TITLE (SHORT, 200 CHARACTERS MAX.):

PAIN AFTER CARDIAC ARREST AND RESUSCITATION – PAIN CARE SUBSTUDY

MAIN HYPOTHESES TESTED (2 MAX)

Main hypothesis:

Patients experience pain in the ICU after cardiac arrest, which can be described and explored in terms burden to pain exposure during the first 7 days of ICU stay

Secondary hypothesis:

1. Burden of pain in the ICU, after cardiac arrest is associated with:
    a. Age
    b. Sex
    c. Time to ROSC
    d. Frailty
    e. Existing Protocol for assessment and management of pain in critically ill patients

2. Presence of pain in the ICU, after cardiac arrest is associated with secondary outcomes:
    a. Level of sedation
    b. Duration of delirium
    c. Level of mobilization
    d. Time on ventilatory support
    e. ICU Length of Stay
    f. Reported pain after 1 and 6 months.
    g. Quality of life at 6 months
    h. Dose of remifentanil

SINGLE CENTER [ ] , MULTICENTER [X]

All sites including patients in the Pain after CArdiac arrest and REsucitation – PAIN CARE sub study of the STEPCARE Trial.

PICO

- Patients: Unconscious, adult, out-of-hospital cardiac arrest survivors, with at least one estimation of level of pain intensity during ICU stay after cardiac arrest.
- Exposure:
    - Primary analysis: NA
    - Secondary analyses: Moderate/severe burden of pain, day 0-7, after cardiac arrest
- Comparator:
    - Primary analysis: NA
    - Secondary analysis: Restricted mean time (hours) in moderate/severe pain while alive & in ICU by 168 h
- Outcome:
    - Primary analysis: Restricted mean time (hours) in moderate/severe pain while alive & in ICU by 168 h
    - Secondary analysis:
        - Proportion of ICU time in moderate/severe pain(Descriptive)
        - Burden of pain: Proportion of time alive and in ICU spent in moderate/severe pain by 168 h

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- Delirium free days alive in the ICU by 168 h
- Level of mobilization>1
- Hours alive and free of invasive ventilatory support at day 30
- Alive free ICU days at day 30
- Pain intensity at 1 month (Telephone interview, NRS)
- Pain intensity at 6 months (In person visit, NRS)
- Reported life satisfaction at 6 months (In person visit, WVS)

DATA NEEDED FOR THE ANALYSIS (SPECIFY VARIABLES AND MOTIVATE ANY PROPOSED ADDITIONS TO THE ECRF)

In addition to available data in the eCRF:

- Pain assessments with instruments based on behaviors
    - Behavioral Pain Scale (BPS) or Critical Care Pain Observational Tool (CPOT) and time of rating after randomization, in sedated, non-communicative patients.
    - Numerical Rating Scale (NRS) and time of rating after randomization, when patients able to self-report their pain.

Motivation: Pain is regarded as one of three important factors within the PAD bundle (Pain, Agitation and Delirium) which was implemented through international guidelines (Barr et al., 2013; Devlin et al., 2018). Pain is therefore recommended to be assessed in conjunction with sedation and delirium. A pain-free patient is less likely to have delirium (Mart et al., 2021) and less agitated (Chanque et al., 2006) thus, needing less sedation. An adequate pain treatment is also crucial for mobilization practice, and beneficial for early mobilization which could affect the weaning process from ventilator and length of stay for patients in the ICU (Dubb et al., 2016). OHCA patients might have thoracic trauma/rib fractures after CPR which could generate a risk of pain during and post intensive care.

As described, pain, sedation and delirium are strongly associated and thus, pain could be affecting both presence of delirium, needed sedation levels and early mobilization. Untreated pain could therefore also lead to increased length of stay. In the StepCare study the assessments of sedation and delirium is already being collected why pain assessments could be informative and bring additional insights.

LOGISTICS – HOW WILL ADDITIONAL DATA BE GATHERED?

Worst observed intensity of pain using NRS for awake responsive patients, and CPOT or BPS (according to local routines) for nonresponsive patients. Ordinal variable, categorized as **painless** (CPOT 0, BPS 3, NRS 0), **mild pain** (CPOT 1-2, BPS 4-5, NRS 1-3), or **moderate/severe pain** (CPOT >2, BPS >5, NRS >3). Assessment will estimate highest pain intensity since last datapoint and will be done at: 0, 12, 24, 36, 48, 56, 64, 72, 80, 88, 96, 104, 112, 120, 128, 136, 144, 152, 160, 168 hours. Each scheduled assessment reflects the worst pain since the prior datapoint and is applied to the entire preceding interval to construct time in state (NB, staff recall bias- limitation). If ICU discharge or death occurs within an interval, the interval is split at the exact event time; time after the event does not contribute to ICU pain burden.

