PAINCARE Substudy Protocol v1.0

Characterizing and Quantifying Pain After Cardiac Arrest and Resuscitation: Insights from the PAINCARE Substudy of the STEPCARE Trial

Organization's Unique Protocol ID
STEPCARE_PAINCARE

Brief title
Pain After Cardiac Arrest and Resuscitation

Acronym
PAINCARE

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Parent trial
STEPCARE — Sedation, Temperature and Pressure after Cardiac Arrest and Resuscitation (NCT05564754)

Substudy registration
PAINCARE (NCT07564778)

Study type
Observational

Registry classification
Patient registry

Design
Exploratory observational cohort substudy nested within STEPCARE

Registry note
Registry metadata will be verified before final submission.

1. Rationale

Pain is a clinically important component of intensive care after out-of-hospital cardiac arrest. Patients admitted to intensive care after cardiac arrest may experience pain related to cardiopulmonary resuscitation, thoracic injury, invasive procedures, mechanical ventilation, immobility, and other aspects of ICU care. Pain assessment is challenging in this population because many patients are unconscious, sedated, mechanically ventilated, delirious, or unable to self-report during early ICU treatment.

International ICU guidelines recommend systematic assessment and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in critically ill adults. In

communicative patients, self-report remains the preferred method for assessing pain intensity. In non-communicative patients, validated behavioral tools such as the Critical-Care Pain Observation Tool and Behavioral Pain Scale may be used[1-4].

PAINCARE is nested within STEPCARE (NCT05564754), an international randomized factorial trial evaluating sedation, temperature, and mean arterial pressure strategies after out-of-hospital cardiac arrest[5]. STEPCARE enrolls unconscious adult patients resuscitated from out-of-hospital cardiac arrest with stable return of spontaneous circulation and randomizes participants to sedation, temperature, and mean arterial pressure interventions. PAINCARE uses the STEPCARE trial infrastructure and extended dataset to collect structured pain assessments and related ICU variables during the first 168 hours after randomization.

The aim of PAINCARE is to describe early ICU pain burden after out-of-hospital cardiac arrest and evaluate associations between pain burden and selected ICU and patient-reported outcomes. All analyses are observational. PAINCARE is not designed to determine whether modifying pain burden improves outcomes.

2. Aim, objectives, and hypotheses

2.1 Aim

The aim of PAINCARE is to describe the burden of pain during early intensive care after out-of-hospital cardiac arrest and to evaluate associations between early pain burden and selected ICU and patient-reported outcomes.

2.2 Primary objective

To estimate cumulative time in moderate/severe pain while alive and in ICU from randomization through 168 hours among PAINCARE participants.

2.3 Key secondary objectives

To describe the proportion of evaluable alive-in-ICU time spent in moderate/severe pain during the same period.

To evaluate associations between early moderate/severe pain burden and selected ICU outcomes.

To evaluate associations between early moderate/severe pain burden and moderate/severe pain at 1 month.

2.4 Exploratory objectives

To explore selected treatment and care-process variables in relation to cumulative moderate/severe pain burden.

To evaluate associations between early moderate/severe pain burden and exploratory longer-term outcomes, including moderate/severe pain at 6 months, health-related quality of life at 6 months, and mobilization during ICU care.

2.5 Hypotheses

The primary hypothesis is that moderate/severe pain occurs during early intensive care after out-of-hospital cardiac arrest and can be quantified as cumulative time in moderate/severe pain while alive and in ICU during the first 168 hours after randomization.

The secondary hypothesis is that greater early moderate/severe pain burden is associated with selected ICU and patient-reported outcomes.

3. Population and analysis cohorts

3.1 Source population

The PAINCARE source population will consist of STEPCARE participants at PAINCARE-participating sites who are included under approved PAINCARE substudy procedures and who have not withdrawn consent for use of study data according to parent-trial procedures.

PAINCARE inclusion may occur retrospectively or prospectively. Retrospective PAINCARE participants are STEPCARE participants enrolled before local prospective PAINCARE implementation for whom PAINCARE-relevant pain assessments are available for collection from clinical records or local source documentation. Prospective PAINCARE participants are STEPCARE participants enrolled after local prospective PAINCARE implementation, for whom PAINCARE-specific data collection is performed prospectively.

