



BMJ Open Neurological outcomes with hypothermia versus normothermia in patients with moderate initial illness severity following resuscitation from out-of-hospital cardiac arrest: protocol for a multicentre randomised controlled trial (R-CAST OHCA)

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ABSTRACT

Introduction Temperature control is a fundamental intervention for neuroprotection following resuscitation from cardiac arrest. However, evidence regarding the efficacy of hypothermia in post-cardiac arrest syndrome (PCAS) remains unclear. Retrospective studies suggest that the clinical effectiveness of hypothermia may depend on the severity of PCAS. The R-CAST OHCA trial aims to compare the efficacy of hypothermia versus normothermia in improving 30-day neurological outcomes in patients with moderately severe PCAS following out-of-hospital cardiac arrest.

Methods and analysis The multicentre, single-blind, parallel-group, superiority, randomised controlled trial (RCT) is conducted with the participation of 35 emergency and critical care centres and/or intensive care units at academic and non-academic hospitals. The study enrolls moderately severe PCAS patients, defined as those with a revised post-Cardiac Arrest Syndrome for induced Therapeutic Hypothermia score of 5.5–15.5. A target number of 380 participants will be enrolled. Participants are randomised to undergo either hypothermia or normothermia within 3 hours after return of spontaneous circulation. Patients in the hypothermia group are cooled and maintained at 34°C until 28 hours post-randomisation, followed by rewarming to 37°C at a rate of 0.25°C/hour. Patients in the normothermia group are maintained at normothermia (36.5°C–37.7°C). Total periods of intervention, including the cooling, maintenance and rewarming phases, will occur 40 hours after randomisation. Other treatments for PCAS can be determined by the treating physicians. The primary outcome is a favourable neurological outcome, defined as Cerebral Performance Category 1 or 2 at 30 days after randomisation and compared using an intention-to-treat analysis.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This is a multicentre randomised controlled trial comparing neurological outcomes in patients with out-of-hospital cardiac arrest treated with hypothermia or normothermia.
- ⇒ Outcome assessments are performed by physicians blinded to group allocation.
- ⇒ The study targets post-cardiac arrest syndrome patients with moderate illness severity, using the validated revised post-Cardiac Arrest Syndrome for induced Therapeutic Hypothermia score.
- ⇒ The trial is conducted primarily in Japan, reflecting the characteristics of its healthcare system.

Ethics and dissemination This study has been approved by the Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences and Okayama University Hospital, Ethics Committee (approval number: R2201-001). Written informed consent is obtained from all participants or their authorised surrogates. Results will be disseminated via publications and presentations.

Trial registration number jRCT1062220035.

INTRODUCTION

Background and rationale

Out-of-hospital cardiac arrest (OHCA) remains one of the leading causes of disability and death worldwide, despite significant advancements in public training for cardiopulmonary resuscitation and critical care.¹ OHCA and subsequent resuscitation frequently result in severe brain injury, which impedes functional recovery and significantly

contributes to mortality.² The inability to regain consciousness often leads to the withdrawal of life-sustaining therapy, further exacerbating mortality.³ Therefore, interventions that aim to minimise brain injury are crucial for improving patient outcomes.

Temperature control is a widely recognised strategy for mitigating ischaemic-reperfusion brain injury in post-cardiac arrest syndrome (PCAS). Strategies for temperature control include hypothermic temperature control (hypothermia), which involves actively maintaining body temperature below the normal range; normothermic temperature control (normothermia), where temperature is actively regulated within the normal range; and fever prevention temperature control, which focuses on temperature monitoring and preventing or reducing elevated body temperature.⁴ Normothermic temperature control and fever prevention temperature control have generally been included in normothermia in past studies. The efficacy of hypothermia versus normothermia has been examined. Animal cardiac arrest studies have consistently demonstrated a favourable effect of post-resuscitation hypothermia compared with normothermia, leading to improved neurological outcomes.⁵ Additionally, some earlier clinical randomised studies have suggested that hypothermia contributes to improved survival and neurological outcomes.^{6–8} However, recent large randomised controlled trials (RCTs) reported no significant differences in outcomes between hypothermia and normothermia,^{9–10} while hypothermia has been associated with a higher incidence of arrhythmias.¹⁰ Based on these findings, the 2024 international guidelines suggest actively preventing fever by targeting a temperature $\leq 37.5^{\circ}\text{C}$ for patients who remain comatose after return of spontaneous circulation (ROSC) from cardiac arrest.¹¹

