GODIF

Protocol title	**GODIF** Goal-directed fluid removal with furosemide in intensive care patients with fluid overload – A randomised, blinded, placebo-controlled trial (GODIF) EU CT no: 2024-512186-14-00; ClinicalTrials.gov: NCT04180397
SOP name	Trial medication
Version	1.2
Applied from	24.09.2024

Target population: Site investigators and research staff

Responsible party: Sponsor, Professor Morten Bestle

Created by: Coordinating Investigator; Sine Wichmann

1. Objective

- To define starting dose of trial drug
- To describe how to adjust the infusion of the trial drug
- To describe how to pause and re-activate trial medication
- To describe stopping criteria
- To ensure uniform working procedures for pausing and re-activation of trial medication

2. Description:

2.1 Starting dose:
0,5-4 ml of trial drug as a bolus injection according to the treating physician's discretion, followed by infusion of trial drug starting at 2 ml/hour.

2.2 Adjustment of Trial Drug Infusion:
The infusion rate of the trial drug must be adjusted based on the therapeutic effect and the target for daily negative fluid balance. The permissible infusion rate ranges from 0 to 4 mL/hour. The goal is to achieve a negative fluid balance as outlined in Table 1. A minimum of three daily assessments of the trial drug's effectiveness is required, typically during the calculation of fluid balance by nursing staff. However, it is recommended to evaluate the infusion rate more frequently to ensure the dosage remains appropriate in achieving the target balance.

If the target negative fluid balance is not achieved, the infusion rate should be gradually increased up to the maximum allowed rate of 4 mL/hour. If the target fluid balance remains unmet despite reaching the maximum infusion rate, the infusion rate must be maintained at maximum. The maximum permissible dose of furosemide is 1500 mg within a 24-hour period. Maximum infusion in 24 hours (4ml x 24 = 960mg) the leaves up to 540 mg which can be administered as escape furosemide should the escape criteria be met.

The trial drug infusion should be replaced with a fresh preparation every 24 hours, or sooner if necessary.

Table 1. Intended daily minimum fluid removal

Height	Men	Women
≤ 159 cm	-1300 ml	-1200 ml
160-169 cm	-1500 ml	-1400 ml
170-179 cm	-1700 ml	-1600 ml
180-189 cm	-1900 ml	-1800 ml
≥ 190 cm	-2000 ml	-1900 ml

2.3 Pausing and re-activating trial medication:
When the patient has reached neutral fluid status the fluid removal must be stopped. Trial drug must be *paused or adjusted* to keep the patient's fluid balance neutral for the rest of the ICU stay. If the trial drug has been paused, then it must be restarted if the patients begin to accumulate fluid again.

In case *of circulatory instability* (MAP < 50 mmHg *or* lactate ≥ 4.0 *or* mottling beyond the edge of the kneecaps the trial drug must be paused, and the resuscitation algorithm may be started. Fluid bolus of 250-500 mL crystalloids and re-evaluate the circulation within 30 min. Repeat re-evaluation and optional fluid therapy until adequate circulation (lactate < 4.0, MAP > 50 mmHg, and no mottling beyond kneecaps). The trial drug and fluid removal should be resumed when the clinician find the patient stable enough to tolerate further fluid removal.

In case *of escape renal replacement therapy*, the trial drug must be paused, but re-activated when the renal replacement therapy is paused or terminated if the patient still has fluid accumulation.

2.4 Stopping criteria:

- Neutral fluid status assessed according to fluid balances, body weights and clinical signs
- Discharge from the ICU
- Transferal to another ICU (not participating in GODIF)
- Death in the ICU
- 90 days post randomisation

Responsible party for administration and registration of trial drug:
Site investigators and research staff.

Approved 24.09.2024: Sponsor, Professor Morten Bestle