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Wichmann, Sine; Itenov, Theis S.; Berthelsen, Rasmus E.; Lange, Theis; Perner, Anders; Gluud, Christian; Lawson-Smith, Pia; Nebrich, Lars; Wiis, Jørgen; Brøchner, Anne C.; Hildebrandt, Thomas; Behzadi, Meike T.; Strand, Kristian; Andersen, Finn H.; Strøm, Thomas; Järvisalo, Mikko; Damgaard, Kjeld A. J.; Vang, Marianne L.; Wahlin, Rebecka R.; Sigurdsson, Martin I.; Thormar, Katrin M.; Ostermann, Marlies; Keus, Frederik; Bestle, Morten H.

Published in:
Acta Anaesthesiologica Scandinavica

DOI (link to publication from Publisher):
10.1111/aas.14121

Publication date:
2022

Document Version
Publisher's PDF, also known as Version of record

Received: 14 June 2022 | Accepted: 3 July 2022

DOI: 10.1111/aas.14121

RESEARCH ARTICLE

acta Anaesthesiologica Scandinavica

Goal directed fluid removal with furosemide versus placebo in intensive care patients with fluid overload: A trial protocol for a randomised, blinded trial (GODIF trial)

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Funding information
Jakob Madsen's and wife Olga Madsen's Foundation; Merchant Jakob Ehrenreich and wife Grete Ehrenreich's Foundation; Novo Nordisk Fonden; Svend Andersen's Foundation; Sygeforsikringen Danmark

Abstract

Background: Fluid overload is a risk factor for mortality in intensive care unit (ICU) patients. Administration of loop diuretics is the predominant treatment of fluid overload, but evidence for its benefit is very uncertain when assessed in a systematic review of randomised clinical trials. The GODIF trial will assess the benefits and harms of goal directed fluid removal with furosemide versus placebo in ICU patients with fluid overload.

Methods: An investigator-initiated, international, randomised, stratified, blinded, parallel-group trial allocating 1000 adult ICU patients with fluid overload to infusion of furosemide versus placebo. The goal is to achieve a neutral fluid balance. The primary outcome is days alive and out of hospital 90 days after randomisation. Secondary outcomes are all-cause mortality at day 90 and 1-year after randomisation; days alive at day 90 without life support; number of participants with one or more serious adverse events or reactions; health-related quality of life and cognitive function at 1-year follow-up. A sample size of 1000 participants is required to detect an improvement of 8% in days alive and out of hospital 90 days after randomisation with a power of 90% and a risk of type 1 error of 5%. The conclusion of the trial will be based on the point estimate and 95% confidence interval; dichotomisation will not be used. ClinicalTrials.gov identifier: NCT04180397.

Perspective: The GODIF trial will provide important evidence of possible benefits and harms of fluid removal with furosemide in adult ICU patients with fluid overload.

KEYWORDS
critical care, de-resuscitation, diuretics, fluid accumulation, fluid overload, fluid removal, furosemide, intensive care, loop diuretics, protocol, randomised clinical trial

1 | INTRODUCTION

Fluid therapy and fluid status are central to clinical practice in ICUs. Substantial amounts of fluids are used in ICU patients for resuscitation, correction of fluid deficits, and administration of medicines and nutrition.[1] Combined with common retention of salt and water in critical illness this often results in fluid overload which may lead to acute kidney injury (AKI)[2–5] (PMID: 26263435) and dysfunction of other organs.[6,7]

Observational studies show that fluid overload is a risk factor for death,[6–18] but sparse evidence exists on how and when to start removing fluid. Studies investigating strategies of restrictive fluid therapy and/or diuretics in ICU patients with fluid overload have found conflicting results with regards to mortality.[19–21] A systematic review of randomised clinical trials (RCT) in ICU patients with fluid overload found inconclusive evidence on the effects of loop diuretics versus placebo/no intervention on mortality.[22]

Up to 50% of ICU patients are treated with diuretics during their ICU stay, and the predominant diuretic is furosemide, used in more than 94% of the patients receiving diuretics.[23,24] Despite the awareness of the detrimental effects of fluid overload and frequent practice of prescribing diuretics, solid evidence and guidelines on timing, choice and rate of removal are lacking.