Sites approved for retrospective PAINCARE inclusion may include eligible STEPCARE participants from the start of STEPCARE recruitment at that site through the end of STEPCARE recruitment, according to local approvals and substudy procedures. Participant ascertainment mode will be classified at participant level as retrospective or prospective according to whether PAINCARE-relevant pain data were retrospectively or prospectively collected.

3.2 Descriptive population

The descriptive population will consist of PAINCARE source-population participants admitted to ICU for whom at least one PAINCARE pain assessment was attempted or collected during the first 168 hours after randomization.

The descriptive population will be used to summarize cohort derivation, baseline characteristics, ascertainment mode, pain-assessment availability, pain-measurement instrument use, non-scorable intervals, ICU discharge, death, and missingness.

3.3 Primary analysis population

For the primary analysis, pain-data completeness will be calculated as the proportion of scorable alive-in-ICU time that is evaluable. Scorable alive-in-ICU time includes intervals during which pain assessment would have been clinically possible using NRS, CPOT, or BPS. It excludes time after ICU discharge or death and excludes intervals classified as non-scorable because pain could not be validly assessed.

Evaluable scorable time will be defined as scorable alive-in-ICU time covered by a valid scheduled, prospectively or retrospectively collected, or deterministically imputed pain assessment. Missing scorable time will be defined as scorable alive-in-ICU time not covered by a valid or deterministically imputed pain assessment. Non-scorable time will not be counted as missing for the primary completeness threshold but will be reported separately.

The primary analysis will use the highest prespecified pain-data completeness threshold that retains at least 75% of the descriptive population. Candidate thresholds will be evaluated in descending order: at least 80%, at least 70%, and at least 50% evaluable scorable alive-in-ICU time.

If more than one threshold retains at least 75% of the descriptive population, the highest such threshold will be used. If no threshold retains at least 75%, the 50% threshold will be used, and this limitation will be reported.

As a representativeness safeguard, if the selected threshold produces clear differential exclusion by ascertainment mode, defined as an absolute difference in exclusion proportions greater than 20 percentage points between retrospective and prospective participants, the next lower threshold may be selected before outcome analysis. The final threshold and rationale will be documented before analysis.

3.4 Endpoint-specific analysis populations

Secondary and exploratory analyses will use endpoint-specific populations according to availability of the relevant outcome, required covariates, and sufficient pain-burden exposure data.

Participants excluded from the primary analysis because of insufficient pain-data completeness will remain in the descriptive population and may contribute to sensitivity or endpoint-specific analyses where analysis-specific requirements are met.

4. Time origin and follow-up windows

Time zero for PAINCARE analyses will be the time of randomization in STEPCARE.

The primary pain-burden window will extend from randomization through 168 hours, ICU discharge, or death, whichever occurs first.

If ICU discharge or death occurs within an assessment interval, contribution to ICU pain burden will end at the recorded time of ICU discharge or death. Time after ICU discharge or death will not contribute to ICU pain burden.

Follow-up pain assessments will be collected at 1 month and 6 months according to PAINCARE procedures.

5. PAINCARE dataset and pain-state construction

5.1 Extended PAINCARE dataset

Pain assessments are collected in the extended PAINCARE dataset from randomization through 168 hours. Each assessment records the highest pain intensity since the previous assessment using NRS, CPOT, or BPS according to patient communicative status and local routine. The planned pain-assessment times are 0, 12, 24, 36, 48, 56, 64, 72, 80, 88, 96, 104, 112, 120, 128, 136, 144, 152, 160, and 168 hours after randomization.

The extended PAINCARE dataset also includes delirium status, RASS, and FOUR-motor score at 56, 64, 80, 88, 104, 112, 128, 136, 144, 152, 160, and 168 hours after randomization, and ICU Mobility Scale at 144 and 168 hours. PAINCARE-specific data will be captured in a substudy eCRF module within the main STEPCARE eCRF. The substudy eCRF also records whether the patient received a working pain block during the ICU admission. Site-level availability of a protocol for assessment and management of pain in critically ill patients will be collected from site investigators at substudy initiation.