NRS will also be collected as worst pain on movement in last 24 h at 30 day and 6 month follow up.

Delirium, sedation FOUR-motor score, and ICU mobility are synchronized with the STEPCARE main dataset, and additional datapoints will be collected at 56, 64, 80, 88, 104, 112, 128, 136, 144, 152, 160, 168 hours for:

- Delirium present assessed by CAM-ICU, or ICDSC: Binary, Yes/No
- Richmond Agitation and Sedation Scale (RASS). Ordinal scale, numeric, range -5/+5.
- FOUR-motor score, ordinal variable, numeric, integers, range 0/4.

Additional data points for ICU mobility: 144, 168 hours

Additional question regarding pain treatment: “Did the patient receive a successful pain block while in the ICU?”, Communicative: NRS reduction ≥2 points or ≥30% within 60 min, and no rescue opioid within 6 h. Non-communicative: CPOT reduction ≥2 or BPS reduction ≥2 within 60 min, and no rescue opioid within 6 h.

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These additional datapoints will be captured by an extended eCRF form.

Additional question on site level: Does the site have a protocol for assessment and management of pain in critically ill conscious and unconscious patients (Captured outside eCRF by direct communication with site investigator at initiation of study)

Training: Sites participating in substudy will receive initiation training by video meeting and receive a brief CPOT/BPS/NRS module with 3 vignettes; require short quiz.

BRIEF STATISTICAL ANALYSIS PLAN AND SAMPLE SIZE ESTIMATE

Burden of pain

- Primary outcome:
  - Burden of moderate/severe pain (BmsP), defined as restricted mean time: nonparametric multi-state (Aalen–Johansen) to estimate state-occupancy and integrate time in moderate/severe pain through 168 h; covariate-adjusted contrasts via pseudo-observations with GEE, clustering by site. Discharge and death terminate risk time.
- Secondary outcome
  - Proportion: beta (or fractional logistic) regression for A_i/T_i with robust site-clustered SEs. The proportion of ICU time in pain will be reported descriptively to facilitate interpretation but not used as an independent inferential endpoint.

If pain is not assessable (e.g., active neuromuscular blockade or RASS ≤−4), classify the interval as 'not scorable' (imputation via multiple imputation using pain trajectory, sedation, and patient covariates).

Time-updated (interval) exposure model: discrete-time mixed-effects logistic for moderate/severe vs painless with random intercepts for patient (and site) and 8–12 h lagged time-varying covariates to mitigate reverse causation. As sensitivity, we fit MSM/IPTW with stabilized weights, weight trimming (1st–99th percentile), and covariate balance diagnostics.

Competing risks: Mechanistic explanatory time-to-event outcomes (Ventilator free days, death) will be modelled by cause-specific hazards model. Fine-Gray modelling may be considered as sensitivity analysis.

Covariates for secondary analyses:

- Number of covariates in regression models will be adjusted in relation to event rate. A guesstimate of 30% event rate for moderate/severe pain intensity allows for ≤ 6 variables (≥20 EPV) for secondary outcomes. Larger covariate sets may be analyzed with penalized regression (ridge) and interpreted descriptively.
- All analyses will be adjusted for STEPCARE Interventions (MAP, Sedation and Temperature), as well as key outcome variables: Time to ROSC, Age, sex, pre-arrest frailty and BmsP
- Timedependent and survival models will also be adjusted for shockable rhythm, witnessed arrest
- Explanatory models for burden of pain and length of delirium will be adjusted for: Cumulative remifentanil dose at 72h, presence of protocol for assessment and treatment of pain, severe neurologic disability (FOUR-motor score M<2)
- Life satisfaction and pain at 1 month/6 months will be adjusted for: Modified Rankin scale (dichotomized 0-3 vs 4-6).

Sample size/Power:

- Population: Estimating recruitment of 50% of the sites in Sweden, Norway, Finland, Switzerland and United Kingdom with the ongoing recruitment rate and approximately a 6-month inclusion window would yield approximately 400 patients
- Primary analysis: Descriptive/explorative, and no sample size has formally been calculated.

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- Secondary analyses: Explorative, descriptive, however, minimal detectable odds ratio 1.9 [1.21-2.99] for restricted mean time in moderate/severe pain, given a population of 400 patients, 30% event rate and a power of 80% with a two tailed alpha of 0.05.

All secondary analyses are considered explorative and will be reported with adjusted estimates with 95% CIs. Adjustment for multiple analysis will not be performed due to the explorative nature.

Missing data, up to 20% per variable (missingness > 20% precludes the use of this variable in analysis), will be handled by multiple imputation (20 datasets) of observed covariates, by chained equations.

MNAR will be explored in sensitivity analyses, patients dead within 96 h vs alive >96h for secondary analyses of burden of pain

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NA

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