The aim of this RCT is to investigate the benefits and harms of goal directed fluid removal with furosemide versus placebo in adult ICU patients with fluid overload. We hypothesise that treatment with furosemide, as compared with placebo, will increase the number of days alive and out of hospital at day 90 post-randomisation.

2 | METHODS

2.1 | Trial design

The GODIF trial is an investigator-initiated, international, randomised, blinded, parallel-group, clinical trial investigating furosemide versus placebo in adult ICU patients with fluid overload. The results of the trial will be reported according to the Consolidated Standards of Reporting Trials (CONSORT) Statement.[25]

2.2 | Trial conduct

The protocol was written in accordance with the Standard Protocol Items: Recommendation for Interventional Trials

(SPIRIT) 2013 statement (Supplementary S1).[26] The trial will be conducted in compliance with the Helsinki Declaration,[27] the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines,[28] and national laws in the participating countries.

2.3 | Randomisation

A central web-based randomisation system administered by the Copenhagen Trial Unit allocates participants in a 1:1 ratio to furosemide or placebo using a computer-generated allocation sequence stratified by AKI, Simplified Mortality Score for the Intensive Care Unit (SMS-ICU),[29] and trial site with varying block sizes.

2.4 | Allocation concealment and blinding

The allocation sequence list is exclusively known by the data manager at Copenhagen Trial Unit. Investigators, outcome assessors, clinical staff, patients, and statisticians are blinded. After the last participant has been followed for 90 days and the 90-day outcomes have been analysed, the management committee will write two versions of the abstract before the blinding will be demasked. The patients, researchers, and the staff doing the 1-year follow-up will remain blinded until the 1-year outcomes have been analysed.

Unblinding of the intervention for a participant may be done if deemed necessary by the clinician or investigator for safety reasons. Unblinding will be performed by data manager on request form the coordinating investigator.

The trial drug is furosemide 10 mg/ml or placebo (0.9% saline) and contained in identical vials containing 50 ml. The solution of furosemide is colourless and cannot be visually distinguished from saline. Each vial will be marked with an identification number which is used in a web-based program to allocate trial drugs to the participants.

2.5 | Inclusion and exclusion criteria

Inclusion and exclusion criteria are presented in Table 1.

A detailed description of the criteria is presented in Supplementary S2.

TABLE 1 Inclusion and exclusion criteria

Inclusion criteria All must be met	Exclusion criteria None must be met
• Acute admission to the ICU • Age 18 years or older • Clinically stable (minimum criteria: mean arterial blood pressure > 50 mmHg and maximum infusion of 0.20 μg/kg/min of noradrenaline and lactate < 4.0 mmol/L) • Fluid accumulation according to table below (>5% of ideal body weight)	• Allergy to furosemide or sulphonamides • Pre-hospitalisation advanced chronic kidney disease (eGFR < 30 ml/min/1.73 m^2 or chronic renal replacement therapy) • Ongoing renal replacement therapy • Anuria for ≥6 h • Rhabdomyolysis with indication for forced diuresis • Ongoing life-threatening bleeding • Acute burn injury of more than 10% of the body surface area • Severe dysnatraemia (plasma sodium <120 mmol/L or >155 mmol/L) • Severe hepatic failure • Patients undergoing forced treatment • Pregnancy • Consent not obtainable as per the model approved for the specific trial site

Minimum fluid accumulation on inclusion		
Height in cm	**Men**	**Women**
≤159 cm	+3000 ml	+2500 ml
160–169 cm	+3500 ml	+3000 ml
170–179 cm	+4000 ml	+3500 ml
180–189 cm	+4500 ml	+4000 ml
≥190 cm	+5000 ml	+4500 ml

Abbreviations: eGFR, estimated glomerular filtration rate; ICU, intensive care unit.

