Check for updates

Received: 8 August 2023 | Accepted: 12 August 2023

DOI: 10.1111/aas.14320

RESEARCH ARTICLE

acta Anaesthesiologica Scandinavica

Furosemide versus placebo for fluid overload in intensive care patients—The randomised GODIF trial second version: Statistical analysis plan

Sine Wichmann[1] | Theis Lange[2] | Anders Perner[3,4] | Christian Gluud[5,6] | Theis S. Itenov[7] | Rasmus E. Berthelsen[4] | Lars Nebrich[8] | Jørgen Wiis[4] | Anne C. Brøchner[9] | Louise G. Nielsen[10] | Meike T. Behzadi[11] | Kjeld Damgaard[12] | Anne S. Andreasen[13] | Kristian Strand[14] | Mikko Järvisalo[15] | Thomas Strøm[16] | Camilla T. Eschen[17] | Marianne L. Vang[18] | Thomas Hildebrandt[19] | Finn H. Andersen[20,21] | Martin I. Sigurdsson[22,23] | Katrin M. Thomar[22] | Sandra K. Thygesen[24] | Thomas T. Troelsen[24] | Panu Uusalo[25] | Ville Jalkanen[26] | Dorte Illum[27] | Christoffer Sølling[28] | Frederik Keus[29] | Carmen A. Pfortmueller[30] | Rebecka R. Wahlin[31] | Marlies Ostermann[32] | Anders Aneman[33,34] | Morten H. Bestle[1,4]

Correspondence
Sine Wichmann, Department of Anaesthesia and Intensive Care, Copenhagen University Hospital—North Zealand, Dyrehavevej 29, 3400 Hilleroed, Denmark.
Email: sine.wichmann@regionh.dk

Funding information
Grosserer Jakob Ehrenreich og Hustru Grete Ehrenreichs Fond; Jakob Madsens og Hustru Olga Madsens fond; Novo Nordisk Fonden; Svend Andersen Fonden; Sygeforsikringen danmark

Abstract

Background: Fluid overload is associated with increased mortality in intensive care unit (ICU) patients. The GODIF trial aims to assess the benefits and harms of fluid removal with furosemide versus placebo in stable adult patients with moderate to severe fluid overload in the ICU. This article describes the detailed statistical analysis plan for the primary results of the second version of the GODIF trial.

Methods: The GODIF trial is an international, multi-centre, randomised, stratified, blinded, parallel-group, pragmatic clinical trial, allocating 1000 adult ICU patients with moderate to severe fluid overload 1:1 to furosemide versus placebo. The primary outcome is days alive and out of hospital within 90 days post-randomisation. With a power of 90% and an alpha level of 5%, we may reject or detect an improvement of 8%. The primary analyses of all outcomes will be performed in the intention-to-treat population. For the primary outcome, the Kryger Jensen and Lange method will be used to compare the two treatment groups adjusted for stratification variables supplemented with sensitivity analyses in the per-protocol population and with further adjustments for prognostic variables. Secondary outcomes will be analysed with

For affiliations refer to page 5

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.
© 2023 The Authors. *Acta Anaesthesiologica Scandinavica* published by John Wiley & Sons Ltd on behalf of Acta Anaesthesiologica Scandinavica Foundation.

multiple linear regressions, logistic regressions or the Kryger Jensen and Lange method as suitable with adjustment for stratification variables.

Conclusion: The GODIF trial data will increase the certainty about the effects of fluid removal using furosemide in adult ICU patients with fluid overload.

Trial Registrations: EudraCT identifier: 2019-004292-40 and ClinicalTrials.org: NCT04180397.

