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| **Protocol title** | **GODIF**  Goal directed fluid removal with furosemide in intensive care patients with fluid overload – A randomised, blinded, placebo-controlled trial (GODIF)  EudraCT: 2019-004292-40; ClinicalTrials.gov: NCT04180397 |
| **SOP name** | Trial medication |
| **Version** | 1.2 |
| **Applied from** | 06.05 2021 |

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| **Target population**: Site investigators and research staff |
| **Responsible party**: Sponsor, Senior staff specialist and Associate 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 |
| 1. **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 with 2 ml/hour.  **2.2 Adjustment of trial drug infusion**:  Infusion of trial drug must be adjusted according to effect and fluid balance. The infusion rate is 0-4 ml/hour. Target is a negative fluid balance per day according to chart below. Assessment of the effect of trial drug must be done minimum 3 times a day when the nurses calculate the fluid balance (often at 06:00 am, 2:00 pm and 10:00 pm). It will be beneficial to assess the infusion rate more often to ensure the correct dose. If the target fluid balance cannot be reached on maximum infusion rate of 4 mL/hour no further interventions must be done. Continue maximum infusion rate of 4 mL/hour.   |  |  |  | | --- | --- | --- | | **Minimum fluid removal for 24 hours.** | | | | 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 | -2000 mL | -1900 mL |   When a vial of trial drug is opened – the trial drug must be used within 24 hours. Infusion of trial drug must be replaced with new trial drug every 24 hours or more often.  **2.3 Pausing and re-activating trial medication:**  When the patient *has reached neutral fluid balance* assessed by the treating physician according to the cumulative fluid balance, daily fluid charts, changes in body weight, and clinical examination (oedemas, congestion on X-ray, e.c.t.) the fluid removal must be stopped. Trial drug must be adjusted to keep the patient’s fluid balance neutral. If possible, the trial drug can be paused. It must be re-activated in case the patients show signs of fluid accumulation again. Starting bolus should only be administered the first time the trial drug is started.  The fluid status of the patient must be documented daily in the patient file.  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 iv 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). When all the criteria have been resolved and the patient is assessed stable enough to tolerate fluid removal. The trial drug must be restarted if the patient still has fluid overload.  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. In case of escape *open label furosemide* is used, the infusion of trial drug must continue on maximum infusion. The maximum dose of escape furosemide per day is 540 mg.  **2.4 Stopping criteria:**   * Neutral fluid balance (according to fluid charts, changes in body weight, and clinical examination). * Hemodynamic instability (trial drug must be restarted when the patient is assessed stable enough to tolerate fluid removal by the clinical staff) * 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 06.05 2021**: Sponsor, Morten Bestle |