STEP-PRESS Substudy Protocol

STEPCARE Pulse PRESSure substudy

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Full title	STEP-PRESS: Association of Pulse Pressure with Early Mortality and Biomarker Outcomes after Out-of-Hospital Cardiac Arrest
Short title	STEP-PRESS
Parent trial	STEPCARE - Sedation, Temperature and Pressure after Cardiac Arrest and Resuscitation
STEPCARE main trial registration	NCT05564754
STEPCARE biomarker substudy registration	NCT06471972
Protocol version, date	1.0, 2026-05-08
Design	Predefined exploratory observational substudy nested within STEPCARE

1. Rationale

Pulse pressure, calculated as systolic blood pressure minus diastolic blood pressure, reflects the interaction between ventricular ejection, arterial compliance, vascular tone, and wave reflection. In simplified physiology, a low pulse pressure may occur when stroke volume is reduced, but this interpretation is context-dependent and may be modified by arterial compliance, vasopressor therapy, myocardial stunning, vasoplegia, heart rate, and mechanical circulatory support [1-3]. After out-of-hospital cardiac arrest, these factors may change rapidly during early intensive care.

STEP-PRESS evaluates pulse pressure as a pragmatic, routinely captured hemodynamic marker rather than as a direct measure of stroke volume or cardiac output. The primary focus is whether early low pulse-pressure burden is associated with early mortality and selected organ-injury markers within the STEPCARE data structure.

STEPCARE (NCT05564754) is an international, multicenter, randomized factorial trial studying three post-cardiac-arrest ICU strategies: continuous versus minimal sedation, fever management with versus without a feedback-controlled device, and a mean arterial pressure target of >85 mmHg versus >65 mmHg. STEPCARE enrolls unconscious adults resuscitated from out-of-hospital cardiac arrest with stable return of spontaneous circulation [4-7].

Outside out-of-hospital cardiac arrest, pulse pressure has been associated with cardiovascular outcomes, perioperative myocardial injury, and outcomes in sepsis and septic shock cohorts [8-11]. These studies provide background biological plausibility but do not validate STEP-PRESS exposure thresholds in post-cardiac-arrest care.

Diastolic arterial pressure is physiologically relevant after cardiac arrest because it contributes to coronary perfusion pressure and reflects vascular tone [12]. Diastolic arterial pressure will not be included in the primary adjustment model because it is mathematically related to pulse pressure and closely linked to early MAP

management and vasoactive therapy. Baseline diastolic arterial pressure will be included in an expanded sensitivity model.

2. Objectives

The primary objective is to evaluate whether longer cumulative time with pulse pressure below 40 mmHg during the first 12 hours after randomization is associated with all-cause mortality from 12 hours to day 7.

Secondary objectives are to evaluate whether early pulse-pressure burden is associated with:

1. mortality in a 24-hour landmark analysis;
2. 30-day mortality and 6-month survival;
3. 6-month functional outcome;
4. neurological injury biomarkers;
5. myocardial injury biomarkers;
6. lactate as a marker of metabolic stress;
7. renal-support outcomes.

Exploratory objectives are to evaluate whether associations differ by randomized MAP target arm or retrospectively presumed cause of arrest, and to describe associations involving markedly widened pulse pressure.

All objectives are associational. STEP-PRESS is not designed to test whether modifying pulse pressure improves outcome.

3. Population and analysis cohorts

3.1 Source population

The STEP-PRESS source population will consist of all randomized STEPCARE participants, excluding consent withdrawals.

3.2 Descriptive population

The STEP-PRESS descriptive population will consist of source-population participants with at least one valid recorded pulse-pressure measurement and available vital status. This population will be used to describe cohort derivation, baseline characteristics, blood-pressure data availability, and missingness.

Analyses of associations with clinical and biomarker outcomes will use prespecified analysis populations with sufficient blood-pressure data to estimate the relevant exposure over time.

3.3 Primary 12-hour landmark analysis population

The primary analysis population will be restricted to participants alive 12 hours after randomization, without mechanical circulatory support initiated before or within 24 hours after randomization, and with at least three valid recorded blood-pressure observations during 0-12 hours after randomization.

