Place in Site Master File #9av

**Instruction for the GODIF trial – serious adverse reactions (SARs) and serious adverse events (SAEs) and suspected unexpected serious adverse reactions (SUSARs)**

The treating clinician should be aware of the precautions and potential adverse reactions as listed in the Furosemide product information (please see appendix 3 in the protocol or 10b in site master file). Patients should be monitored for known adverse reactions. Adverse events and adverse reactions must be documented routinely in the patient health record.

Definitions of serious adverse event reactions:

**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).

In the ICU the patients are critically ill and experience numerous SAEs. The authorities have approved that we only document the following SAEs relevant to fluid removal:

**SAE to be documented daily in the eCRF:**

* 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 ≥ 354 μmol/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 to be documented daily in the eCRF:**

* 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.

All SARs and SAEs must be reported to the coordinating centre within 24 hours. Complete the SAR/SAE/SUSAR form in site master file (14a) at the website (www.cric.nu/godif) and sent it by email to the coordinating centre (godif@cric.nu). You will receive an email from the coordinating centre when the report has been registered.

For every SAR, the investigator and the Sponsor must assess if it is related to trial drug according to summary of product characteristic. In case of any other unexpected SAE/SAR not mentioned above the investigator must report them to 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. In case of SUSAR the trial medication will be demasked.

The intervention might be stopped if the participant experiences a SAR or SUSAR. If the situation allows it, please call the coordinating centre to discuss if unblinding the trial medication or stopping the trial intervention is relevant.

**Call the GODIF hotline: +45 4829-6773**

Investigators at all participating sites will receive information by email if a SUSAR is reported and a yearly report of all registered SARs.