discontinued from the trial by the choice of the patient or the clinician for other reasons than SAR/SAEs or SUSARs.

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-variables:

- 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.

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 patient number 100 and number 500 has been followed for 90 days. Interim analyses of our primary outcome and number of patients with one or more SARs will be conducted. The independent Data Monitoring and Safety Committee (DMSC) will recommend pausing or stopping the trial if group-difference in the primary outcome measure or mortality, SARs or SUSARs are found at the interim analyses with statistical significance levels adjusted according to the Lan-DeMetz 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-DeMetz 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-DeMetz stopping criterion according to the group sequential monitoring boundaries the DMSC will recommend stopping the trial. Furthermore, the DMSC 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 DMSC (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 performed⁶⁰. If missing data are more than 5 % multiple imputation 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 (5.082.180 DKK) and Jakob Madsens og Hustru Olga Madsens fond (100.000 DKK). 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 one-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 (400 EUR) 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 will be admitted to two ICU sites participating in the GODIF trial during the 90-day trial, the first sites will get paid 300 EUR because they must do the 1-year follow-up and the second site will be paid 100 EUR..

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 preferably in a peer-reviewed medical journal. Furthermore, the results will be published at 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 the agreement in 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 DMSC 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 have no influence on 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 ethic 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, Jonas Egebart.

12.6 Organisational framework

The GODIF trial will be managed by the Management Committee and possibly overseen by the CRIC Steering Committee (Appendix 1). The day-to-day running of the trial will be done by the Sponsor, the Coordinating Investigator.

12.7 Trial timeline

- Primo 2020: authority approvals in DK
- August 2020: 1st participant randomised in DK and authority approvals elsewhere
- Ultimo 2020: 1st interim analysis
- Medio 2021: 2nd interim analysis
- Medio 2022: last participant randomised
- Primo 2023: primary report on 90-day outcomes submitted.
- October 2023: last participant followed for 1 year (last patient, last visit)
- Ultimo 2023: long-term outcome report submitted

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14. Appendix

Appendix 1: Research program organization

Appendix 2: Trial definitions

Appendix 3: Adverse reactions not registered in the GODIF trial and summary of product characteristic