KEYWORDS

deresuscitation, diuretics, fluid accummulation, fluid overload, fluid removal, intensive care, randomised clinical trial, statistical analysis plan

1 | INTRODUCTION

Patients treated in the intensive care unit (ICU) often receive substantial amounts of fluid, medicine, drug diluent and nutrition, which may lead to fluid overload.[1] Fluid overload is associated with organ dysfunction and mortality.[2,3] The evidence for treating fluid overload is, however, sparse. Two systematic reviews of randomised clinical trials (RCTs) assessing treatment with loop diuretics in ICU patients with fluid overload or septic shock were inconclusive and found only very low-quality evidence.[4,5] No large RCTs have been reported on therapies targeting fluid overload.[4]

Here, we present the detailed statistical analysis plan of the to-date largest and ongoing RCT of furosemide versus placebo in stable adult ICU patients with moderate to severe fluid overload (the GODIF trial second version).[6] This statistical analysis plan is published before finalising patient enrolment to increase transparency, prevent selective outcome reporting and data-driven analyses following the International Conference on Harmonisation (ICH) of Good Clinical Practice (GCP) guidelines.[7]

2 | METHODS

The GODIF trial is an international, multi-centre, randomised, stratified, blinded, parallel-group trial of furosemide versus placebo in 1000 ICU patients with fluid overload (EudraCT identifier: 2019-004292-40; NCT04180397).[6] Acutely admitted, clinically stable, adult (≥18 years) ICU patients with fluid overload (≥5% fluid accumulation according to ideal body weight) are randomised 1:1 to furosemide versus placebo. Randomisation is stratified for site, acute kidney injury (AKI) (yes/no), and simplified mortality score for the intensive care unit (SMS-ICU score) > 25 (yes/no).[8] The intervention continues until the clinician assesses the participant to be in a neutral fluid balance. The aim is to explore the effects of goal-directed fluid removal with furosemide in ICU patients with fluid overload.

The trial is blinded to participants, clinical staff, outcome assessors, investigators, and study statisticians. An independent data manager will provide the data in a blinded form. Unblinding will take place after all analyses have been performed, and the steering committee has drafted the abstract for the primary publication in two versions—one where the results favour the furosemide group and one where they favour the placebo group if a difference between the interventions is found.

The coordinating centre of the GODIF trial is located at the Copenhagen University Hospital—North Zealand, Hilleroed, Denmark. The current protocol is version 2.7 from 20 February 2022 (http://www.cric.nu/godif-protocol/). The trial has been approved by the 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) and all required authorities in all participating countries.

3 | OUTCOMES

The primary outcome is days alive and out of hospital at Day 90 after randomisation. The secondary outcomes are (1) all-cause mortality at Day 90; (2) days alive at Day 90 without organ support (vasopressor/inotropic support, mechanical ventilation or renal replacement therapy); (3) all-cause mortality at 1 year; (4) the number of participants with one or more serious adverse events (SAE) and serious adverse reactions (SAR); (5) health-related quality of life after 1 year as assessed with EuroQoL five-dimension, five-level questionnaire (EQ-5D-5L)[9,10]; (6) EQ visual analogue scale (EQ-VAS score) after 1 year[9,10]; (7) participants' subjective assessment of their quality of life after 1 year (unacceptable/neutral/acceptable); and (8) cognitive function after 1 year assessed by the Montreal Cognitive Assessment (MoCA; 5 min/telephone) test.[11]

4 | REGISTERED VARIABLES

Variables will be registered on screening, at baseline, daily during the admission to the ICU for up to 90 days, and on follow-up at Day 90 and 1 year. The 1-year follow-up will be performed as a telephone interview. All registered variables are published with the protocol article.[6]

All data are registered in an online OpenClinica database built and hosted by the Copenhagen Trial Unit in Denmark. For participants transferred to an ICU not participating in the GODIF trial within the 90-day follow-up period, attempts will be made to retrieve data on

organ support by contacting the non-trial sites to maximise the data necessary for the outcome of days alive without organ support at Day 90.

The screened and enrolled participants will be described using the consolidated standard of reporting trials (CONSORT) diagram.[12]

5 | SAMPLE SIZE AND POWER ESTIMATIONS

Sample size and power estimations are made according to the primary outcome of days alive and out of hospital within 90 days. The estimations are based on observational data from an international ICU cohort[13] and a 90-day mortality of 27%. We defined the minimal clinically relevant difference as a decrease in mortality of 15% and a total improvement of 8% in days alive and out of hospital at Day 90. The distribution of observational data for days alive and out of hospital was skewed and presented two peaks. A high frequency of deaths accounted for the first peak with the score zero, and close to Day 90, a second peak accounted for the survivors with very short admissions. A continuum of observations in between the two peaks with relatively few survivors with admissions beyond 7–14 days.