This discrepancy in clinical trial results is considered likely due to the substantial heterogeneity of PCAS patients. Whether the clinical effectiveness of hypothermia depends on providing the appropriate dose (target temperature) based on brain injury severity remains unknown.⁴ Identifying subgroups of patients most likely to benefit from hypothermia can be a crucial step to enhance the efficacy of temperature control.¹²

Stratification of patients based on OHCA severity may be a key to identifying subgroups of patients who are most likely to benefit from hypothermia. A retrospective analysis suggests that hypothermia may be particularly effective for patients with moderate PCAS severity. Nishikimi *et al* used the revised post-Cardiac Arrest Syndrome for induced Therapeutic Hypothermia (rCAST) score to stratify patients and analysed data from a Japanese cardiac arrest registry. Hypothermia was associated with favourable outcomes in patients with moderate PCAS severity, which provides the rationale for our study design.¹³ Callaway *et al* stratified OHCA patients based on the Full Outline of UnResponsiveness score and the Sequential Organ Failure Assessment score and found that hypothermia was associated with increased survival in patients with the most severe post-cardiac arrest illness, excluding

those with severe cerebral oedema or malignant electroencephalogram (EEG) patterns.¹⁴ Additionally, Nutma *et al* conducted a retrospective analysis of post-cardiac arrest patients stratified by severity of hypoxic encephalopathy based on EEG patterns and revealed that patients with moderate hypoxic encephalopathy were associated with better neurological outcomes with therapeutic hypothermia compared with normothermia.¹⁵ These studies emphasise the need for a clinical trial to confirm the hypothesis that these tailored treatment approaches would optimise patient outcomes.

Hypothesis and aim

We hypothesise that hypothermia will improve neurological outcomes in patients with moderately severe PCAS. The R-CAST OHCA trial aims to compare the efficacy of hypothermia and normothermia in improving 30-day neurological outcomes in patients with moderately severe PCAS following OHCA.

METHODS AND ANALYSIS

Trial design and setting

The Randomised Controlled Trial Assessing Temperature Management after Out-of-Hospital Cardiac Arrest with Moderate Initial Illness Severity (R-CAST OHCA) is a multicentre, single-blind, parallel-group, superiority RCT including adult OHCA patients with moderate PCAS severity. This trial is conducted at emergency and critical care centres and/or certified intensive care units, at both academic and non-academic hospitals in both urban and rural areas across Japan. The recruitment of additional hospitals is also planned both domestically and internationally. The trial is registered in the jRCT (Japan Registry of Clinical Trials; <https://jrct.niph.go.jp>, trial registration number: jRCT1062220035).

Participants and interventions

This trial is supported by the Japanese Association for Acute Medicine, which facilitates the participation of trial sites and posts information about the trial on its website. Institutions that routinely implement temperature control as part of standard care and manage PCAS patients voluntarily participate with the expectation of actively enrolling patients. The trial enrolment process is shown in [figure 1](#). The inclusion criteria for patients are as follows: (1) OHCA with medical causes, including cardiac causes, presumed cardiac causes, and other medical causes, or causes not clearly identified at the time of eligibility¹⁶; (2) between 18 and 79 years old; (3) sustained ROSC (defined as 20 min with signs of circulation without the need for chest compressions) and unconscious (defined as Glasgow Coma Scale (GCS) score of 8 or lower and GCS motor response score of 5 or lower); (4) eligible for intensive care without any restrictions or specific limitations (no limitations in therapy and does not have a do-not-attempt-resuscitation order); (5) randomisation conducted within 180 min after ROSC and