TABLE 2 Goal of daily negative fluid balance until resolution of fluid overload

Height in cm	Men	Women
≤159 cm	−1300 ml/24 h	−1200 ml/24 h
160–169 cm	−1500 ml/24 h	−1400 ml/24 h
170–179 cm	−1700 ml/24 h	−1600 ml/24 h
180–189 cm	−1900 ml/24 h	−1800 ml/24 h
≥190 cm	−2000 ml/24 h	−1900 ml/24 h

2.6 | Trial interventions

The aim is to achieve neutral fluid balance as fast as possible by daily goal directed fluid removal according to Table 2 and details in Supplementary S3.

Fluid balance is assessed daily by the treating clinicians based on one or more of the following: cumulative fluid balance, daily fluid balance, change in body weight and clinical examination. When a neutral fluid balance is obtained, the trial drug administration is paused or decreased to maintain a neutral fluid balance throughout the remaining time in ICU up to a maximum of 90 days. If the participant is discharged and readmitted to an ICU participating in GODIF trial during the 90-day period, the allocated intervention continues.

FIGURE 1 Escape procedures

Open-label furosemide can only be used in the case of:

- Hyperkalaemia (plasma-potassium > 6.0 mmol/L)
- Respiratory failure (PaO_2/FiO_2-ratio < 26 kPa (200 mmHg)) and the treating physician suspects the respiratory failure or deterioration is due to fluid overload or pulmonary oedema.

Renal replacement therapy (RRT) may only be started in the case of:

- Hyperkalaemia (plasma-potassium > 6.0 mmol/L)
- Respiratory failure (PaO_2/FiO_2-ratio < 26 kPa (200 mmHg)) and the treating physician suspects the respiratory failure or deterioration is due to fluid overload or pulmonary oedema
- Severe metabolic acidosis attributable to AKI (pH < 7.20 and standard base excess (SBE) < -10 mmol/L)
- Persistent AKI > 72 hours (defined as oliguria/anuria or plasma creatinine that has not declined to 50% from the peak value).

2.7 | Trial drug

Dosing of trial drug follows the same algorithm in both intervention groups: an IV bolus of 0.5–4.0 ml (5–40 mg of furosemide or matching placebo) at the treating clinician's discretion followed by a continuous IV infusion starting at 2 ml/h. The infusion must be titrated according to effect and daily target fluid balance. Allowed infusion rates are 0–4 ml/h. If the trial drug is infused at a maximum rate and the target fluid balance is not reached, no further interventions should be administered.

2.8 | Escape procedures

Escape procedures are presented in Figure 1.

The infusion of trial drug must continue in case of indication of escape open-label furosemide. The maximum recommended dose of furosemide is 1500 mg per day, which should not be exceeded.

If RRT is initiated, the trial drug must be paused. When the indication for RRT has subsided, RRT should be stopped, and the trial drug be restarted if the participant still has fluid overload.

2.8.1 | Resuscitation algorithm

In case of severe hypoperfusion defined as lactate ≥ 4.0 mmol/L or mean arterial blood pressure < 50 mmHg (resistant to vasopressor/inotropes) or mottling beyond the kneecaps (mottling score >2),[30] the trial drug should be paused. A bolus of isotonic crystalloid solution of 250–500 ml IV may be given followed by a re-evaluation of circulatory status. Trial drug and fluid removal should be restarted when the participant does not have any signs of hypoperfusion and is assessed as sufficiently stable to tolerate fluid removal.

2.8.2 | Co-interventions

Fluid therapy is administered at the clinicians' discretion. Habitual diuretics may be continued. Thiazides may be administered to treat hypernatremia. All other diuretics must not be administered. The use of vasopressors and inotropes is permitted.

TABLE 3 Outcomes for the GODIF trial

Primary outcome
Days alive and out of hospital at 90 days
Secondary outcomes
1. All-cause mortality at 90 days
2. Days alive without life support (vasopressor/inotropic support, invasive mechanical ventilation, or renal replacement therapy) at 90 days
3. All-cause mortality at 1-year
4. Number of participants with one or more serious adverse events (SAE) or serious adverse reactions (SAR).
5. Health-related quality of life as EuroQoL 5 dimensions, five-level questionnaire (EQ-5D-5L) index value at 1-year[31,32]
6. EQ visual analogue scale (EQ VAS) score at 1-year[31,32]
7. Participants subjective assessment of their quality of life (unacceptable/neutral/acceptable) at 1-year
8. Cognitive function as assessed by the Montreal Cognitive Assessment (MoCA) 5 min/telephone test at 1-year[33]

2.9 | Outcomes

All outcomes are presented in Table 3.