A simulation strategy[14] was used to identify the sample size that would yield a power of 90% ($\beta = .1$) with an alpha level of 5% ($\alpha = .05$). The total improvement of 8% was superimposed on the distribution of observational data that allowed simulations of outcomes under both interventions. A Wilcox rank sum test was applied to the distributions and the resulting *p*-value was stored. This was repeated 1000 times. The power was calculated as the fraction of these 1000 samples where the *p*-value was <.05. The above steps were applied for the incremental number of patients until the power requirement was achieved. A sample size of 500 participants in each treatment group would yield the desired power.

5.1 | Power estimations for the secondary outcomes

1. All-cause mortality at Day 90. An assumed risk of 30% for all-cause mortality in the control group at Day 90[13,15–17] resulted in about 60% power to detect a relative risk reduction of 15% at a 5% alpha level and 37% power at a 1% alpha level.
2. Days alive at Day 90 without life support. An assumed in-hospital mortality similar to the primary outcome[13] resulted in a power of 80% to detect a 10% increase in days alive at Day 90 without life support in the furosemide group at a 5% alpha level and 59% power at a 1% alpha level.
3. All-cause mortality at 1 year. An assumed risk of 37% for all-cause mortality at 1 year in the control group[18] resulted in about 75% power to detect a relative risk reduction of 15% at a 5% alpha level and 52% power at a 1% alpha level.
4. Number of patients with one or more SAEs/SARs at Day 90. An assumed incidence of 30% of one or more SAEs/SARs[15] at Day 90 for the participants in the control group resulted in a power of about 60% to detect a relative reduction of 15% at a 5% alpha level and 37% power at a 1% alpha level.

There are insufficient data to make a meaningful power estimation for the outcomes concerning health-related quality of life and cognitive functions.

6 | MISSING DATA

A complete case analysis will be performed if missing data are less than 5% for any variable in an analysis. If missing data are 5% or more, multiple imputations with chained equations will be performed by creating 50 input data sets under the assumption that the data are missing at random.[19,20] The imputation will use relevant outcomes, stratification variables (site, AKI, SMS-ICU score) and the following baseline variables: sex, age, percentage of fluid overload, type of admission (medical/surgical), septic shock, COVID-19 status, vasopressor/inotrope support, respiratory support and co-morbidities (ischaemic heart disease/heart failure, chronic obstructive pulmonary disease, diabetes mellitus, stroke/neurodegenerative illness, metastatic cancer/haematological malignancy, treatment with diuretics before hospital admission). If multiple imputations are used, the primary results will be based on these data.

Since the assumption that the data are missing at random might not always be satisfied, sensitivity analyses will be added with best–worst and worst–best scenarios to assess the pattern of missing data and the potential impact of data not missing at random.[19] For the 'best-worst-case' scenario, it is assumed that all participants lost to follow-up in the furosemide group had the best possible outcome (survived, had no SAE, etc.) and all those with missing outcome data in the placebo group had the worst possible outcome (death, SAE, etc.). For the 'worst-best-case' scenario the opposite is assumed. For continuous outcomes, the 'best outcome' will be defined as the group mean plus two standard deviations (SD) or highest possible value whichever is smallest, and the 'worst outcome' will be defined as the group mean minus two SD or lowest possible value whichever is highest.[19] Unadjusted analyses without imputation will also be made available.

7 | GENERAL ANALYTICAL PRINCIPLES

All primary analyses will be based on the intention-to-treat population defined as all participants who consented to the use of their data. Secondary analyses will be performed on the per-protocol population defined as all participants who consented to the use of their data and in whom no major protocol violation occurred during the intervention period. Secondary analyses will be performed for all outcomes.

Major protocol violations are (1) participants receiving other types of diuretics than allowed per trial protocol during the intervention; (2) participants receiving open-label furosemide without escape

criteria being met; and (3) initiation of renal replacement therapy without escape criteria being met.