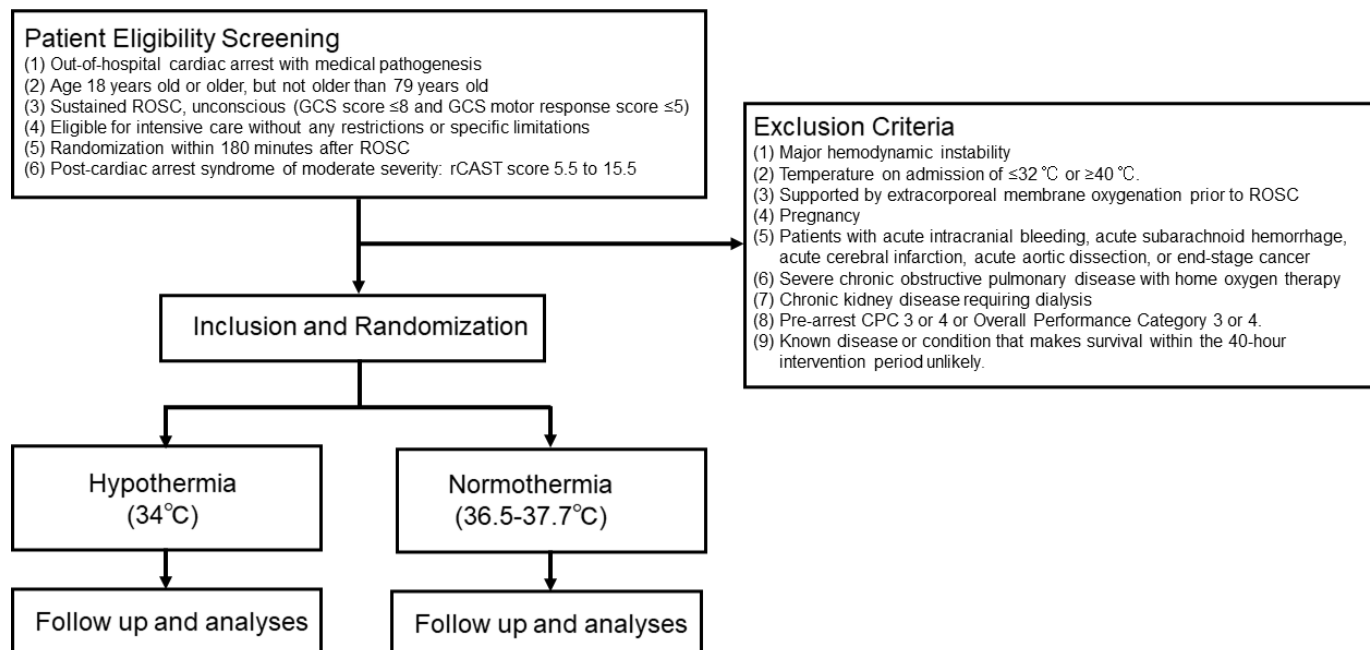


Figure 1 Flow chart for patient recruitment into the R-CAST OHCA trial. CPC, Cerebral Performance Category; GCS, Glasgow Coma Scale; rCAST, revised post-Cardiac Arrest Syndrome for induced Therapeutic Hypothermia (score); ROSC, return of spontaneous circulation.

(6) PCAS of moderate severity (defined by rCAST score of 5.5–15.5). Patient exclusion criteria are as follows: (1) major haemodynamic instability (systolic blood pressure 80 mm Hg or lower despite fluid resuscitation/vasopressors or inotropic support); (2) temperature on admission of 32°C or lower or 40°C or higher; (3) supported by extracorporeal membrane oxygenation prior to ROSC; (4) pregnancy; (5) acute intracranial bleeding, acute subarachnoid haemorrhage, acute cerebral infarction, acute aortic dissection or end-stage cancer; (6) severe chronic obstructive pulmonary disease with home oxygen

therapy; (7) chronic kidney disease requiring dialysis; (8) pre-arrest Cerebral Performance Category (CPC) of 3 or 4 or Overall Performance Category of 3 or 4 and (9) known disease or condition that makes survival within the 40-hour intervention period unlikely. **Figure 2** demonstrates the rCAST scoring system, which is used to define moderate severity for eligibility in this trial.