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

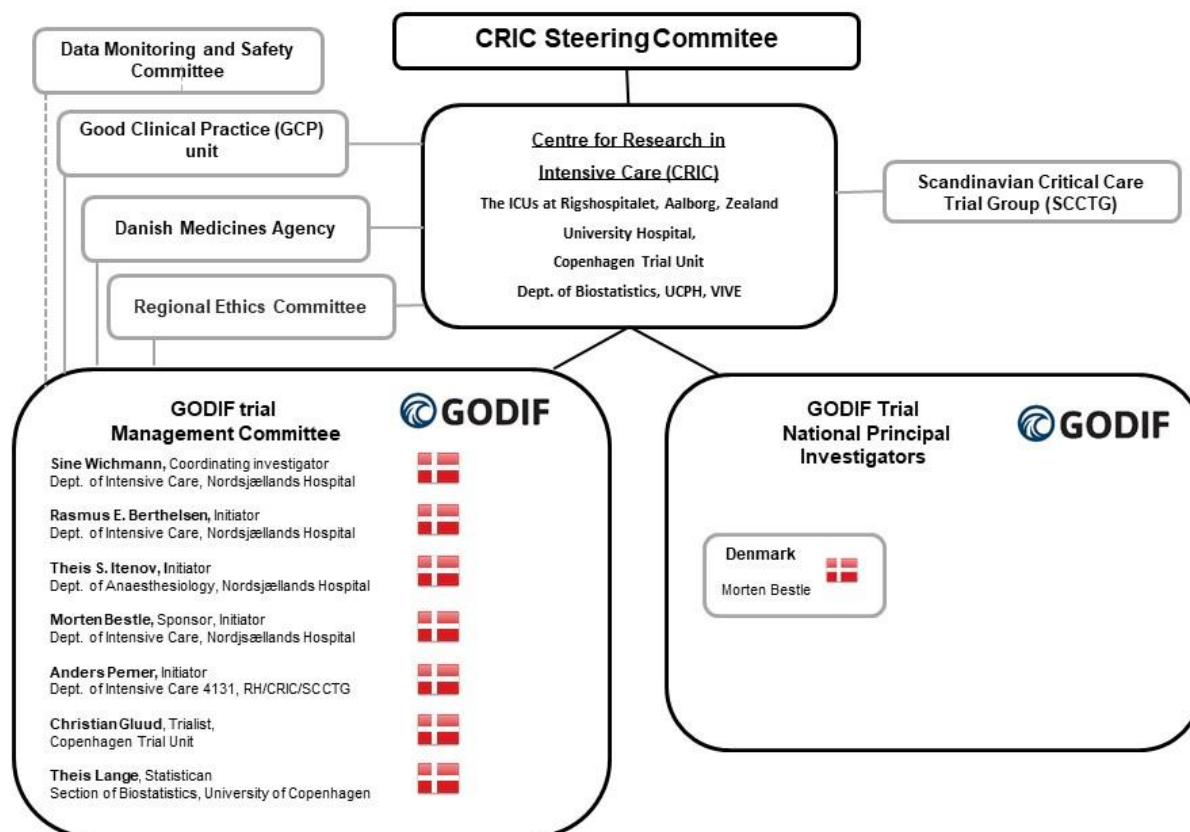
Appendix 12: Mottling score

Appendix 13: 5 % Fluid overload - Mortality and morbidity

Appendix 14: GODIF algorithm

14.1 Appendix 1. Research programme organisation

GODIF trial 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 KDIGO⁶²: as any of the following:
 - Increase in serum creatinine by ≥ 0.3 mg/dl (≥ 26.5 μ mol/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 planned 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 overload defined as a positive cumulative fluid balance (according to the daily fluid charts) corresponding ≥ 5 % of ideal bodyweight. 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. Ideal body weight is calculated as $22 \times (\text{height in meters})^2$. The percentage of fluid overload is calculated as the cumulative fluid overload in litres divided with the ideal body weight in kg multiplied with 100.
- Clinical stable defined as 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 m² 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.
- 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.
- 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 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).

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 clinically stable? Y/N. Definition of clinical stable is MAP > 50 mmHg and maximum infusion of 20 microgram/kg/minute of noradrenaline and lactate < 4.0 mmol/L.
 - Cumulative 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.
 - Actual body weight in kg.
 - Height in cm.
 - Ideal body weight and percentages of fluid overload will be calculated automatically.
- Exclusion criteria:
 - Allergy towards furosemide or sulphonamides.
 - Advanced chronic kidney disease.
 - Ongoing renal replacement therapy.
 - Anuria for > 6 hours.
 - 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 levosimendan).
 - 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.

Baseline variables:

- 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 levosimendan) to maintain a mean arterial blood pressure of 65 mmHg or above.
 - Lactate \geq 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?

Daily during entire ICU stay:

- 24 hours diuresis (measured at 06:00 am).
- Cumulative fluid balance in mL (calculated at 06:00 am) This includes all fluid input and output in mL cumulated over 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-creatinine measured on this day.

- Indication for new estimation of neutral fluid balance? Y/N. This question will appear when the cumulative fluid balance is < + 750 mL. In case of clinical evidence of *significant* fluid overload (e.g. edemas / weight higher than habitual weight/other reason or dehydration (weight lower than habitual weight/other reason) the clinician can revise the estimate for neutral fluid balance. In case of indication of a new estimate it MUST be documented in the patient file and reasons described. This new estimate for the cumulative fluid balance MUST be used to guide the further goal directed fluid removal during this study.
- Major protocol violations on this day.
 - Discontinuation of fluid removal with trial drug for 2 days before neutral cumulative fluid balance has been achieved (cumulative fluid balance > + 750 ml).
 - Continuation of administration of trial drug for 2 days despite fulfilling pausing criteria resulting in a negative cumulative fluid balance (< - 750 ml).
 - 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).
 - Participants withdrawing or withdrawn from the allocated intervention despite having fluid overload. This includes patients discontinued from the trial by the choice of the patient or the clinician for other reasons than SAR/SAEs or SUSARs.
- 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) 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.
3. Cognitive function at 1-year (+/- 2 weeks): the Montreal Cognitive assessment (MoCa) MINI score (or '5-minute protocol') using the translations of the MoCa full v. 7.1 (<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. If the MoCa MINI, which is validated for phone interview⁶³, has not been released at the time of the first assessment (1-year after randomisation of the first patient), we will adapt the MoCa MINI from the MoCa full v. 7.1.