The interpretation of the results will be based on the point estimate of the primary analysis of the primary outcome and the uncertainty described by the 95% confidence interval (CI). The *p*-value will be reported, but no specific *p*-value as the cut-off for statistical inference or the term 'statistical significance' will be used.[21–23] For the secondary outcomes, the results will be based on point estimates and 99% CIs to adjust for statistical multiplicity. *p*-values will be reported.

8 | STATISTICAL ANALYSES

8.1 | Primary outcome

The primary outcome days alive and out of hospital at Day 90 is a composite outcome and it will be analysed using a test by Kryger Jensen and Lange designed for continuous outcomes truncated by death.[24] The test is based on a logistic model for mortality and a linear regression for days alive outside hospital at Day 90. The effect of the intervention will be quantified using means with 95% CIs in the two groups and the mean difference was obtained by bootstrap adjusted for stratification variables. The results from both components of the composite outcome will also be presented.

A sensitivity analysis of the primary outcome will be performed with further adjustment for ischaemic heart disease, septic shock, chronic obstructive pulmonary disease, diabetes, and stroke/neurodegenerative illness. Secondary analyses of the per-protocol population will be performed with the same adjustment strategy.

8.2 | Secondary outcomes

All-cause mortality at 90 days and 1 year will be analysed using a logistic regression model combined with G-computation and non-parametric bootstrapping to convert effect measures into risk ratios and differences with corresponding 99% CIs. Adjustment will be made for stratification variables.

Kaplan–Meier plots will be used to illustrate the time dynamics of survival outcomes. Days alive without life support at Day 90 will be analysed with the same method as the primary outcome. The number of participants with one or more SAEs/SARs at Day 90 will be analysed as the mortality outcome.

EuroQol EQ-5D-5L index score and EQ-VAS scores will be used for the assessment of health-related quality of life at 1 year.[9,10] The scores are based on a specific country value set. If a country-specific value set is not available, we will use an available value set from a country most similar to the country in question according to demographics and medical practices. Participants who died within 1 year will be assigned the EQ-5D-5L index score of zero, which equals a health state of death, and zero in the EQ-VAS score (lowest possible score). MoCA (5 min/telephone) will be used to assess the participants' cognitive function at 1 year.[11] Non-survivors will be given the lowest possible score of zero. This procedure will result in a skewed distribution of data with a large proportion of zero values. The effect will be presented with adjusted mean differences and ratios of means with 99% CIs based on linear regression models adjusted for stratification variables using G-computation and non-parametric bootstrapping. The Kryger Jensen and Lange test will be used to calculate the *p*-value.[24] Data from survivors only will also be presented for both EQ-5D-5L and MoCA. The scores of the subdomains of the EQ-5D-5L and the MoCA test will be reported.

Participants will be asked to rate their quality of life during the 1-year follow-up differentiating between unacceptable, neutral or acceptable. Non-survivors will be given the category unacceptable. The results will be analysed by an ordinal logistic regression with adjustment for stratification variables. If this model does not converge (because of too few observations in some groups), then we will instead assign integer values starting from 1 and employ a simple linear regression.

The outcomes at 90 days and 1 year will be reported in separate publications. The statistical software R, the latest version available (https://www.r-project.org/), will be used to carry out the analyses.

8.3 | Subgroup analyses

Assessment of heterogeneity of the treatment effect on the primary outcome will be explored in the following subgroups in the intention to treat population based on baseline characteristics: (1) participants with SMS-ICU score <25 compared to ≥25; (2) participants with AKI compared to participants without AKI; (3) participants with COVID-19 compared to those without COVID-19; (4) participants with septic shock according to Sepsis 3 criteria before enrolment compared to those without septic shock; (5) participants receiving vasopressors support compared to those who did not; and (6) participants with fluid overload ≥10% compared to <10%.

If we recruit trial sites in new countries where the sites provide their own trial drug instead of the trial drug provided by the sponsor, we will conduct subgroup analyses of the primary outcome in all participating countries. It will be stated which countries use the different procedures according to trial medication and blinding (Appendix S1).