3.4 Key secondary 24-hour landmark analysis population

The key secondary 24-hour landmark analysis population will include participants alive 24 hours after randomization, without mechanical circulatory support initiated before or within 24 hours after randomization, and with at least four valid recorded blood-pressure observations during 0-24 hours after randomization, including at least one valid observation in each of the 0-12 h and 12-24 h intervals.

3.5 Mechanical circulatory support

Participants receiving mechanical circulatory support before or within 24 hours after randomization will be excluded from the primary and 24-hour landmark analyses. Mechanical circulatory support initiated after 24 hours will be summarized as a post-exposure event. A sensitivity analysis will exclude participants receiving mechanical circulatory support at any time during 0-72 hours.

3.6 Biomarker analysis populations

Biomarker analyses will use endpoint-specific complete-case populations, restricted to participants alive and eligible for sampling at the relevant biomarker timepoint with an available biomarker result. NFL analyses will be restricted to participants in the STEPCARE biomarker substudy (NCT06471972).

3.7 Time origin

Time zero for STEP-PRESS exposure construction will be the time of randomization. Pulse-pressure exposure windows, landmark times, biomarker timepoints, and follow-up intervals will be defined relative to randomization unless otherwise specified. Arrest-related timings, including time to ROSC, will be used as baseline covariates and descriptive variables.

4. Exposure definitions

4.1 Pulse-pressure calculation

Pulse pressure will be calculated as systolic blood pressure minus diastolic blood pressure using recorded STEPCARE blood-pressure values.

4.2 Blood-pressure validity rules

Individual blood-pressure observations will be excluded from exposure construction if systolic blood pressure ≤ diastolic blood pressure, pulse pressure <5 mmHg, systolic blood pressure <30 or >300 mmHg, diastolic blood pressure <5 or >225 mmHg, or MAP <20 or >250 mmHg where MAP is available. Observations will also be excluded if recorded MAP lies outside the interval between diastolic and systolic blood pressure.

Pulse-pressure values ≥100 mmHg will not be automatically excluded but will be flagged for review. The number and proportion of excluded blood-pressure observations will be reported overall and by exposure window.

4.3 Primary exposure

The primary exposure will be cumulative low pulse-pressure burden, defined as the number of hours during 0-12 hours after randomization in which interpolated pulse pressure is below 40 mmHg. This exposure will be modeled continuously, with the primary effect estimate reported per additional hour below 40 mmHg.

4.4 Key secondary exposure

The key secondary exposure will be cumulative low pulse-pressure burden below 40 mmHg during 0-24 hours after randomization, analyzed in the 24-hour landmark population.

4.5 Interpolation and missing exposure time

Pulse-pressure burden will be calculated using linear interpolation between adjacent valid pulse-pressure observations within the relevant exposure window. Interpolation will not be performed across gaps greater than 6 hours. Time within non-interpolable gaps will be treated as missing exposure time.

Participants with more than 4 hours of missing or non-interpolable exposure time during the 0-12 h primary exposure window will be excluded from the primary analysis. Participants with more than 8 hours of missing or non-interpolable exposure time during the 0-24 h key secondary exposure window will be excluded from that analysis.

4.6 Sensitivity thresholds

Sensitivity analyses will repeat the low pulse-pressure burden definition using thresholds of PP <30, <35, <45, and <50 mmHg.

4.7 Area under threshold

Area under the low pulse-pressure threshold will be analyzed as a lower-priority exploratory exposure. AUT incorporates both the duration and magnitude of pulse pressure below the prespecified threshold and may therefore capture severity of low pulse-pressure exposure beyond cumulative time below threshold. AUT will be interpreted cautiously because it is more sensitive to interpolation assumptions and extreme values than cumulative low pulse-pressure burden.

4.8 High pulse pressure

High pulse pressure will be evaluated as an exploratory exposure. A threshold of PP >80 mmHg will be used to identify markedly widened pulse pressure. This cutoff is prespecified for exploratory analysis and is not presented as a validated post-arrest cutoff. High-PP burden will be calculated as cumulative hours above 80 mmHg during the same landmark exposure windows used for low-PP analyses.

4.9 Flexible pulse-pressure modeling

As an exploratory analysis, the association between pulse pressure and mortality will be modeled using restricted cubic splines for time-weighted mean pulse pressure during the landmark exposure window.