Investigators explain the study concept and protocol to the authorised surrogates of potential trial participants. The informed consent form, approved by the Institutional Review Board, is provided to obtain voluntary

A

Variables	Score point	0	1	2	3
Initial rhythm		Shockable	Non shockable		
Witness / until ROSC time		< 20 min	20 min ≤	No witness	
pH		≥ 7.31	7.30 – 7.16	7.15 – 7.01	7.00 ≥
Lactate (mmol/L)		≤ 5.0	5.1 – 10.0	10.1 – 14.0	14.1 ≤
GCS M		≥ 2	1		

B

Calculation formula for rCAST

$$1.0 \times (\text{Initial rhythm}) + 2.0 \times (\text{Witness / until ROSC time}) + 2.5 \times (\text{pH}) + 0.5 \times (\text{Lactate}) + 4.5 \times (\text{GCS M}) = \square \text{ points}$$

Figure 2 Revised post-Cardiac Arrest Syndrome for Therapeutic Hypothermia score (rCAST). (A) The rCAST score consists of five variables: initial rhythm, time from cardiac arrest until ROSC (until ROSC time), arterial blood pH and lactate level obtained within 30 min after ROSC, and the motor component of the Glasgow Coma Scale (GCS M). (B) The rCAST score is calculated by summing the products of each categorical variable and its corresponding weight. Time until ROSC, time from cardiac arrest until return of spontaneous circulation.

written consent (online supplemental file 1). If immediately obtaining face-to-face written consent is not feasible, consent is obtained via telephone, followed by written consent when the representative arrives at the hospital. Patients meeting the eligibility criteria are randomly assigned to one of two groups within 180 min: (1) the hypothermia group in which patients are managed using a temperature control device to a target temperature of 34°C (hypothermic temperature control) and body temperature is maintained at 34°C until 28 hours post-randomisation, followed by rewarming to 37°C at a rate of 0.25°C/hour until 40 hours and (2) the normothermia group in which patients are maintained at normothermia (36.5°C–37.7°C) until 40 hours (normothermic temperature control and fever prevention temperature control). The temperature control settings were based on those used in a previous trial.¹⁰ In both groups, temperature control is initiated as early as possible after randomisation to achieve the assigned target range. The use of a feedback-controlled cooling device is not mandated for either group, and both surface and intravascular cooling methods are permitted. Antipyretic agents such as acetaminophen or non-steroidal anti-inflammatory drugs may also be used as needed. If a feedback-controlled cooling device is used in the normothermia group, the target temperature is encouraged to be set at 37.0°C. Fever prevention is encouraged until 72 hours in both groups. The timeline for temperature control in the hypothermia and normothermia groups from randomisation is shown in figure 3. Other treatments for PCAS may be determined by the treating physicians; however, patients in both groups will generally remain sedated until the end of the intervention period. Shivering is managed using the Bedside Shivering Assessment Scale¹⁷ and controlled with antipyretic agents, temperature control devices or muscle relaxants, as appropriate. If withdrawal of life-sustaining therapy is considered, participants who remain

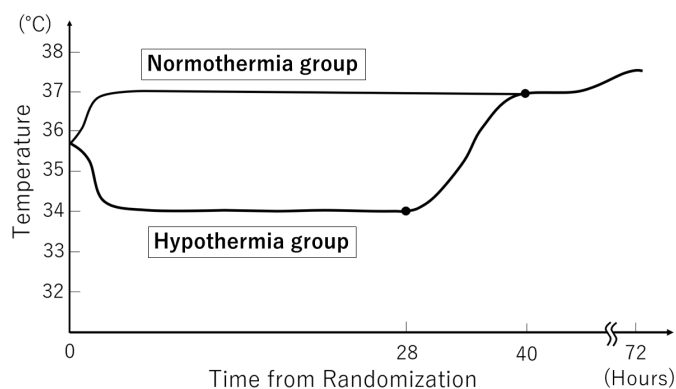


Figure 3 Temperature control protocol in the hypothermia and normothermia group. Hypothermia group: 34°C until 28 hours followed by rewarming to 37°C at a rate of 0.25°C/hour until 40 hours. Normothermia group: normothermia (36.5°C–37.7°C) until 40 hours. If a feedback-controlled cooling device is used in the normothermia group, the target temperature is encouraged to be set at 37.0°C. Fever prevention is encouraged until 72 hours in both groups.

unconscious are evaluated using at least two modalities. Neurological prognostication is generally performed no earlier than 96 hours after cardiac arrest. Investigators are expected to adhere to the study protocol. However, the treating physician may discontinue the intervention at their discretion based on the patient's condition. There are no restrictions on other treatments during the trial. All patients who suffer harm from participation in the trial will be covered by the healthcare system of their respective country.