9 | INTERIM ANALYSES

An independent data monitoring committee (DMC) consisting of an independent biostatistician, a clinician and a trialist will monitor the trial and assess the safety and efficacy of the intervention. The DMC will make their recommendations to the Management Committee of the GODIF trial after the evaluation of both of the two planned interim analyses.[6]

The statistical significance level will be adjusted according to the Lan-DeMets sequential monitoring boundaries based on O'Brien

Fleming alpha-spending function.[25] The charter for the DMC has been published with the protocol article.[6]

10 | DISCUSSION

Fluid therapy is widely discussed and observational data suggest that fluid overload is associated with increased mortality.[3] The benefits of restrictive versus liberal fluid therapy with regard to mortality in the ICU population have still not been proven.[16,26–30] Several RCTs are currently investigating the question further for septic shock patients (NCT05179499; NCT04569942). The practice of treating fluid overload with diuretics is common.[31–33] Systematic reviews found very low and uncertain evidence for administering diuretics to patients with fluid overload in the ICU or septic shock patients.[4,5] This large international, randomised, blinded, clinical GODIF trial investigating protocolised fluid removal with furosemide versus placebo in stable adult ICU patients with moderate to severe fluid overload was designed to gain more high-quality evidence in the field.

10.1 | Strengths

The GODIF trial second version is using a revised improved protocol based on experiences from the GODIF trial first version.[34] The protocol has been published[6] and this detailed statistical analysis plan provides transparency in the conduct of the trial to prevent selective reporting and publication of research outcomes.

A composite outcome is used as the primary outcome. Composite outcomes can be difficult to interpret because it may be unclear how the treatment is affecting the individual components of the outcome. Each component of the primary outcome (90-day mortality and hospital length of stay at 90 days) will be reported in the primary publication to ensure transparency and ease of interpretation.

10.2 | Limitations

Our primary outcome will be affected by the risk of finding no treatment effect in case the results of 90-day mortality and length of hospital stay go in opposite directions (one showing benefit and one harm).

The secondary outcomes have low power, which must be considered when interpreting the results. Power estimations for health-related quality of life and cognitive functions were not conducted because of a lack of available data. The lack of baseline data for the EQ-5D-5L questionnaires and MoCA 5-min test precludes baseline differences between the groups to be detected.

ICU survivors often require long rehabilitation, and some might suffer from physical and psychological challenges. This can make 1-year follow-up more difficult and might have an impact on missing data and risk of selection bias.[35] MoCA 5-min test only detects mild cognitive impairment which represents a potential risk that cognitive deficits may be underestimated.

11 | TRIAL STATUS

The second version of the GODIF trial was launched on 1 June 2021 with complete enrolment expected in December 2024. On 31 July 2023, 307 participants were enrolled in the GODIF trial at 21 trial sites in Denmark, Norway, Finland and Iceland. More sites and countries are expected to join the trial.

AUTHOR CONTRIBUTIONS

Sine Wichmann drafted the manuscript. The statistical analysis plan was developed by Theis Lange, Sine Wichmann, Morten H. Bestle, Anders Perner, Christian Gluud and Theis S. Itenov. All authors have read, revised and approved the final manuscript.

AFFILIATIONS

[1]Department of Anaesthesia and Intensive Care, Copenhagen University Hospital—North Zealand, Hilleroed, Denmark
[2]Section of Biostatistics, Department of Public Health, University of Copenhagen, Copenhagen, Denmark
[3]Department of Intensive Care, Copenhagen University Hospital—Rigshospitalet, Copenhagen, Denmark
[4]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark
[5]Copenhagen Trial Unit, Centre for Clinical Intervention Research, The Capital Region, Copenhagen University Hospital—Rigshospitalet, Copenhagen, Denmark
[6]The Faculty of Health Sciences, Department of Regional Health Research, University of Southern Denmark, Odense, Denmark
[7]Department of Anaesthesia, Copenhagen University Hospital—Bispebjerg, Copenhagen, Denmark
[8]Department of Anaesthesia and Intensive Care, Zealand University Hospital, Koege, Denmark
[9]Department of Anaesthesia and Intensive Care, University Hospital of Southern Denmark, Kolding, Denmark
[10]Department of Intensive Care, Odense University Hospital, Odense, Denmark
[11]Department of Intensive Care, Aalborg University Hospital, Aalborg, Denmark
[12]Department of Anaesthesia and Intensive Care, Regionshospital Nordjylland, Hjoerring, Denmark
[13]Department of Intensive Care, Copenhagen University Hospital—Herlev, Herlev, Denmark
[14]Department of Intensive Care, Stavanger University Hospital, Stavanger, Norway
[15]Department of Internal Medicine, Kanta-Häme Central Hospital, Hameenlinna, Finland
[16]Department of Anaesthesia and Intensive Care, Sygehus Soenderjylland, Aabenraa, Denmark