2.10 | Registered variables

Variables are registered on enrolment, daily during the trial period in the ICU, and at 90-days and 1-year follow-up. Detailed description of all variables is in Supplementary S4. All data will be entered on web-based electronic case-report forms (OpenClinica). Further information on data management, confidentiality, and responsibility in Supplementary S5.

2.11 | Serious adverse reactions and events

SAEs likely due to fluid removal and SARs likely due to furosemide will be registered daily in the database as detailed in Supplementary S6.

2.12 | Statistics

A detailed statistical analysis plan will be published before enrolment of the last participant.

Our primary analyses will be performed in the intention-to-treat population, defined as all randomised participants who have consented to the use of their data. Secondary analyses of the primary outcome will be performed in a per protocol population defined as all participants in the intention-to-treat population except those with a major protocol violation during the intervention period, defined as:

- Participants receiving other types of diuretics than allowed per trial protocol.
- Participants receiving open-label furosemide without fulfilling escape criteria.
- Initiation of RRT, without an indication as listed above.

The primary analyses will be adjusted for stratification variables (site, AKI, SMS-ICU score). As a sensitivity analysis, the primary outcome will also be adjusted for the following risk factors: ischaemic heart disease, septic shock, chronic obstructive pulmonary disease, diabetes, and stroke/neurodegenerative illness.

The primary publication of the GODIF trial will include the outcomes for day 90. The outcomes for 1-year follow-up will be published separately.

2.12.1 | Missing data

Complete case analysis will be performed if missing data is less than 5% for an outcome. If missing data are more than 5% multiple imputation will be performed.

2.12.2 | Primary outcome

The primary outcome will be compared between the treatment groups using a likelihood ratio test[34] building on a logistic model for mortality and a linear regression for days alive outside hospital within 90 days for patients discharged alive within 90 days. This is done to obtain maximal statistical power. The treatment effect will be quantified using raw means with 95% confidence intervals in the two groups and the mean difference obtained by bootstrap. The inference of the results will be based on the 95% CIs, but the *p*-value will also be reported. As the primary outcome is a composite outcome, results from each component will also be presented.

2.12.3 | Secondary outcomes

Binary secondary outcomes will be analysed with a logistic regression with the same adjustment strategy as the primary outcome. Using G-computation based on the logistic regression, we will compute risk ratios and risk differences and corresponding confidence intervals. Survival outcomes will also be analysed with Kaplan–Meier plots to illustrate time dynamics. Continuous secondary outcomes will be analysed using linear regression with the same adjustment strategy as the primary outcome. As the sample size is large non-normality is not deemed problematic.

Health-related quality of life at 1-year will be assessed with EuroQoL EQ-5D-5L index score based on the country value set and EQ-VAS scores[31,32] (the Danish value set will be used for those without a country-specific one). Participants who have died at 1-year will be assigned the value zero (EQ-5D-5L index score), which corresponds to a health state as bad as being dead and the worst possible value for EQ-VAS. Participants' subjective assessment of their quality of life will be presented in three categories (unacceptable/neutral/acceptable). Non-survivors will be assigned the value 'unacceptable'.

Cognitive function 1-year after randomisation will be assessed using the Montreal Cognitive Assessment (MoCA 5 min/telephone) score.[33] Non-survivors will be given the worst possible score.

Sensitivity analyses on health-related quality of life and cognitive function will be performed on the survivors.

2.12.4 | Sample size estimation

Sample size estimation for the primary outcome

A Wilcoxon rank sum test was used for the calculations as observational data were not normally distributed.[35] With the assumption of (1) lowering in-hospital mortality by 15% in the intervention group and (2) shifting the distribution of 'days alive out of hospital at day 90' to the right for the remaining population with a combined effect on the mean as an improvement of 8%, we will have 90% power ($\beta = .1$) to detect the described improvement at the 5% alpha level with 500 participants in each intervention group.