Outcome measures

The primary outcome is neurological status, defined as a favourable outcome (CPC 1 or 2), assessed 30 days after cardiac arrest. Secondary outcomes include the following: neurological status, defined as a favourable outcome (CPC 1 or 2), assessed 90 days after cardiac arrest; all-cause mortality assessed 30 days after cardiac arrest; and all-cause mortality assessed 90 days after cardiac arrest. Outcome assessments are conducted by physicians blinded to the group assignments. If a participant is discharged or transferred from the hospital before the 90-day follow-up, investigators contact the participant, the participant's authorised surrogates, or the receiving hospital attending physician via telephone and the blinded physician obtains information about their status. To ensure consistency in follow-up assessments, assessors use a structured evaluation sheet, which they thoroughly review before conducting assessments.

Randomisation and blinding

This trial employs an open-label design with blinded outcome assessors. Participants are randomly assigned to the hypothermia group or the normothermia group at a 1:1 ratio. Randomisation is performed using stratified block randomisation via the Electronic Data Capture (EDC) system using a centralised internet-based allocation process. The specific block size is known only to the EDC system developer, ensuring that both statisticians and investigators remain blinded to this aspect of the allocation process. The randomisation list is automatically generated with a random sequence at each participating hospital, stratified by two factors: facility and initial recorded rhythm (shockable/non-shockable). Once physicians input the inclusion of a new participant in the EDC system, the allocation is immediately displayed as either the hypothermia group or the normothermia group. The allocation results are visible in the EDC system for each hospital; however, researchers remain blinded to the assignments and outcomes of patients enrolled at other hospitals. Due to the nature of the trial, care providers cannot be blinded to the assigned intervention. However, outcome assessments are conducted by physicians blinded to group assignments.

Participant timeline

The schedule for the trial is summarised in figure 4. Assessment data are recorded using a secure EDC system

Time point	Patient arrival / resuscitation / ROSC	ROSC / diagnosis of cardiac arrest cause	Temperature control	28 hours	Day 3 Day 5	Day 30	Day 90	WLST decided	Intervention canceled
Inclusion / exclusion criteria	●								
Informed consent	●								
Patient demographics		●							
rCAST score		●							
Intervention period		←————→							
Adverse events		←————→							
GCS score		●	●	●	●			●	●
SOFA score		●	●	●	●			●	●
Baseline demographic data (blood pressure / heart rate / SpO ₂ / etc.)		●	●	●					
Core temperature measurement		●	●	●				●	●
Sedatives / other drugs		●	●	●				●	●
Laboratory tests	Complete blood count	●							
	Coagulation test	●							
	Blood chemistry test	●							
	Blood gas analysis	●	●	●					
Chest x-ray	●								
Electrocardiogram	●								
Head CT	●								
Neurological prognostication					●				
Neurological examination						●	●	●	●

Figure 4 Time schedule for the trial. Assessment data are recorded using an electronic data capture system. Participants are followed up for 90 days after randomisation. If a participant is discharged or transferred from the hospital before the 90-day follow-up, investigators contact the participant or the receiving hospital via telephone to obtain information about their status. GCS, Glasgow Coma Scale; rCAST, revised post-Cardiac Arrest Syndrome for induced Therapeutic Hypothermia (score); ROSC, return of spontaneous circulation; SOFA, Sequential Organ Failure Assessment (score); SpO₂, oxygen saturation of peripheral artery; WLST, withdrawal of life-sustaining therapy.

(NEXT Stage EDC, TXP Medical, Tokyo), ensuring the protection of participant information. Independent trial monitoring experts ensure that the data reported by the investigators are collected accurately. Participants are followed up for 90 days after randomisation. The planned duration of the study is from 6 June 2022 to 31 December 2028.

Statistical methods

This trial is designed to enrol a total of 380 participants across approximately 20–40 tertiary care centres in Japan

and medical institutions in other countries with comparable standards of care.