[17]Department of Anaesthesia and Intensive Care, Copenhagen University Hospital—Gentofte Hospital, Gentofte, Denmark
[18]Department of Intensive Care, Regionshospitalet Randers, Randers, Denmark
[19]Department of Anaesthesia and Intensive Care, Zealand University Hospital, Roskilde, Denmark
[20]Department of Intensive Care, Aalesund Hospital, Moere and Romsdal Health Trust, Aalesund, Norway
[21]Faculty of Medicine and Health Science, Department of Health Science, Norwegian University of Science and Technology, Aalesund, Norway
[22]Department of Anaesthesia and Intensive Care, Landspitali, Reykjavik, Iceland
[23]Faculty of Medicine, University of Iceland, Reykjavik, Iceland
[24]Department of Anaesthesia and Intensive Care, Regionshospitalet Goedstrup, Herning, Denmark
[25]Department of Perioperative Services, Intensive Care and Pain Medicine, Turku University Hospital, Turku, Finland
[26]Department of Intensive Care, Tampere University Hospital, Tampere, Finland
[27]Department of Intensive Care, Aarhus University Hospital, Aarhus, Denmark
[28]Department of Intensive Care, Regionshospitalet Viborg, Viborg, Denmark
[29]Department of Critical Care, University Medical Centre Groningen, Groningen, The Netherlands
[30]Department of Intensive Care, Bern University Hospital, Bern, Switzerland
[31]Department of Anaesthesia and Intensive Care, Sodersjukhuset AB, Stockholm, Sweden
[32]Department of Intensive Care, King's College London, Guy's & St. Thomas' Hospital, London, UK
[33]Department of Intensive Care, Liverpool Hospital, South Western Sydney Local Health District, Sydney, Australia
[34]South Western Clinical School, University of New South Wales, Sydney, Australia

ACKNOWLEDGEMENTS

We thank all participants, relatives, and clinical and research staff on participating sites as well as the DMC members: Paul Young, Jon Silversides and Andreas Kryger Jensen, and funding resources.

FUNDING INFORMATION

GODIF trial has received funding from Novo Nordisk Foundation, Jakob Madsen's and wife Olga Madsen's Foundation, Svend Andersen's Foundation, Ehrenreich's Foundation, and Sygeforsikringen 'danmark' (Health insurance 'denmark').

CONFLICT OF INTEREST STATEMENT

Morten H. Bestle and Sine Wichmann: Funding for the GODIF trial as described above. No personal financial gain was applied. Anders Perner, Rasmus E. Berthelsen and Jørgen Wiis are affiliated with the Department of Intensive Care, Rigshospitalet, which receives support for research from the Novo Nordisk Foundation, Sygeforsikringen 'danmark' (Health insurance 'denmark'), Beckett's Foundation, Ehrenreich's foundation and does contract research for AM-Pharma. Anders Perner has received an honorarium from Novartis for participation in an advisory board. Carmen A. Pfortmueller reports grants from Orion Pharma, Abbott Nutrition International, B. Braun Medical AG, CSEM AG, Edwards Lifesciences Services GmbH, Kenta Biotech Ltd., Maquet Critical Care AB, Omnicare Clinical Research AG, Nestle, Pierre Fabre Pharma AG, Pfizer, Bard Medica S.A., Abbott AG, Anandic Medical Systems, Pan Gas AG Healthcare, Bracco, Hamilton Medical AG, Fresenius Kabi, Getinge Group Maquet AG, Dräger AG, Teleflex Medical GmbH, Glaxo Smith Kline, Merck Sharp and Dohme AG, Eli Lilly and Company, Baxter, Boehringer-Ingelheim, Aseptuva, Astellas, Astra Zeneca, CSL Behring, Novartis, Covidien, Aseptuva and Nycomed outside the submitted work. The money was paid into departmental funds; no personal financial gain applied. Marlies Ostermann has received research funding from Fresenius Medical, Baxter and Biomerieux. All other authors have no conflict of interest.

