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 of highest level of pain intensity during the first 7 days of ICU stay

Secondary hypothesis:

1. Presence 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 6 months.
    g. Quality of life at 6 months

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 during initial ICU.

Exposure: Pain during the first 168 hours of ICU stay

Comparator: No/low pain vs Moderate/High level of pain

Outcome: NA

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

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- 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?

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

Additional datapoints 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.
- FOURmotor score, ordinal variable, numeric, integers, range 0/4.

Additional data points for ICU mobility: 144, 168 hours

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

BRIEF STATISTICAL ANALYSIS PLAN AND SAMPLE SIZE ESTIMATE

Primary outcome: Description of pain presence, categorized as painless (CPOT 0, BPS 3, NRS 0), mild pain (CPOT 1-2, BPS 4-5, NRS 1-3), moderate/severe pain (CPOT>2, BPS>5, NRS>3).

Primary analysis: Pain intensity categorized as painless, mild, moderate to severe pain intensity during ICU stay (maximum 7 days).

Secondary analysis:

- Pain intensity during the first 7 days of ICU care
  - Daily frequency of maximum pain categorized as painless, mild, moderate or severe intensity.
- Temporal development of pain during the first 7 days of ICU stay:
  - Timing of maximum pain intensity
  - Timing of minimum pain intensity
- Percentage of time in the ICU with moderate/severe level of pain intensity during day 1-3 in:
    - Full cohort
    - Subgroups of: Age (18-65 vs 66+), sex (Male vs female), frailty (0-4 vs 5+). Time to ROSC (0-25 vs 26 + min)

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- The association of moderate to severe pain intensity with Time to ROSC (0-25 vs 26+ min), Age (18-65 vs 65+), sex (Male vs female), frailty (0-4 vs 4+), deep sedation level (RASS<-3), and severe neurologic disability (fourscore M<2)
- The association of presence of delirium with moderate to severe pain intensity adjusted for time after OHCA, Age (18-65 vs 65+), sex (Male vs female), frailty (0-4 vs 4+), Time to ROSC (0-25 vs 26+ min), severe neurologic disability (fourscore M<2) and deep sedation level (RASS<-3).
- The association of level of mobilization (ICUMS<1) with moderate to severe pain intensity adjusted for time after OHCA, Age (18-65 vs 65+), sex (Male vs female), frailty (0-4 vs 4+), Time to ROSC (0-25 vs 26+ min), severe neurologic disability (fourscore M<2) and deep sedation level (RASS<-3)
- The association of time on ventilatory support with moderate to severe pain intensity adjusted for age, sex, time to ROSC (25/25+min, Shockable rhythm, witnessed arrest, neurologic disability (fourscore M<2), frailty (0-4/4+) and deep sedation level (RASS<-3)
- The association of length of time in the ICU with moderate to severe pain intensity adjusted for age, sex, time to ROSC (25/25+min), Shockable rhythm, witnessed arrest, neurologic disability (fourscore M<2), frailty (0-4/4+), any safety event and deep sedation level (RASS<-3)
- The association of reported pain (according to EQ-5D-5L) at 6 months with moderate/severe pain intensity within the first 7 days of ICU care, adjusted for age, fraility, sex
- The association of reported life satisfaction at 6 months with moderate to severe pain intensity at any time during during index ICU stay, adjusted for age, fraility, sex, and modified Rankin scale(dichotomized 0-3 vs 4-6)
- The association of moderate/severe pain with remifentanil dose the first 72 h in the ICU, adjusted for Time to ROSC (0-25 vs 26+ min), Age (18-65 vs 65+), sex (Male vs female), frailty (0-4 vs 4+), deep sedation level (RASS<-3), dose of propofol 0-72h, and severe neurologic disability (fourscore M<2)
- The association of duration of delirium with remifentanil dose the first 72 h in the ICU, adjusted for Time to ROSC (0-25 vs 26+ min), Age (18-65 vs 65+), sex (Male vs female), frailty (0-4 vs 4+), deep sedation level (RASS<-3), dose of propofol 0-72h, and severe neurologic disability (fourscore M<2).

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