For prospectively collected PAINCARE data, participating sites will receive substudy initiation training by video meeting, including a brief NRS/CPOT/BPS training module with clinical vignettes and a short knowledge check before prospective data collection.

5.2 Pain-assessment instruments

Pain will be assessed using NRS in communicative patients and CPOT or BPS in non-communicative patients according to local routine.

Patient state	Instrument
Communicative patient	Numerical Rating Scale
Non-communicative patient	Critical-Care Pain Observation Tool or Behavioral Pain Scale

5.3 Pain-state categories

Category	NRS	CPOT	BPS
No pain	0	0	3
Mild pain	1–3	1–2	4–5
Moderate/severe pain	>3	>2	>5

5.4 Interval assignment

Each scheduled pain assessment will represent the worst pain intensity since the previous assessment and will be assigned to the corresponding preceding interval.

If ICU discharge or death occurs during an interval, contribution to ICU pain burden will end at the recorded time of ICU discharge or death. Time after ICU discharge or death will not contribute to ICU pain burden.

5.5 Missing scorable intervals and deterministic imputation

If a scheduled assessment is missing, the corresponding interval will initially be classified as missing scorable time unless it meets prespecified deterministic imputation criteria.

A single isolated missing scorable interval may be deterministically imputed if the nearest preceding and nearest following evaluable scorable intervals are both available, occur within adjacent scheduled assessment windows, and assign the same pain category. In that case, the missing interval will be assigned the same pain category.

Missing scorable intervals will not be deterministically imputed if two or more consecutive scheduled scorable intervals are missing, if adjacent evaluable intervals assign different pain categories, or if the gap spans ICU discharge, death, or a non-scorable interval.

5.6 Non-scorable intervals

Intervals during which pain cannot be validly assessed, for example because of active neuromuscular blockade or sedation level precluding behavioral pain assessment, will be classified as non-scorable.

Non-scorable intervals will not be imputed in the primary analysis. Non-scorable time will be reported separately and evaluated in sensitivity analyses.

6. Exposure and endpoint definitions

6.1 Primary endpoint

The primary endpoint will be cumulative time, in hours, in moderate/severe pain while alive and in ICU from randomization through 168 hours, ICU discharge, or death, whichever occurs first.

6.2 Key secondary descriptive endpoint

The key secondary descriptive endpoint will be the proportion of evaluable alive-in-ICU time spent in moderate/severe pain during the same window.

This proportion will be calculated as cumulative evaluable time in moderate/severe pain divided by total evaluable alive-in-ICU time, excluding time after ICU discharge or death and excluding non-scorable and remaining missing scorable intervals.

6.3 Main exposure for secondary association analyses

For secondary association analyses, the main exposure will be the proportion of evaluable alive-in-ICU time spent in moderate/severe pain during the primary 0–168-hour pain-burden window.

Cumulative hours in moderate/severe pain will be analyzed as a supportive exposure to assess whether findings are consistent when pain burden is expressed on an absolute time scale.

7. Outcome hierarchy and outcome definitions

7.1 Primary endpoint

Cumulative time, in hours, in moderate/severe pain while alive and in ICU from randomization through 168 hours, ICU discharge, or death, whichever occurs first.

7.2 Key secondary descriptive endpoint

Proportion of evaluable alive-in-ICU time spent in moderate/severe pain during the same window.

7.3 Key secondary association outcomes

1. **Delirium burden through 168 hours**, defined as the proportion of evaluable point-prevalence delirium assessments with delirium present among assessments recorded as delirium present or absent.

2. **Hours alive and free of invasive ventilatory support through day 30**, defined as the number of hours from randomization to day 30 during which the participant is alive and not receiving invasive ventilatory support. Participants who die before day 30 will be assigned zero hours alive and free of invasive ventilatory support.
3. **ICU-free days alive through day 30**, defined as the number of days from randomization to day 30 during which the participant is alive and discharged from ICU. Participants who die before day 30 will be assigned zero ICU-free days.
4. **Moderate/severe pain at 1 month**, defined as NRS >3 for worst pain on movement during the preceding 24 hours at the 1-month follow-up assessment.