DATA AVAILABILITY STATEMENT

Data from the trial will be made available after publication of the planned papers.

ORCID

Sine Wichmann https://orcid.org/0000-0003-0360-8655
Anders Aneman https://orcid.org/0000-0003-2096-5304

REFERENCES

1. Van Regenmortel N, Verbrugghe W, Roelant E, Van den Wyngaert T, Jorens PG. Maintenance fluid therapy and fluid creep impose more significant fluid, sodium, and chloride burdens than resuscitation fluids in critically ill patients: a retrospective study in a tertiary mixed ICU population. *Intensive Care Med*. 2018;44:409-417.
2. Malbrain MLNG, Marik PE, Witters I, et al. Fluid overload, de-resuscitation, and outcomes in critically ill or injured patients: a systematic review with suggestions for clinical practice. *Anestezjol Intensywna Ter*. 2014;46:361-380.
3. Messmer AS, Zingg C, Müller M, Gerber JL, Schefold JC, Pfortmueller CA. Fluid overload and mortality in adult critical care patients—a systematic review and meta-analysis of observational studies. *Crit Care Med*. 2020;48:1862-1870.
4. Wichmann S, Barbateskovic M, Liang N, et al. Loop diuretics in adult intensive care patients with fluid overload: a systematic review of randomised clinical trials with meta-analysis and trial sequential analysis. *Ann Intensive Care*. 2022;12:52.
5. Messmer AS, Dill T, Müller M, Pfortmueller CA. Active fluid de-resuscitation in critically ill patients with septic shock: a systematic review and meta-analysis. *Eur J Intern Med*. 2023;109:89-96. doi:10.1016/j.ejim.2023.01.009
6. 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;66:1138-1145.
7. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Expert Working