The sample size calculation was based on an alpha error of 0.048 for the final analysis and a statistical power of 80% (0.80). Based on previous study data, we anticipated that favourable neurological outcomes, defined as a CPC of 1 or 2, would occur in 50% of participants in the hypothermia group and 35% of participants in the normothermia group.¹³ To detect this difference, 172 participants are required in each group. Considering the

loss of follow-ups, the required sample size was increased by 10% (ie, an extra 18 participants per group), resulting in 190 participants in each group. Consequently, the overall target sample size for this trial is 380 participants.

The primary efficacy analysis will be conducted using the full analysis set (FAS), which includes all randomised participants with at least one post-randomisation measurement of an efficacy endpoint, either primary or secondary. This analysis will adhere to the intention-to-treat principle. Additionally, a per protocol set, comprising participants who comply with the protocol and meet predefined eligibility criteria, will be used for sensitivity analyses to validate and compare the findings obtained from the FAS. Missing, excluded or aberrant data will be handled using available data. In cases where missing data are substantial, exploratory analyses will be conducted to estimate their impact. Detailed procedures for managing such data will be outlined in the finalised statistical analysis plan before data lock.

Baseline demographic and clinical characteristics will be summarised for each treatment group (hypothermia and normothermia) using descriptive statistics. Frequencies and percentages will be calculated for categorical variables, while medians and IQRs will be used for continuous variables. For both primary and secondary outcomes, summary statistics will be calculated for each treatment group. Fisher's exact test will be used for group comparisons, while survival time analyses will be performed using HRs to evaluate differences in survival between groups. Additionally, subgroup analyses will be conducted based on the following factors: initial rhythm (shockable vs non-shockable), sex (male vs female), age (≥ 65 vs < 65 years), time to ROSC (short vs long, categorised by the median value) and rCAST score (low vs high, categorised by the median value). Statistical analyses will use a two-sided significance level of 5%, and CIs will be reported at the 95% confidence level.

An interim analysis will be performed after approximately 50% of the target sample size has been enrolled. To control the overall alpha error rate at 0.05, the alpha levels for the interim and final analyses will be set at 0.005 and 0.048, respectively, using the O'Brien-Fleming method. The steering committee and the Data and Safety Monitoring Committee (DSMC) will assess the results of the interim analyses and make recommendations on the continuation, modification or termination of the trial. Based on the recommendations of the steering committee and DSMC, the primary investigator will make the final decision to continue or terminate the trial. When trial continuation is decided, the results of the interim analysis will remain concealed. The statistician and DSMC will have exclusive access to all participants' data on the EDC.

Any changes to the original statistical analysis plan will be documented in an amended protocol or analysis plan and will be detailed in the final study report.

For additional analysis, researchers at participating facilities may conduct post-hoc analyses using data obtained

from this study, after receiving Institutional Review Board approval.

Oversight and monitoring

The steering committee, comprising 12 researchers, supervises the trial. The steering committee designed the study in collaboration with the clinical research centre at the principal institution, the Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences and participating facilities. The DSMC, comprising three independent clinical researchers without competing interests, meets regularly to review trial data management and assess the safety of continuing the trial. All investigators are responsible for collecting, assessing, recording and managing adverse events. Personally identifiable information is managed at each research facility, and only deidentified information is recorded in the EDC system. The DSMC, independent of the trial's conduct, ensures the protection of participants' rights, safety and welfare while maintaining the trial's reliability. To ensure compliance with the study protocol and research plan, the DSMC monitors the first three enrolled cases from each site. If there are severe adverse events related to the trial intervention, the principal investigator will promptly report the incident to the DSMC and the ethics review board of the principal institution, and share the information with other investigators. The ethics review board will review the report and provide written recommendations to the principal investigator. If modifications to the study protocol are deemed necessary, the steering committee, including the principal investigator, will discuss and determine the necessary changes and then formally notify the trial group. Auditing is not planned.

Patient and public involvement

No patients or public entities were involved in the design and planning of this study. The design and implementation were guided by existing literature and expert opinion. However, we recognise the importance of patient and public involvement and plan to engage patient representatives in future studies to improve the relevance and dissemination of our findings.