Power estimations for the secondary outcomes

1. Assuming a risk of 30% for all-cause mortality at day 90 after randomisation in the control group[35,36] we have about 37% power to detect a relative risk reduction of 15% at the 1% alpha level.
2. Assuming the same in-hospital mortality as in the primary outcome[35] and a 10% increase in days alive at day 90 without life support (vasopressor/inotropic support, invasive mechanical ventilation, or RRT) in the intervention group, then we have about 59% power at the 1% alpha level.
3. Assuming a risk of 37% for all-cause mortality at 1-year after randomisation in the control group,[37] we have about 52% power to detect a relative risk reduction of 15% at the 1% alpha level.

4. Assuming a control group proportion of participants with one or more SAEs and/or SARs of 30%,[36] we have about 37% power to detect a relative reduction of 15% at the 1% alpha level.

Because of a lack of sufficient knowledge, no meaningful power estimation could be performed for the outcomes health-related quality of life and cognitive function.

2.12.5 | Pre-planned subgroup analyses

We will compare the primary outcome in the following pre-specified subgroups:

1. Participants with SMS-score < 25 compared to ≥25
2. Participants with AKI compared to those without
3. Participants with SARS-CoV-2 infection compared to those without
4. Participants with septic shock prior to randomisation compared to those without
5. Participants on vasopressors compared to those without
6. Fluid overload ≥10% compared to <10%.

2.12.6 | Statistical inference

The conclusion of the trial will be based on the point estimate of the primary analysis of the primary outcome including a description of the uncertainty based on the 95% confidence interval. The *p* value will also be reported, but we will not dichotomise the results based on a specific *p* value cut-off. The term 'statistical significance' will not be used. For the secondary outcomes point estimates with 99% confidence intervals will be reported. *p* values will also be reported in the same way as for the primary outcome.

2.13 | Data Monitoring Committee (DMC)

An independent DMC will monitor the trial. The DMC consists of an independent clinician, a biostatistician, and a trialist with experience in conducting, monitoring, and analysis of randomised clinical trials. Charter for the DMC is available in Supplementary S7.

2.14 | Interim analysis for process variables

We will conduct an interim analysis when 100 participants (10%) have completed 90-day follow-up on the process variables: mean cumulative fluid balance after 3 days with censoring at discharge, and number of days with escape medicine. This is to ensure possible separation between the intervention groups. The DMC will make recommendations to the Management Committee regarding continuing, pausing, or stopping the trial after a qualitative assessment of the results.

2.15 | Interim analysis for clinical outcomes

The first interim analysis of clinical outcomes will be conducted after 500 participants (50%) have completed 90-day follow-up. The DMC will assess group-difference in the primary outcome and number of patients with one or more SAEs/SARs with statistical significance levels adjusted according to the Lan-DeMets group sequential monitoring boundaries based on O'Brien Fleming α spending function.[38] The DMC will make recommendations to the Management Committee regarding continuing, pausing, or stopping the trial.

2.16 | Monitoring during the study

The study will be monitored according to Good Clinical Practise (GCP)[28] and a pre-specified monitoring plan. The trial will also be monitored by the coordinating centre through the electronic case report form to ensure protocol adherence.

3 | DISCUSSION

Fluid accumulation in ICU patients is common and considered a risk factor for morbidity and mortality. Furosemide is the most frequently used agent in the treatment.[23,39] No guidelines for treating fluid accumulation in the general adult intensive care population exist and the evidence for using loop diuretics is sparce.[22] We want to investigate goal directed fluid removal in adult ICU patients with moderate to severe fluid overload with furosemide versus placebo and assess benefits and harms.

3.1 | Strengths

The GODIF trial is an international, randomised, blinded, placebo-controlled trial with high methodological standards designed to provide evidence of efficacy and safety of fast de-resuscitation with furosemide in adult ICU patients with fluid overload. The trial is conducted following the international guidelines for clinical trials and GCP. We will report patient-important outcomes. The trial is monitored according to GCP and an independent DMC.