Group. Integrated addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2). 2016 Accessed January 2023. https://www.ich.org/page/efficacy-guidelines
8. Granholm A, Perner A, Krag M, et al. External validation of the simplified mortality score for the intensive care unit (SMS-ICU). *Acta Anaesthesiol Scand*. 2019;63:1216-1224.
9. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res*. 2011;20:1727-1736.
10. Badia X, Diaz-Prieto A, Gorriz M, et al. Using the EuroQol-5D to measure changes in quality of life 12 months after discharge from an intensive care unit. *Intensive Care Med*. 2001;27:1901-1907.
11. Katz MJ, Wang C, Nester CO, et al. T-MoCA: a valid phone screen for cognitive impairment in diverse community samples. *Alzheimers Dement (Amst)*. 2021;13:e12144. doi:10.1002/dad2.12144
12. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *Int J Surg*. 2012;10:28-55.
13. The AID-ICU Cohort Study Co-authors, Collet MO, Caballero J, et al. Prevalence and risk factors related to haloperidol use for delirium in adult intensive care patients: the multinational AID-ICU inception cohort study. *Intensive Care Med*. 2018;44:1081-1089.
14. Arnold BF, Hogan DR, Colford JM, Hubbard AE. Simulation methods to estimate design power: an overview for applied research. *BMC Med Res Methodol*. 2011;11:94.
15. Krag M, Marker S, Perner A, et al. Pantoprazole in patients at risk for gastrointestinal bleeding in the ICU. *N Engl J Med*. 2018;379:2199-2208.
16. Meyhoff TS, Hjortrup PB, Wetterslev J, et al. Restriction of intravenous fluid in ICU patients with septic shock. *N Engl J Med*. 2022;386:2459-2470. doi:10.1056/NEJMoa2202707
17. Andersen-Ranberg NC, Poulsen LM, Perner A, et al. Haloperidol for the treatment of delirium in ICU patients. *N Engl J Med*. 2022;387:2425-2435. doi:10.1056/NEJMoa2211868
18. Marker S, Krag M, Perner A, et al. Møller MH, the SUP-ICU trial investigators. Pantoprazole in ICU patients at risk for gastrointestinal bleeding—1-year mortality in the SUP-ICU trial. *Acta Anaesthesiol Scand*. 2019;63:1184-1190.
19. Jakobsen JC, Gluud C, Wetterslev J, Winkel P. When and how should multiple imputation be used for handling missing data in randomised clinical trials—a practical guide with flowcharts. *BMC Med Res Methodol*. 2017;17:162. doi:10.1186/s12874-017-0442-1
20. Heymans MW, Twisk JWR. Handling missing data in clinical research. *J Clin Epidemiol*. 2022;151:185-188.
21. Amrhein V, Greenland S, McShane B. Retire statistical significance. *Nature*. 2019;567:306-307.
22. McShane BB, Gal D, Gelman A, Robert C, Tackett JL. Abandon statistical significance. *Am Stat*. 2019;73:235-245.
23. Diaz-Quijano FA, Calixto FM, da Silva JMN. How feasible is it to abandon statistical significance? A reflection based on a short survey. *BMC Med Res Methodol*. 2020;20:140.
24. Jensen AK, Lange T. A novel high-power test for continuous outcomes truncated by death. arXiv: Statistics. 2019.
25. Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. *Biometrika*. 1983;70:659-663.
26. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network, Wiedemann HP, Wheeler AP, et al. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med*. 2006;354:2564-2575.
27. Reynolds PM, Stefanos S, MacLaren R. Restrictive resuscitation in patients with sepsis and mortality: a systematic review and meta-analysis with trial sequential analysis. *Pharmacotherapy*. 2023;43:104-114.
28. Silversides JA, Major E, Ferguson AJ, et al. Conservative fluid management or deresuscitation for patients with sepsis or acute respiratory distress syndrome following the resuscitation phase of critical illness: a systematic review and meta-analysis. *Intensive Care Med*. 2017;43:155-170.
29. The National Heart, Lung, and Blood Institute Prevention and Early Treatment of Acute Lung Injury Clinical Trials Network. Early restrictive or liberal fluid management for sepsis-induced hypotension. *N Engl J Med*. 2023;388:499-510.
30. Sivapalan P, Ellekjaer KL, Jessen MK, et al. Lower vs higher fluid volumes in adult patients with sepsis: an updated systematic review with meta-analysis and trial sequential analysis. *Chest*. Published online. 2023. doi:10.1016/j.chest.2023.04.036
31. Zeuthen E, Wichmann S, Schønemann-Lund M, et al. Nordic survey on assessment and treatment of fluid overload in intensive care. *Front Med*. 2022;9:1067162 https://www.frontiersin.org/articles/10.3389/fmed.2022.1067162
32. Silversides JA, McAuley DF, Blackwood B, Fan E, Ferguson AJ, Marshall JC. Fluid management and deresuscitation practices: a survey of critical care physicians. *J Intensive Care Soc*. 2020;21:111-118.
33. McCoy IE, Chertow GM, Chang TI-H. Patterns of diuretic use in the intensive care unit. *PloS One*. 2019;14:e0217911.
34. Wichmann S, Schønemann-Lund M, Perner A, et al. Goal-directed fluid removal with furosemide versus placebo in intensive care patients with fluid overload: a randomised, blinded trial (GODIF trial—first version). *Acta Anaesthesiol Scand*. 2023;67:470-478.
35. Dumville JC, Torgerson DJ, Hewitt CE. Reporting attrition in randomised controlled trials. *BMJ*. 2006;332:969-971.

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, Lange T, Perner A, et al. Furosemide versus placebo for fluid overload in intensive care patients—The randomised GODIF trial second version: Statistical analysis plan. *Acta Anaesthesiol Scand*. 2023;1-7. doi:10.1111/aas.14320