The primary flexible pulse-pressure analysis will use the primary 12-hour landmark analysis population and time-weighted mean pulse pressure during 0-12 hours after randomization. A corresponding exploratory analysis may be repeated in the 24-hour landmark population using time-weighted mean pulse pressure during 0-24 hours. Pulse-pressure values recorded after the landmark exposure window will not be used in these spline exposure summaries.

Three knots will be used, placed at the 10th, 50th, and 90th percentiles of the observed pulse-pressure distribution. The spline model will use the same adjustment set as the primary mortality model and will be used to assess non-linearity, not to define a treatment threshold.

5. Outcomes

5.1 Primary outcome

The primary outcome will be all-cause mortality from the 12-hour landmark to day 7.

5.2 Key secondary outcomes

Key secondary outcomes will include:

- mortality in the 24-hour landmark analysis;
- prespecified neurological biomarker endpoints;
- 30-day mortality;
- 6-month survival;
- 6-month functional outcome.

Six-month functional outcome will follow the parent STEPCARE definition, with poor functional outcome defined as mRS 4-6.

5.3 Biomarker outcomes

Key neurological biomarker endpoints will be:

- NFL at 12 hours, restricted to participants in the STEPCARE biomarker substudy;
- NSE at 48 hours.

NFL at 24 hours will be analyzed as a supportive endpoint.

NSE at 48 hours will be analyzed using available STEPCARE NSE measurements. The data source will be described (Biobank or from clinical sampling captured within the eCRF).

Exploratory biomarker outcomes will include:

- peak troponin within 0-72 hours;
- lactate at 12 hours.

Troponin analyses will distinguish clinically measured troponin from centrally measured biomarker-substudy troponin where applicable. Source and assay type will be summarized where available.

5.4 Exploratory clinical outcomes

Exploratory outcomes will include:

- ICU mortality;
- arrhythmia and safety events using parent STEPCARE definitions;
- ventilator-free days to day 30;
- hospital-free days to day 30;
- hierarchical renal support outcome;
- peak troponin within 0-72 hours;
- lactate at 12 hours.

Noradrenaline use and dose will be summarized descriptively where available.

5.5 Ventilator-free and hospital-free days

Ventilator-free days and hospital-free days will be calculated through day 30. Participants who die before day 30 will be assigned zero ventilator-free and hospital-free days.

5.6 Renal support outcome

The exploratory renal outcome will classify participants hierarchically as:

- death before hospital discharge;
- survival with renal replacement therapy during hospital stay or dialysis dependence at hospital discharge;
- survival without renal replacement therapy or dialysis dependence.

This hierarchy accounts for death as a competing event and avoids classifying participants who die early as free of severe renal failure. The outcome will be summarized descriptively.

6. Statistical analysis plan

6.1 General principles

STEP-PRESS is an exploratory observational substudy nested within STEPCARE. No separate formal sample-size calculation will be performed. The available sample size will be determined by STEPCARE enrolment, consent status, survival to the relevant landmark, absence of mechanical circulatory support before or within 24 hours after randomization, availability of valid recorded blood-pressure observations, and biomarker-substudy participation for biomarker analyses.

Results will be interpreted according to effect size and precision rather than formal power.

A participant flow diagram will report the number of participants in the STEP-PRESS source population, descriptive population, primary 12-hour landmark analysis population, key secondary 24-hour landmark analysis population, biomarker-analysis populations, and exclusions due to early mechanical circulatory support or insufficient blood-pressure data.

6.2 Primary analysis

The primary analysis will use a 12-hour landmark design. Follow-up will begin at 12 hours after randomization and continue until death, censoring, or day 7, whichever occurs first.

The primary exposure will be cumulative low pulse-pressure burden below 40 mmHg during 0-12 hours after randomization, modeled continuously. Results will be reported as hazard ratios with 95% confidence intervals per additional hour of low-PP burden.

The primary model will be a Cox proportional hazards model adjusted for age, sex, initial rhythm, witnessed arrest, bystander CPR, time to ROSC, arrest location, randomized STEPCARE intervention assignments, and site.

Site will be included using a shared frailty or random-intercept term. If this model fails to converge or produces unstable estimates, the model will be fitted with robust variance estimation clustered by site. A fixed-effect site model may be performed as a sensitivity analysis if the number of sites and events per site is sufficient.