7.4 Exploratory outcomes

1. **Moderate/severe pain at 6 months**, defined as NRS >3 for worst pain on movement during the preceding 24 hours at the 6-month follow-up assessment.
2. **Health-related quality of life at 6 months**, assessed using EQ-5D-5L[6]. For exploratory binary analyses, clinically relevant HRQoL problems will be defined as at least one EQ-5D-5L dimension scored at level 3 or higher. EQ-5D-5L dimension profiles and EQ VAS will also be summarized descriptively.
3. **Mobilization during ICU care**, categorized as ICU Mobility Scale >1 versus ≤1.

7.5 Exploratory explanatory variables

Exploratory analyses will evaluate associations between selected treatment and care-process variables and cumulative moderate/severe pain burden during the primary 0–168-hour pain-burden window.

Candidate explanatory variables will include cumulative remifentanil dose through 72 hours, cumulative non-remifentanil opioid dose through 72 hours expressed as intravenous morphine equivalents, propofol exposure, RASS, and delirium status. Site-level availability of a pain-assessment or pain-management protocol will be reported descriptively.

Receipt of a working pain block during ICU admission will be reported descriptively as captured in the PAINCARE eCRF. Because this variable is based on local clinical judgment and is not operationally standardized, it will not be used as a main explanatory variable in inferential analyses.

8. Statistical analysis plan

8.1 General principles

PAINCARE is an exploratory observational substudy. Analyses will be primarily descriptive and associational. The primary analysis will estimate cumulative time in moderate/severe pain while alive and in ICU during the first 168 hours after randomization. Secondary

analyses will evaluate associations between early pain burden and selected ICU and patient-reported outcomes.

No analyses will be interpreted as estimating causal effects unless explicitly stated and supported by the analysis design.

Continuous variables will be summarized using mean with standard deviation or median with interquartile range, as appropriate. Categorical variables will be summarized using counts and percentages. Estimates will be reported with 95% confidence intervals where appropriate.

Baseline characteristics, arrest characteristics, STEPCARE intervention assignments, PAINCARE ascertainment mode, and selected ICU process variables will be summarized overall and stratified by the presence or absence of moderate/severe pain during the primary pain-burden window. Participants will be categorized as having any moderate/severe pain if cumulative moderate/severe pain time is greater than zero hours after interval construction. These stratified summaries will be descriptive and will not define the main exposure for secondary association analyses.

8.2 Statistical modeling and diagnostics

Statistical models will be selected according to outcome type and data structure.

Binary outcomes, including moderate/severe pain at 1 month, moderate/severe pain at 6 months, clinically relevant HRQoL problems at 6 months, and mobilization category, will be analyzed using logistic regression where event counts and model stability permit. Penalized logistic regression may be used for sparse binary outcomes.

Composite duration outcomes, including hours alive and free of invasive ventilatory support through day 30 and ICU-free days alive through day 30, will be summarized descriptively and analyzed using linear regression where distributional assumptions are acceptable.

If linear regression is unsuitable because of marked skewness, zero inflation, or influential outliers, the primary fallback analysis will dichotomize the outcome at its observed median among participants in the endpoint-specific analysis population and use logistic regression where event counts and model stability permit. If the median is not informative because of a large mass at one value, especially zero, the fallback dichotomization will be any versus none of the outcome. If logistic regression is unstable, the prespecified model-simplification hierarchy will apply, ending in descriptive reporting if model-based estimation remains unstable.

Delirium burden will be summarized descriptively and analyzed using a fractional/binomial model where the number of delirium-positive assessments is modeled relative to the number of evaluable delirium assessments, if model stability permits. If this model is not

supported, the prespecified fallback analysis will use any observed delirium at one or more evaluable assessments versus none.

Model diagnostics will include assessment of outcome distributions, residual patterns for linear models, convergence, sparse cells, and separation for binary models. Collinearity among adjustment variables will be assessed using correlation matrices and variance inflation factors.