Ethics and dissemination

This trial is conducted in accordance with the principles of the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects. Ethical approval for the study was granted by the Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences and Okayama University Hospital Ethics Committee (R2201-001) in April 2022, following an application process initiated in 2021. Written informed consent to participate is obtained from all participants or their authorised surrogates. The trial results will be shared with collaborators and disseminated through presentations at scientific meetings and publications in peer-reviewed journals. Upon completion of post hoc analyses by the study group, the data sets

and statistical codes will be made available by the corresponding author on reasonable request, in accordance with ethical and data-sharing guidelines.

DISCUSSION

The R-CAST OHCA trial will investigate the efficacy of hypothermia in PCAS patients, focusing on those with moderate illness severity as determined by rCAST score. The findings are expected to provide important insights into whether the efficacy of hypothermia varies by illness severity, in terms of neurological outcomes and mortality, and contribute to the ongoing debate regarding optimal temperature control strategies in post-cardiac arrest care by focusing on a well-defined population of patients with moderate severity.

The concept of illness severity in PCAS has recently been explored, and several studies have examined scoring systems to predict outcomes after cardiac arrest.^{18–21} The rCAST score, developed by Nishikimi *et al*, incorporates factors such as initial rhythm, time to ROSC, initial arterial blood gas pH and initial lactate level to predict neurological outcomes. While various prognostic scores are available, the rCAST score was chosen for this study due to its extensive use, validation and strong support from robust clinical experience.^{22–25} PCAS encompasses a broad spectrum of neurological injuries influenced by factors such as ischaemic duration and underlying pathophysiology. Clinicians encounter a wide variety of cases, ranging from patients with mild neurological impairment to those in deep coma. Despite this clinical variability, current guidelines lack specific recommendations for tailoring temperature control strategies based on illness severity. The relationship between PCAS severity and the effectiveness of temperature control remains underinvestigated.

This study has several potential limitations. First, the trial is conducted across multiple centres, including both academic and non-academic hospitals, which may introduce variability in the implementation of temperature control. However, all participating facilities in Japan are emergency and critical care centres and/or nationally certified intensive care units with extensive experience in managing PCAS and performing temperature control as part of routine care. International sites are planned to be included, and comparable standards of care will be required for their participation. Nevertheless, as of July 2025, this remains a single-country study conducted exclusively in Japan, and the majority of data will be derived from Japanese institutions, which may limit the generalisability of the findings to international settings. Second, the inclusion criteria focus on patients with moderate illness severity as determined by the rCAST score. Although the rCAST score is validated for assessing the severity of PCAS and has been shown to effectively predict neurological outcomes, it does not directly incorporate measures of brain function or neurological injury, such as EEG findings or neuro biomarkers, into its scoring system. Third, the open-label design, while necessary for the practical

implementation of temperature control, might introduce a risk of bias despite the use of blinded outcome assessors. Finally, the anticipated loss to follow-up, although accounted for in the sample size calculation, could affect the robustness of the results, particularly for secondary outcomes.

Trial status

The trial protocol V.1.0 was approved on 6 April 2022 (approval number: R2201-001), with the approval process initiated in November 2021. The latest protocol is V. 1.7, which was approved on 27 August 2024, after minor revisions regarding the addition and elimination of participating hospitals and modification of the study period due to the lower-than-expected enrolment of patients. The first participant was recruited on 10 July 2022. The trial is ongoing, and approximately 140 patients had been enrolled as of the end of February 2025. The estimated primary completion date is 31 December 2028. The full protocol (version 1.7) is available at: https://www.jaam.jp/info/2022/info-R-CAST_OHCA.html.

The trial was registered in The Japan Registry of Clinical Trials (jRCT1062220035) on 13 June 2022.

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Contributors The R-CAST OHCA trial is led by HN. HN is responsible for the overall content as guarantor. The funding application was drafted by HN and AN. The initial protocol (version 1.0) was drafted by HN, MN, YO, HM, TK, TY, KeN, SM, YK, KaN, TI and AN. All authors developed the final study protocol and procedures. HN, MN, YO and KaN drafted this manuscript, and all authors contributed to its critical review and read and approved the final version.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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