The primary model will not include achieved MAP, achieved diastolic arterial pressure, vasopressor dose, inotrope use, revascularization, or shock on admission during the exposure window, because these variables may be collinear with pulse pressure, reflect treatment responses to early hemodynamic status, or lie on causal pathways between pulse pressure and outcome. An expanded sensitivity model will additionally adjust for shock on admission and baseline diastolic arterial pressure.

Achievement of randomized MAP target and revascularization will be summarized descriptively.

6.3 Model checks and effect reporting

The proportional hazards assumption will be assessed using Schoenfeld residuals and visual inspection of scaled residual plots. If there is evidence of non-proportional hazards, time-varying exposure effects or flexible parametric survival models may be used as exploratory sensitivity analyses.

Collinearity will be assessed in adjusted models, including expanded sensitivity models, using variance inflation factors and inspection of correlations among continuous covariates. No covariate will be removed solely on the basis of an automated threshold; interpretation of expanded models will account for evidence of collinearity.

Adjusted absolute mortality risks by day 7 will be estimated for representative low-PP burdens of 0, 2, and 6 hours below 40 mmHg during 0-12 hours, provided these values are supported by the observed exposure distribution.

6.4 Key secondary mortality analyses

A key secondary 24-hour landmark analysis will evaluate cumulative low-PP burden below 40 mmHg during 0-24 hours after randomization among participants alive at 24 hours. Follow-up will begin at 24 hours and continue until death, censoring, or day 7. The model structure and adjustment set will follow the primary analysis where feasible.

Additional time-to-event outcomes, including 30-day mortality and 6-month survival, will be analyzed using Cox models from the relevant landmark.

6.5 Functional outcome

Six-month poor functional outcome, defined as mRS 4-6, will be analyzed using logistic regression among participants with available 6-month functional outcome data.

6.6 Biomarker analyses

Biomarker analyses will evaluate associations between early pulse-pressure burden and prespecified markers of neurological, myocardial, and metabolic injury.

Biomarker analyses will use endpoint-specific complete-case populations, restricted to participants alive and eligible for sampling at the relevant biomarker timepoint with an available biomarker result.

Biomarker concentrations with right-skewed distributions will be log-transformed before regression. Results from log-transformed models will be reported as ratios of geometric means with 95% confidence intervals.

Biomarker models will use the primary core adjustment set where feasible. If biomarker-substudy size, sparse data, or convergence problems do not support the full adjustment set, models will be simplified by prioritizing age, sex, initial rhythm, time to ROSC, randomized STEPCARE intervention assignments, and site.

Death before biomarker sampling will be reported separately. Missing biomarker measurements due to missed sampling, processing failure, or assay failure will be reported with reasons where available.

6.7 Exploratory clinical outcomes

Binary outcomes, including ICU mortality and arrhythmia/safety events, will be analyzed using logistic regression where event counts permit. Arrhythmia and safety-event outcomes will use parent STEPCARE definitions and eCRF coding.

Ventilator-free days and hospital-free days will be analyzed as exploratory outcomes, with descriptive summaries and regression-based analyses if distributional assumptions are reasonable.

The hierarchical renal support outcome will be summarized descriptively.

Noradrenaline use and dose will be summarized descriptively where available.

6.8 Effect modification

The primary prespecified interaction analysis will evaluate whether the association between low-PP burden and mortality differs by randomized MAP target arm.

Exploratory interaction analyses will evaluate heterogeneity by retrospectively presumed cause of arrest, initial rhythm, shock on admission, and sex.

Retrospectively presumed cause of arrest, categorized as cardiac versus non-cardiac, will be used for exploratory analyses evaluating whether the association between low-PP burden and mortality differs by cause of arrest. This classification is expected to be more clinically informed than cause assigned at randomization because additional diagnostic information is available by discharge. These analyses will be interpreted as exploratory because the classification may incorporate information obtained after randomization.

Interaction analyses will be interpreted cautiously and reported with interaction estimates and stratum-specific estimates.

6.9 Sensitivity analyses

Sensitivity analyses will repeat the primary model using alternative PP thresholds of <30, <35, <45, and <50 mmHg; the 24-hour landmark exposure window; expanded adjustment for shock on admission and baseline diastolic arterial pressure; a stricter primary-window BP requirement of at least four valid recorded BP observations during 0-12 hours; exclusion of participants receiving mechanical circulatory support at any time during 0-72 hours; and logistic regression for day-7 mortality among 12-hour survivors.