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 10⁹/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 10⁹/l, thrombocytes < 20 x 10⁹/l, reticulocytes < 1 %.
- Pancreatitis
- Circulatory collapse leading to cardiac arrest.
- Steven Johnsons syndrome
- Toxic epidermal necrolysis
- Hearing impairment/loss

SAE to be registered daily in the CRF:

- Ischemic events defined as either
 - Cerebral ischemia defined as any form of cerebral ischemia on a CT- OR MRI scan
 - Acute myocardial ischemia 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 ischemia defined as ischemia 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 characteristic

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 from 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.
- Arrhythmias 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.
- Arrhythmias are a very common condition in the ICU population. About 27 %⁶⁴ will experience atrial fibrillation during their ICU stay. Other arrhythmias are also seen regularly because of the patients' severe illness and co-morbidities. For that reason, we will not register arrhythmias as a serious adverse reaction in the ICU setting.

summary of product characteristic:



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

Generelt:

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 dosis anbefalinger:

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 hjerterinsufficiens 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 encephalopati
- 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 urinsyre-niveauer 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
- Lægemedler, 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-baseforstyrrelser 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.

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

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 kardiotoxisk 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 varmekøbsfølelse, 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 blodtryksnedsættende 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 samtidig 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). Kaliumplasma 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 cytotoxiske virkninger, hvis cisplatin og furosemid gives samtidig.

Derudover kan cisplatinets 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 urinsyreigt.

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 embryoet/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 ($\geq 1/10$)

Almindelig ($\geq 1/100$ til $< 1/10$)

Ikke almindelig ($\geq 1/1.000$ til $< 1/100$)

Sjældent ($1/10.000$ til $< 1/1.000$)

Meget sjældent ($< 1/10.000$). 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.

Sjældent: eosinofili, leukopeni, knoglemarvsdepression. Forekomst af dette symptom nødvendiggør seponering af behandling.

Meget sjældent: hæmolytisk anæmi, aplastisk anæmi, agranulocytose.

Alvorlig dehydrering kan føre til hæmokoncentration med en tendens til at thromboser udvikles især hos ældre patienter.

Immunsystemet

Sjældent: 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.

Hos patienter med øget renalt magnesiumtab blev der i sjældne tilfælde observeret tetania eller hjerterytmi som følge af hypomagnesiæmi.

Urinsyre niveauer 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 (blæretømningsslidelser, prostatahyperplasi eller forsnævring af urinrør), vaskulitis, glukosuri, forbigående stigning af blodkreatinin og urinstofniveauer. Sjældent: 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

Sjældent: febrile tilstande. Efter IM-injektion kan der forekomme lokale reaktioner såsom smerte.

Undersøgelser

Sjældent: 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 glukokortikoid (fx. 250 mg methylprednisolon), hvilket gentages om nødvendigt.

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

Korriger 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

B

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 hypertonicere.

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 udskillelshastighed med urinen) og den natriuretiske virkning. Furosemids minimale effektive udskillelshastighed 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 intrakraniell hypotension.

6. FARMACEUTISKE OPLYSNINGER

6.1 Hjælpemidler

Natriumchlorid
Natriumhydroxid
Vand til injektionsvæsker

6.2 Uforlideligheder

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 forseget 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 indsprøjtningstilbeholdningen.

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 and Safety Committee (DMSC)

Introduction

The DMSC will constitute its own plan of monitoring and meetings. However, this charter will define the minimum of obligations and primary responsibilities of the IDMSC as perceived of the Management Committee (MC), its relationship with other trial components, its membership, and the purpose and timing of its meetings. The charter will also outline the procedures for ensuring confidentiality and proper communication, the statistical monitoring guidelines to be implemented by the DMSC, and an outline of the content of the open and closed reports which will be provided to the DMSC.

Primary responsibilities of the IDMSC

The DMSC will be responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial, and for monitoring the overall conduct of the clinical trial. The DMSC will provide recommendations about stopping or continuing the trial to the MC of the GODIF trial. To contribute to enhancing the integrity of the trial, the DMSC may also formulate recommendations relating to the selection/recruitment/retention of participants, their management, improving adherence to protocol-specified regimens and retention of participants, and the procedures for data management and quality control.