Covariates will not be removed solely on the basis of automated diagnostic thresholds. Any model simplification will follow the prespecified adjustment hierarchy and will be documented.

State-occupancy curves and Aalen–Johansen estimates of restricted mean time in moderate/severe pain may be performed as supportive analyses if the observed data structure, timing, and missingness are compatible with valid estimation.

8.3 Covariate adjustment

Adjusted analyses will use a prespecified baseline/core adjustment set where supported by event counts, outcome distribution, missingness, and model stability.

The target core adjustment set will include age, sex, initial rhythm, witnessed arrest, bystander CPR, time to ROSC, pre-arrest frailty, randomized STEPCARE intervention assignments, PAINCARE ascertainment mode, and site.

If the full core adjustment model is not supported, adjustment will be simplified according to a prespecified hierarchy. The minimum adjustment set will include age, sex, time to ROSC, initial rhythm, randomized STEPCARE intervention assignments, and PAINCARE ascertainment mode. Witnessed arrest, bystander CPR, pre-arrest frailty, and model-based site adjustment will be added where feasible.

Site will be handled using a random intercept where feasible, robust variance estimation clustered by site if appropriate, or descriptive site-level reporting if model-based site adjustment is unstable.

If the minimum model does not converge or shows evidence of quasi-separation or unstable estimates, the analysis will be reported using an unadjusted model. For sparse binary outcomes, penalized logistic regression may be used as a sensitivity or fallback analysis. If model-based estimation remains unstable, results will be summarized descriptively without formal adjusted inference.

8.4 Primary analysis

The primary analysis will estimate cumulative time in moderate/severe pain while alive and in ICU from randomization through 168 hours using prespecified interval-level pain-state construction rules.

Each evaluable interval will be assigned a pain state based on the scheduled, prospectively or retrospectively collected pain assessment representing the worst pain intensity since the previous assessment. Contribution to ICU pain burden will end at ICU discharge or death.

The primary result will be reported as cumulative hours in moderate/severe pain while alive and in ICU through 168 hours, summarized using mean, standard deviation, median, interquartile range, and 95% confidence intervals.

The distribution of no pain, mild pain, moderate/severe pain, non-scorable time, missing scorable time, ICU discharge, and death will be reported descriptively.

8.5 Key secondary analyses

The proportion of evaluable alive-in-ICU time spent in moderate/severe pain will be summarized descriptively.

For secondary association analyses, the main exposure will be the proportion of evaluable alive-in-ICU time spent in moderate/severe pain during the primary 0–168-hour pain-burden window. Cumulative hours in moderate/severe pain will be analyzed as a supportive exposure.

8.5.1 Delirium burden

Delirium is recorded as point prevalence at scheduled assessment timepoints using CAM-ICU or ICDSC. The eCRF records delirium as present, absent, not assessable, or not done. The key secondary delirium outcome will therefore be delirium burden through 168 hours, defined as the proportion of evaluable delirium assessments with delirium present among assessments recorded as delirium present or absent. Assessments recorded as not assessable will be reported separately and will not contribute to the denominator. Assessments recorded as not done will be reported as missing.

The main delirium-burden analysis will include participants with at least one evaluable delirium assessment recorded as delirium present or absent. The number and proportion of delirium assessments recorded as present, absent, not assessable, and not done will be reported overall and by assessment timepoint.

Because delirium assessability may be related to sedation, neurological status, and illness severity, the interpretation of observed delirium burden will consider the extent of non-assessable and missing delirium assessments. As supportive summaries, any observed delirium among participants with at least one evaluable assessment and the proportion of scheduled delirium assessments recorded as not assessable will be reported.

8.5.2 Hours alive and free of invasive ventilatory support through day 30

Hours alive and free of invasive ventilatory support through day 30 will be summarized descriptively and analyzed as a composite duration outcome according to Section 8.2.

8.5.3 ICU-free days alive through day 30

ICU-free days alive through day 30 will be summarized descriptively and analyzed as a composite duration outcome according to Section 8.2.