3.2 | Limitations

Assessment of fluid overload is difficult with no available gold standard method. Cumulative fluid balance, daily fluid balance, changes in body weight, and clinical signs are all surrogate measures and thus inaccurate. During critical illness, patients quickly lose muscle mass[40] and weight loss which is not representing fluid shifts is expected. Clinical assessment is only a rough assessment of fluid overload by estimation of oedema, ascites, pleural effusions, and chest congestion using chest X-rays, CT-scans, echocardiography, ultrasound, and other diagnostic tools. The same is

true for the assessment of neutral fluid balance. This is a challenge for the trial and for future guidelines on the treatment of fluid overload.

4 | PERSPECTIVE

The assessment of fluid overload and neutral fluid balance in this trial is pragmatic. In the light of no available precise reference tool or method to assess fluid balance we believe that this approach provides the best assessments. It is in alignment with daily clinical practice and the method is easy to implement.

4.1 | Ethical considerations

The trial was registered at ClinicalTrials.gov and at the European Union Drug Regulation Authorities Clinical Trials Database. In Denmark, Norway, and Finland, the trial has been approved by national ethics committees and medicine agencies. All required approvals were obtained before the start of enrolment in the participating countries. Participants are enrolled after consent has been obtained according to national regulations.

4.2 | Dissemination

The trial results will be published in international peer-reviewed medical journals regardless of the results. We will adhere to the CONSORT statement in our reporting of results.[25] All documents inclusive protocol amendments will be available on www.cric.nu/godif/. Changes are communicated to relevant parties by newsletters. De-identified data will be made publicly available after ended trial.

4.3 | Trial status

The trial was launched on August 17, 2020 but paused on February 15, 2021 after randomisation of 41 participants. Protocol changes were made, and the trial was restarted on June 1, 2021 aiming to include 1000 participants more. The trial is expected to complete enrolment in December 2024. The first 41 participants will not be included in the primary analyses for the GODIF trial due to protocol changes but reported in a separate paper. The trial has currently 13 active trial sites in Denmark, Norway, and Finland. More European countries are currently applying to their authorities for approval to participate in the GODIF trial.

TRIAL SPONSOR

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APPLICABLE PROTOCOL REGISTRATION NUMBERS

Current protocol version 2.7 dated February 10, 2022. ClinicalTrials.gov identifier: NCT04180397; EudraCT: 2019-004292-40; Committees on Health Research Ethics in the Capital Region of Denmark: H-19080597; The Danish Medicines Agency: 2019121067; The Capital Region Knowledge Centre for Data Compliance: P-2020-170; The Finnish Medicines Agency: KLnro 19/2021; Finnish Ethics Committee, Hospital District of Southwest Finland: Dnro 17/1800/2021; Health Research Ethics Committee of Western Norway: 213330; The Norwegian Medicines Agency: 21/02350-9.

AUTHOR CONTRIBUTIONS

Sine Wichmann and Morten H. Bestle drafted this protocol, which was critically revised by all authors. All authors contributed substantially to development of this protocol, and all authors have read and approved the final manuscript.

ACKNOWLEDGEMENT

We thank all participating sites, research staff and participants.

CONFLICT OF INTEREST

SW has received a grant from Merchant Jakob Ehrenreich and wife Grete Ehrenreich's Foundation to production of trial drug for the GODIF trial. AP has received research funding from the Novo Nordisk Foundation, Health Insurance Denmark (Sygeforsikringen Danmark), Fresenius Kabi, Denmark, and Pfizer, Denmark. MO has received research funding from Fresenius Medical Care, Baxter and Biomerieux. MHB has received research funding for the GODIF trial from Novo Nordisk Foundation, Jakob Madsen's and wife Olga Madsen's Foundation, Svend Andersen's Foundation, and Health Insurance Denmark (Sygeforsikringen Danmark). No authors received any financial gain. All other authors declared no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Wichmann S, Itenov TS, Berthelsen RE, et al. Goal directed fluid removal with furosemide versus placebo in intensive care patients with fluid overload: A trial protocol for a randomised, blinded trial (GODIF trial). *Acta Anaesthesiol Scand*. 2022;66(9):1138-1145. doi:10.1111/aas.14121