The DMSC will be advisory to the MC. The MC will be responsible for promptly reviewing the DMSC recommendations, to decide whether to continue or terminate the trial, and to determine whether amendments to the protocol or changes in trial conduct are required.

The DMSC may meet physically or by phone at their own discretion in order to evaluate the planned interim analyses of the GODIF trial. The interim analyses will be performed by an independent statistician from the Dept. of Biostatistics, University of Copenhagen. The DMSC may additionally meet whenever they decide or contact each other by telephone or e-mail to discuss the safety for trial participants. The sponsor has the responsibility to report the overall number of SARs yearly to the DMSC. The DMSC can, at any time during the trial, request the distribution of events, including outcome measures and SARs according to intervention groups. Further, the DMSC can request unmasking of the interventions if suggested by the data, see section on 'closed sessions. The recommendations of the DMSC regarding stopping, continuing or changing the design of the trial should be communicated without delay to the MC of the GODIF trial. As fast as possible, and no later than 48 hours, the MC has the responsibility to inform all investigators of the trial and all the sites including patients in the trial, about the recommendation of the DMSC and the MC decision hereof.

Members of the DMSC

The DMSC is an independent multidisciplinary group consisting of clinicians and a biostatistician that, collectively, has experience in the management of ICU patients and in the conduct, monitoring and analysis of randomized clinical trials.

DMSC Clinician

Pending

DMSC Trialist

Pending

DMSC Biostatistician

Pending. Dept. of Biostatistics, University of Copenhagen

Conflicts of interest

DMSC members will fill in and sign a declaration of conflicts of interests (Appendix 10). DMSC membership has been restricted to individuals free of conflicts of interest. The source of these conflicts may be financial, scientific, or regulatory in nature. Thus, neither trial investigators nor individuals employed by the sponsor, nor individuals who might have regulatory responsibilities for the trial products, are members of the DMSC. The DMSC members do not own stock in the companies having products being evaluated by the GODIF trial.

The DMSC members will disclose to fellow members any consulting agreements or financial interests they have with the sponsor of the 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 trial.

The DMSC will be responsible for deciding whether these consulting agreements or financial interests materially impact their objectivity.

The DMSC members will be responsible for advising fellow members of any changes in these consulting agreements and financial interests that occur during the trial. Any DMSC members who develop significant conflicts of interest during the trial should resign from the DMSC.

DMSC membership is to be for the duration of the clinical trial. If any members leave the DMSC during the trial, the MC will appoint the replacement(s).

Formal interim analysis meetings

Two formal interim analysis meetings will be held to review data relating to protocol adherence, treatment efficacy, participant safety, and quality of trial conduct. The three members of the DMSC 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

To enhance the integrity and credibility of the trial, procedures will be implemented to ensure the DMSC 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 liaison between the database and the DMSC.

At the same time, procedures will be implemented to ensure that proper communication is achieved between the DMSC and the trial investigators. To provide a forum for exchange of information among various parties who share responsibility for the successful conduct of the trial, a format for open sessions and closed sessions will be implemented. The intent of this format is to enable the

DMSC to preserve confidentiality of the comparative efficacy results while at the same time providing opportunities for interaction between the DMSC and others who have valuable insights into trial-related issues.

Closed sessions

Sessions involving only DMSC membership who generates 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 efficacy and safety of interventions. To ensure that the DMSC will be fully informed in its primary mission of safeguarding the interest of participating participants, the DMSC will be blinded in its assessment of safety and efficacy data. However, the DMSC can request unblinding from the MC.

Closed reports will include analysis of the primary outcome measure. These closed reports will be prepared by independent biostatistician being a member of the DSMC, with assistance from the trial data manager, in a manner that allow them to remain blinded.

The closed reports should provide information that is accurate, with follow-up on mortality that is complete to within two months of the date of the DMSC meeting.

Open reports

For each DMSC meeting, open reports will be provided available to all who attend the DMSC meeting. The reports will include data on recruitment and baseline characteristics, and pooled data on eligibility violations, completeness of follow-up, and compliance. The independent statistician being a member of the DMSC will prepare these open reports in co-operation with the trial data manager.

The reports should be provided to DMSC members approximately three days prior to the date of the meeting.