6.10 MAP-target abandonment

MAP-target abandonment before 72 hours will be summarized by randomized MAP arm and recorded reason. Because the eCRF records whether the MAP target was changed or abandoned before 72 hours but does not capture the time of abandonment, this variable will not be used for before/after pulse-pressure trajectory analyses or time-dependent modeling. Exploratory analyses may describe the association between early PP burden and mortality within strata defined by MAP-target abandonment status, with interpretation limited by confounding by indication and absence of timing information.

6.11 Exploratory time-varying treatment-process analysis

A feasibility-dependent exploratory analysis using methods for time-varying treatment processes may be considered after blinded assessment of data completeness, temporal resolution, temporal ordering, positivity, and weight diagnostics.

Any such analysis will use a 4-hour time grid during 0-24 hours, reflecting the lowest common temporal resolution of key treatment variables. Variables sampled less frequently than every 4 hours will not be modeled as time-varying treatment or confounder processes. The analysis will require that prior covariates, subsequent treatment processes, and later pulse-pressure status can be temporally ordered on this grid.

Diagnostics will include interval-specific missingness, the proportion of participants with usable data across 4-hour intervals, distributions of estimated treatment probabilities, the proportion of observations with estimated probabilities <0.05 or >0.95, stabilized-weight percentiles, and effective sample size after weighting.

If diagnostics indicate extensive or differential missingness, near-deterministic treatment assignment, unstable weights after prespecified truncation, or insufficient outcome events, the analysis will be omitted or reported descriptively. Such analyses will not be used to support claims regarding a dynamic treatment strategy to maintain pulse pressure above a threshold.

6.12 Missing data

Missingness in baseline covariates will be reported. If missingness in covariates included in the primary adjusted model is ≤ 5%, the primary adjusted analysis will use complete cases. If missingness exceeds 5%, multiple imputation by chained equations with 20 imputed datasets will be used for baseline covariates.

The imputation model will include the primary exposure, outcome status, event time where applicable, primary-model covariates, and auxiliary baseline variables associated with missingness or outcome. Mortality outcome, MCS exclusion status, and pulse-pressure exposure values used to define the primary exposure will not be imputed for the primary analysis.

6.13 Multiplicity

The study will specify one primary exposure, one primary endpoint, and one primary analysis model. No formal multiplicity adjustment will be applied to key secondary or exploratory analyses. Secondary and exploratory results will be interpreted according to effect size, precision, biological plausibility, and consistency across analyses, rather than by statistical significance alone. Findings outside the primary analysis will be reported as hypothesis-generating.

7. Data sources and handling

All study data will be derived from the STEPCARE database and eCRF. STEPCARE collects clinical, laboratory, treatment, intervention, safety-event, discharge, and follow-up data within the parent trial data structure.

Blood-pressure data will be derived from recorded systolic, diastolic, and mean arterial pressure values. Pulse pressure will be calculated from systolic and diastolic blood pressure as described above.

Baseline and clinical variables will include demographics, arrest characteristics, initial rhythm, witnessed status, bystander CPR, time to ROSC, arrest location, randomized STEPCARE intervention assignments, baseline hemodynamic variables, and site.

Mechanical circulatory support, revascularization, MAP-target abandonment, noradrenaline use and dose, renal replacement therapy, dialysis status at hospital discharge, creatinine variables, safety events, and follow-up outcomes will be derived from STEPCARE data where available.

A descriptive data-quality report will summarize:

- number of valid BP observations per participant;
- timing of BP observations;
- excluded BP observations and reasons for exclusion;
- missing exposure time in each landmark window;
- mechanical circulatory support exclusions;
- biomarker availability by timepoint;
- death before biomarker sampling.

8. Ethics and data governance

STEP-PRESS is an observational substudy nested within STEPCARE and will use data collected under the parent STEPCARE protocol and applicable substudy approvals. No additional intervention, patient contact, or deviation from STEPCARE clinical management is planned for STEP-PRESS.

Data will be handled according to the parent trial data-management procedures, applicable ethics approvals, and relevant data-protection regulations. Analyses will use deidentified or pseudonymized trial data according to STEPCARE governance procedures.

The results of STEP-PRESS will be reported as exploratory observational findings. Time-varying treatment-process analyses, if performed, will be explicitly labeled exploratory and interpreted in light of the assumptions and diagnostic limitations described above.

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