Inclusion criteria

Types of studies
We will include parallel-group RCTs compared to placebo or other treatment, as well as crossover and cluster RCTs. We define ‘randomized’ as studies that were described by the study author as ‘randomized’. Trials are included if they are available in English or German. All trials, published and unpublished, will be eligible for inclusion.

Types of participants
We will consider adults (≥18 years) with HF and refractory dyspnea regardless of the underlying etiology (e.g. cardiomyopathy, pulmonary arterial hypertension). HF will be assumed if the authors declare this and refractory dyspnea is assumed if the studies apply an opioid for the relief of dyspnea or to increase exercise performance.

Types of interventions
Any opioid, regardless of the route of administration used for the treatment of breathlessness compared to placebo.

Types of outcome measures
Primary outcome
Subjective measurement of dyspnea intensity, including but not limited to Borg and the modified Borg scale, verbal categorical scales of dyspnea, and visual analogue scales (VAS) of dyspnea. This may refer to dyspnea at rest, on average or on exertion. If measurements of dyspnea are available on different time points in one RCT, we will choose the data from the time point most closely to the primary endpoint of the respective RCT.

Secondary outcomes
- Validated instruments for quality of life (QoL) and Health related QoL (HRQoL) measure including but not limited to VAS, EQ-5D, Kansas City Cardiomyopathy Questionnaire-short form
- Validated instruments for depression and anxiety
- Mortality

- Adverse events: constipation, nausea, somnolence, dizziness, delirium, bradypnea or oxygen-desaturation

- All serious adverse events (SAE)

- Six-minute walk tests (6MWT), shuttle tests or ergometry

- Physiologic measures: change in SpO₂, PaCO₂, heart- and respiration rate

- Withdrawal