Minutes of the DMSC Meetings

The DMSC will prepare minutes of their meetings. The closed minutes will describe the proceedings from all sessions of the DMSC meeting, including the listing of recommendations by the committee. Because it is possible that these minutes may contain unblinded information, it is important that they are not made available to anyone outside the DMSC.

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.

After the interim analysis meetings, the DMSC will make a recommendation to the MC to continue, hold or terminate the trial.

The independent DMSC will recommend pausing or stopping the trial if group-difference in the primary outcome measure, SARs or SUSARs is found at the interim analyses with statistical significance levels adjusted according to the Lan DeMetz group sequential monitoring boundaries based on O'Brien Fleming alpha-spending function. If the recommendation is to stop the trial the DSMC will discuss and recommend on whether the final decision to stop the trial will be made after the analysis of all participants included at the time (including participants randomized after

participant number 500) and whether a moratorium shall take place (setting the trial at hold) in the further inclusion of participants during these extra analyses. If further analyses of the participants included after 500 participants is recommended the rules for finally recommending stopping of the trial should obey the Lan DeMetz stopping boundary.

Furthermore, the DMSC 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 as intervention effects less than these may be clinically relevant as well.

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

The MC is jointly responsible with the DMSC for safeguarding the interests of participants and for the conduct of the trial. Recommendations to amend the protocol or conduct of the trial made by the DMSC will be considered and accepted or rejected by the MC. The MC will be responsible for deciding whether to continue, hold or stop the trial based on the DMSC recommendations.

The DMSC will be notified of all changes to the trial protocol or conduct. The DMSC concurrence will be sought on all substantive recommendations or changes to the protocol or trial conduct prior to their implementation.

Statistical monitoring guidelines

The outcome parameters are defined in the statistical analyses plan in the GODIF trial protocol. For the two intervention groups, the DMSC will evaluate data on:

First and second interim analyses

The primary outcome measures

Days alive and out of hospital day 90 after randomisation.

The secondary outcome measures

- The occurrence of SAEs/SARs in the ICU

The DMSC 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 DMSC will decide if they want further data from the coordinating centre and when to perform the next analysis of the data.

For analyses, the data will be provided in one file as described below.

DMSC should yearly be informed about SARs occurring in the two groups of the trial.

The DMSC may also 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 doing this should be clearly specified.

Conditions for transfer of data from the Coordinating Centre to the DMSC

The DMSC 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 having entered 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 and second interim analyses**:

1. screening_id: a number that uniquely identifies the participant
2. rand_code: The randomisation code (group 0 or 1). The DMSC is not to be informed on what intervention the groups received.
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. days alive without life support during the 90 days observation period for each patient.
6. SAR_indic: SAR indicator (1 =one or more SARs, 0 = no SARs)
7. Protocol_viol_indic: No. of protocol violations in the two groups

14.5 Appendix 5. Informed consent, Denmark

In Denmark temporarily incompetent patients will be enrolled after informed consent from one medical doctor, who is independent of the trial (first trial guardian). As soon as possible after enrolment, consent will be obtained from the patient's next of kin and a second medical doctor (second trial guardian). The second trial guardian must be different from the first trial guardian and also independent of the trial. Participants, who regain consciousness, 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 is able to 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 the consent form will be subjected to review and approval by the relevant ethic committees.

First trial guardian: The consent can initially be oral if the first trial guardian's full name, date and time for the consent is written in the medical chart. After that the patient can be enrolled in the trial, but as soon as possible written informed consent must be obtained and must be collected within a few days. All attempts of collecting the written consent must be documented in the medical chart or in a log. Before the first guardian is signing the consent form, written information about the GODIF trial is handed out.

Next of kin: After enrolment in the trial consent from next of kin must be obtained as fast as possible and must be obtained within a few days. 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 kind do not give consent the trial intervention must be stopped. The next of kind will be asked permission to continue data collection. All contacts to the next of kind concerning the consent must be documented in the patient files.

Specific situations.

- If the next of kin seem 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 do 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 other.

Second trial guardian: during the same time where consent from next of kin is collected, consent from the second trial guardian must be collected. This consent must be collected within a few days' time. If the next of kin does not consent to the trial, the second trial guardian will not be asked. Before the second trial guardian is signing the consent form, written information about the GODIF trial is handed out. If the second trial guardian does not give their consent, the intervention will be stopped. The second trial guardian can eventually be a designated doctor used for all the participants.