8.5.4 Moderate/severe pain at 1 month

Moderate/severe pain at 1 month will be analyzed as a binary outcome according to Section 8.2.

8.6 Exploratory explanatory analyses

Exploratory analyses will evaluate associations between selected treatment and care-process variables and cumulative moderate/severe pain burden during the primary 0–168-hour pain-burden window.

Cumulative remifentanil dose through 72 hours after randomization will be analyzed as the main opioid-process exposure for cumulative moderate/severe pain burden.

A supportive opioid-process exposure will be cumulative non-remifentanil opioid dose through 72 hours, expressed as intravenous morphine equivalents using prespecified operational conversion factors adapted from the ENCORE intravenous morphine-equivalent conversion table[7]. The planned conversion factors are:

Opioid	Conversion to IV morphine equivalents
Morphine IV	mg × 1
Oxycodone IV	mg × 1.5
Fentanyl IV	microgram × 0.066
Sufentanil IV	microgram × 0.66

Alfentanil will be summarized descriptively unless a prespecified and justified IV morphine-equivalent conversion factor is added to the statistical analysis plan before analysis. Remifentanil will be analyzed separately and will not be included in the morphine-equivalent composite.

Individual opioid doses through 72 hours, including remifentanil, fentanyl, sufentanil, alfentanil, morphine, and oxycodone, will be summarized descriptively.

Opioid-equivalent analyses will be interpreted as exploratory because equianalgesic conversions are approximate, are not clinical dose-conversion rules, and may vary by route, clinical context, tolerance, and source.

Exploratory time-ordered analyses will evaluate whether selected preceding ICU variables, including RASS, propofol exposure, and delirium status, are associated with moderate/severe pain during the subsequent pain interval.

These analyses will use complete analyzable interval pairs only. An interval pair will be analyzable when the preceding predictor measurement and the subsequent pain-state outcome are both available and temporally ordered according to the prespecified interval structure. Missing interval-level predictor values or subsequent pain-state outcomes will not be imputed in the main exploratory time-ordered analyses.

The analyses will be undertaken only if blinded feasibility review shows that at least 50% of otherwise eligible interval pairs are analyzable and at least 50% of participants in the primary analysis population contribute at least one analyzable interval pair. The number of eligible intervals, analyzable interval pairs, contributing participants, and reasons for non-analyzability will be reported.

Where feasible, associations will be analyzed using mixed-effects logistic regression with participant-level random intercepts and moderate/severe pain during the subsequent interval as the binary outcome. Models will be kept parsimonious and will include time since randomization. If sparse events, model non-convergence, or quasi-separation prevent stable estimation, results will be summarized descriptively without formal model-based inference.

8.7 Missing data

Missing data will be reported by variable, timepoint, site, and PAINCARE ascertainment mode where feasible. Missing pain assessments, non-scorable intervals, ICU discharge, and death will be distinguished.

Missing pain assessments used to construct the primary endpoint will be handled according to the prespecified interval-construction rules. A single isolated missing scorable interval may be deterministically imputed only when adjacent evaluable scorable intervals agree on pain category. Remaining missing scorable intervals will not be imputed for the primary analysis. Non-scorable intervals will not be imputed in the primary analysis and will be reported separately.

For adjusted secondary association analyses, multiple imputation will be used only for missing baseline covariates required for the adjustment model. If all required baseline covariates have ≤5% missingness, complete-case analysis will be used. If any required baseline covariate has >5% missingness, multiple imputation by chained equations will be used with 20 imputed datasets.

The imputation model will include the main pain-burden exposure, the observed relevant outcome as a predictor where appropriate, adjustment variables, PAINCARE ascertainment mode, site, and auxiliary baseline variables associated with missingness or outcome where available.

The dependent variable for each main secondary analysis will not be imputed. Participants without the relevant observed outcome will be excluded from that endpoint-specific main

analysis. Primary endpoint values, death, ICU discharge, PAINCARE ascertainment mode, and observed or deterministically imputed pain-state classifications used to construct the primary exposure will not be multiply imputed for the main analysis.

Missing follow-up outcomes may be explored in sensitivity analyses using multiple imputation only for selected prespecified outcomes and only among participants eligible for outcome assessment. These analyses will be clearly labeled as sensitivity analyses. Death will not be imputed as a missing outcome.

8.8 Sensitivity analyses

Sensitivity analyses will evaluate the robustness of the primary pain-burden estimate to prespecified assumptions about pain-data completeness, deterministic imputation, non-scorable intervals, pain-state thresholds, and ascertainment mode.

The primary analysis will be repeated using alternative prespecified minimum completeness thresholds where sample size permits, including 80%, 70%, 50%, and all participants with at least one evaluable pain interval.

The primary analysis will also be repeated without deterministic imputation of isolated missing scorable intervals.

Non-scorable intervals will not be imputed in the primary analysis. Sensitivity analyses will assess their potential influence by treating non-scorable intervals, separately, as not moderate/severe pain and as moderate/severe pain.

The primary pain definition will classify moderate/severe pain as NRS >3, CPOT >2, or BPS >5. A sensitivity analysis may evaluate any pain, defined as NRS >0, CPOT >0, or BPS >3.

Analyses will be repeated or stratified by PAINCARE ascertainment mode, prospective versus retrospective, where sample size permits.

For key secondary association analyses, the proportion of evaluable alive-in-ICU time spent in moderate/severe pain will be the main exposure. Sensitivity analyses will use cumulative hours in moderate/severe pain as an alternative exposure.

8.9 Multiplicity

PAINCARE will specify one primary endpoint and one primary analysis framework. No formal adjustment for multiplicity will be applied to key secondary or exploratory analyses.

Key secondary and exploratory findings will be interpreted according to effect size, precision, clinical plausibility, temporal ordering, and consistency across analyses rather than by statistical significance alone.

Findings outside the primary analysis will be considered hypothesis-generating.

8.10 Sample size

PAINCARE is an exploratory observational substudy nested within STEPCARE. No formal sample-size or power calculation has been performed. The available sample size will be determined by PAINCARE participation, consent status, availability of PAINCARE data, and eligibility for the relevant analysis population.

9. Ethics and data governance

PAINCARE is an observational substudy nested within STEPCARE and will use data collected under the parent STEPCARE protocol and approved PAINCARE substudy procedures. No additional randomized intervention is introduced by PAINCARE.

In Sweden, ethical approval for PAINCARE has been granted by the Swedish Ethical Review Authority (Etikprövningsmyndigheten; Dnr 2025-01116-02). Participating sites outside Sweden will obtain ethics approval in accordance with applicable local legislation and regulatory requirements.

Data will be handled according to parent-trial data-management procedures, applicable ethics approvals, and relevant data-protection regulations.

10. References

1. Devlin JW, Skrobik Y, Gélinas C, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Crit Care Med*. 2018;46(9):e825-e873. doi:10.1097/CCM.0000000000003299.
2. Chanques G, Gélinas C. Monitoring pain in the intensive care unit (ICU). *Intensive Care Med*. 2022;48(10):1508-1511. doi:10.1007/s00134-022-06807-w.
3. Gélinas C, Fillion L, Puntillo KA, Viens C, Fortier M. Validation of the Critical-Care Pain Observation Tool in adult patients. *Am J Crit Care*. 2006;15(4):420-427.
4. Aïssaoui Y, Zeggwagh AA, Zekraoui A, Abidi K, Abouqal R. Validation of a behavioral pain scale in critically ill, sedated, and mechanically ventilated patients. *Anesth Analg*. 2005;101(5):1470-1476. doi:10.1213/01.ANE.0000182331.68722.FF.
5. Kamp CB, Holgersson J, Levin H, et al. Sedation, temperature and pressure after cardiac arrest and resuscitation - The STEPCARE trial: A statistical analysis plan. *Acta Anaesthesiol Scand*. 2025;69(5):e70033. doi:10.1111/aas.70033.
6. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res*. 2011;20(10):1727-1736. doi:10.1007/s11136-011-9903-x.
7. European Society of Anaesthesiology and Intensive Care. IV morphine equivalents for commonly used drugs – ENCORE study. 2023.