The patient: when the patient regains competence, he/she will receive written and oral information about the trial. Most patients are regarded 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 sent home. In case that is not possible the patient must be contacted by phone and the written information about the trial and consent form mailed or send by post.

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 patients consent. The witness can be a nurse or other. The witness must write his/hers name in capital letters, signature, date and that they witness the patients consent.
- If a patient at the time of referral to another department or home is not competent because of delirium/psychosis or other condition 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.
- It must be a doctor who asses if the patient is competent.
- If the patient has a legal guardian. The guardian can give the consent on behalf of the patient (if the guardian has the authorisation to do so).
- If the patient dies before it was 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 or medical students working under the responsibility of a trained medical doctor. Collection of informed consent will be performed by all trial personnel (study nurses, medical students, doctors). If questions arise during informed consent, responsible study personnel can be reached through a 24-h 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		Total score and predicted 90-day mortality risk			
Age					
≤ 39 years → 0		0	3.3 %	22	40.1 %
40-59 years → 5		3	4.8 %	23	43.4 %
60-79 years → 10		4	5.5 %	24	46.7 %
≥ 80 years → 13		5	6.2 %	25	50.1 %
Lowest systolic blood pressure		6	7.1 %	26	53.5 %
≤ 49 mmHg → 6		7	8.0 %	27	56.9 %
50-69 mmHg → 5		8	9.1 %	28	60.2 %
70-89 mmHg → 3		9	10.3 %	29	63.4 %
≥ 90 mmHg → 0		10	11.6 %	30	66.4 %
Acute surgical admission		11	13.1 %	31	69.4 %
No → 3	Yes → 0	12	14.7 %	32	72.2 %
Hematologic malignancy or metastatic cancer		13	16.5 %	33	74.8 %
No → 0	Yes → 7	14	18.4 %	34	77.3 %
Vasopressors/inotropes		15	20.5 %	35	79.6 %
No → 0	Yes → 4	16	22.8 %	36	81.7 %
Respiratory support		17	25.3 %	37	83.7 %
No → 0	Yes → 5	18	28.0 %	38	85.4 %
Renal replacement therapy		19	30.8 %	39	87.0 %
No → 0	Yes → 4	20	33.8 %	41	89.8 %
Total score: 0-42 points		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 ethics⁶⁵.

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 methodology⁶⁶⁻⁶⁸. Patient relatives have limited concerns about co-enrolment⁶⁹.

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 trials⁶⁵.

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 one⁷⁰. Co-enrolment trials and factorial design trials share many similarities⁶⁵.

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 permitted⁷¹.

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-enrolment⁷².

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 interactions⁶⁵.

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 trial⁶⁵.

The National Institute of Health supports co-enrolment⁶⁶, 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 studied⁶⁵.

Co-enrolment does not appear to influence patient safety or trial results^{73,74}.

Empirically, co-enrolment has a small effect on study power⁶⁵.

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:

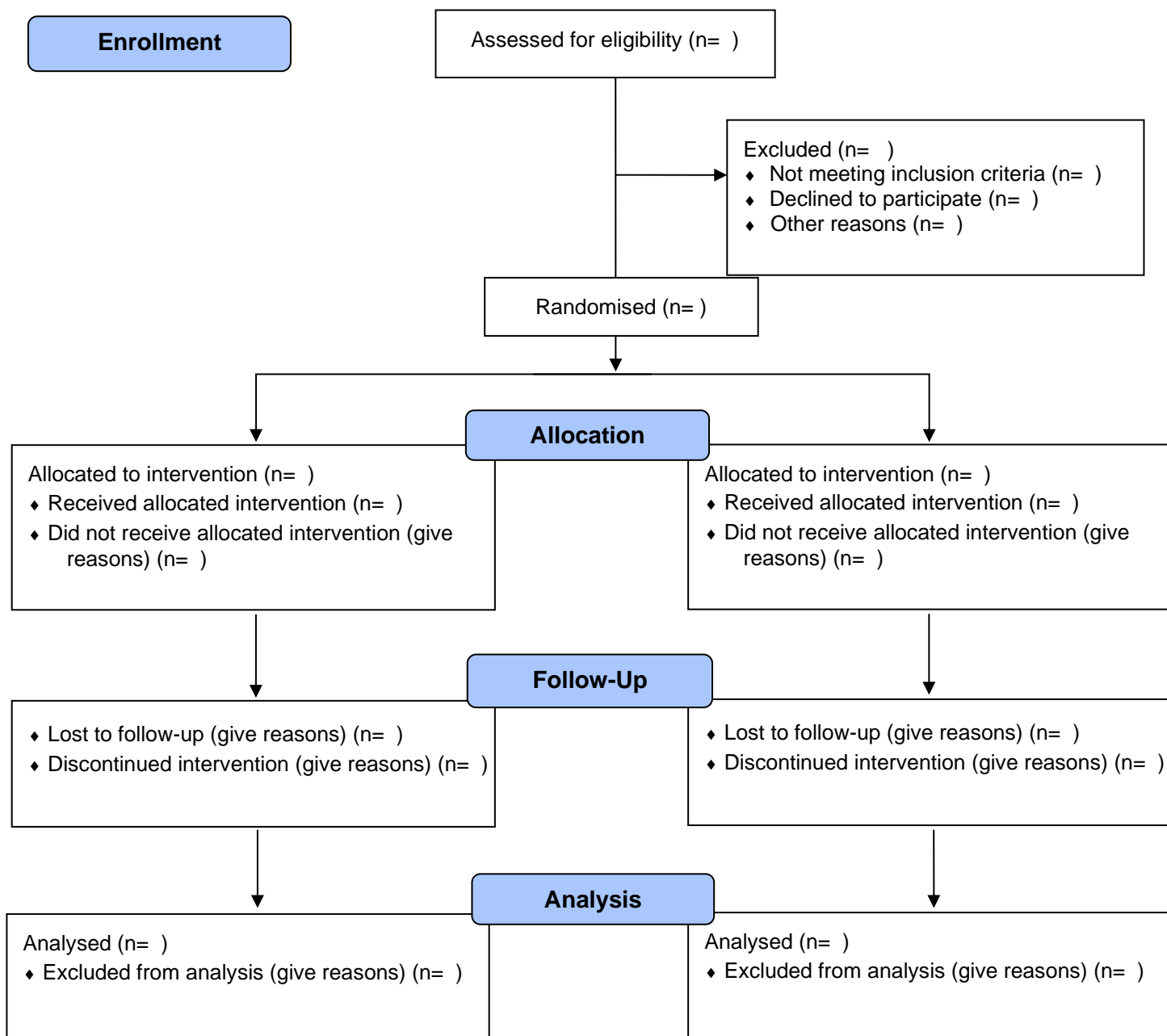
E-mail:

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 in the trial.
- KDIGO grading will be used to describe the severity for AKI.

14.10 Appendix 9. Trial flow chart



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



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

1



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

14.12 Appendix 11 – Budget for 2020 – 2023

Posterings	Budget i DKK
Statistikker/trial manager/Copenhagen Trial Unit/IT (eCRF)	1.300.000
Projektsygeplejersker	350.000
PhD-løn	2.428.596
Betaling af sites (Case money)	3.000.000
GCP-monitorering	650.000
Patientforsikring	300.000
Fee's (publikationer, MoCA certificering, ph.d afgift, konferencer ect.)	280.000
Møder/besøg/opsætning af sites, rejse i ind- og udland	120.000
Forsøgsmedicin (produktion og distribution)	900.000
Budget i alt for 4 år	9.328.596

14.13 Appendix 12 – Mottling score

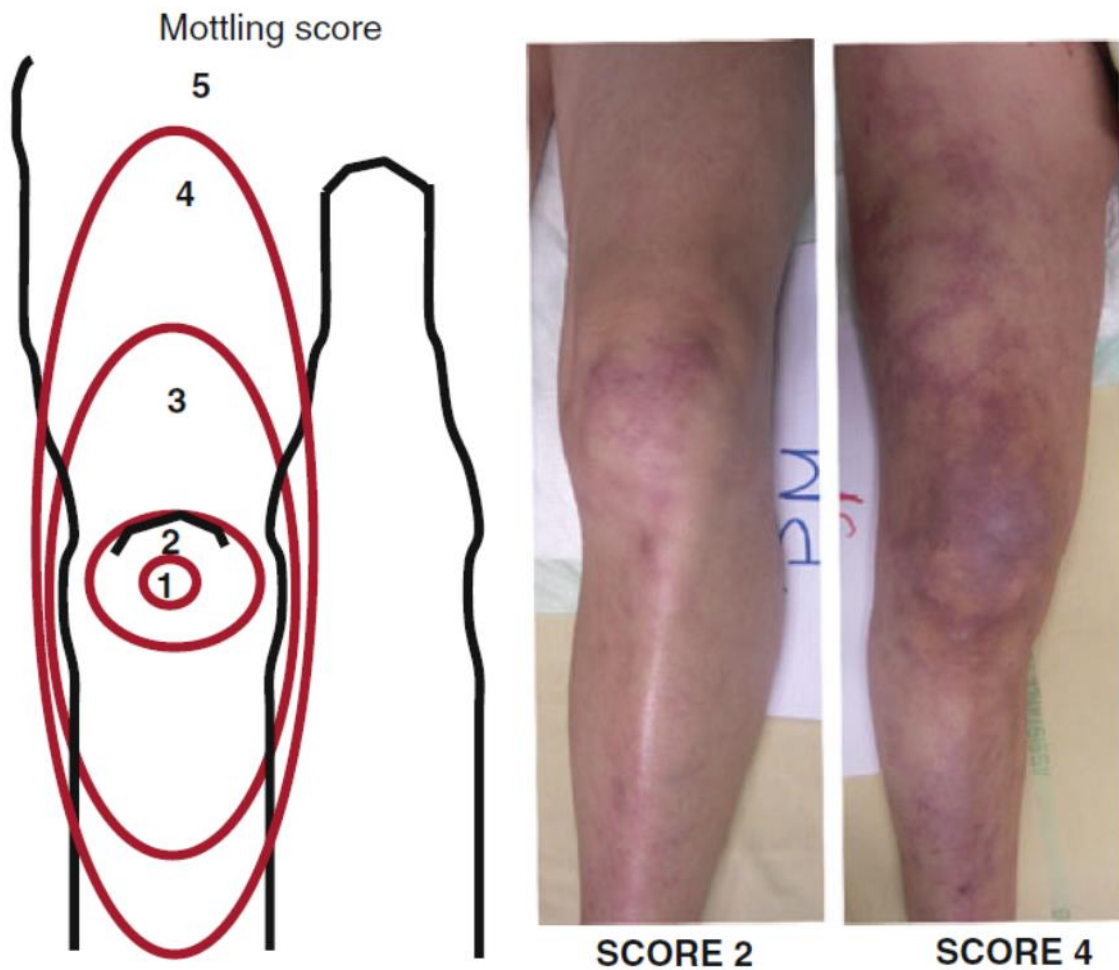


Fig. 1 *Left:* the mottling score is based on a mottling area extension on the legs. Score 0 indicates no mottling; score 1, a modest mottling area (coin size) localized to the center of the knee; score 2, a moderate mottling area that does not exceed the superior edge of the kneecap; score 3, a mild 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

14.15 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

14.16 Appendix 14: GODIF algorithm

FLUID REMOVAL WITH FUROSEMIDE

INITIATED AT INCLUSION

Bolus: 4 ml trialdrug i.v. (only at initiation). Start infusion at 2 ml/h. Infusion rate: 0-4 ml/h adjusted according to effect.
Goal directed fluid removal discontinued when cumulative fluid balance = 0 ± 500 mL

Target: Negative fluid balance of at least 1 mL/kg/h = _____ mL/8 hours

ASSESSMENT OF EFFECT

At 06:00 am, 2:00 pm and 10:00 pm

Therapeutic target achieved ?

YES

NO

NO

Increase trialdrug

Trialdrug at maximum dose (4 ml/h) ?

ASSESSMENT OF CIRCULATION

Lactate ≥ 4 , MAP < 50 or mottling beyond edge of the kneecaps
→ Resuscitation

RESUSCITATION

Resuscitation is initiated in the presence of one or more GODIF-criteria.

GODIF-Criteria:

- Lactate \geq 4 mmol/L
- MAP < 50 mmHg
- Mottling beyond edge of the kneecaps

NO

Resume trialdrug in 25 % reduced dose when all criteria have been resolved for a minimum of 1 hour

YES

Pause fluid removal
AND
Give fluid bolus (250-500 mL)
AND
Reassess within 30 min