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# BMJ Open

**Intensive care with extracorporeal membrane oxygenation rewarming in accident severe hypothermia (ICE-CRASH) study: A protocol for a nationwide prospective, observational study in Japan**

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3 **Title:** Intensive care with extracorporeal membrane oxygenation rewarming in accident severe  
4 hypothermia (ICE-CRASH) study: A protocol for a nationwide prospective, observational  
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## Abstract

**Introduction:** Accidental hypothermia (AH) is a rare but critical disease, leading to death in severe cases. In recent decades, extracorporeal membrane oxygenation (ECMO) has been successfully used to rewarm hypothermic patients with cardiac arrest or circulation instability. However, data on the efficacy of rewarming using ECMO for patients with AH are limited. Therefore, a large-scale, nationwide, multicenter, prospective study is warranted. The primary objective of this study will be to clarify the efficacy of rewarming using ECMO for patients with AH. Our secondary objectives will be to evaluate the incidence of complications, such as bleeding, thrombosis, during ECMO use and to identify the most appropriate management of ECMO for AH.

**Methods and analyses:** The ICE-CRASH study is taking place in 35 tertiary emergency medical facilities in Japan. The inclusion criteria are patients  $\geq 18$  years old with a body temperature  $\leq 32$  °C. We will include patients with AH who present to the ED from December 2019 to March 2022. The research personnel at each hospital will collect several variables, including patient demographics, rewarming method, ECMO data, and complications. Our primary outcome is to compare the 28-day mortality rate between the ECMO and non-ECMO (other treatments) groups among patients with severe AH. Our secondary outcomes are to compare the following values between the ECMO and non-ECMO groups: length of stay in the intensive-care unit and complications. In addition, in cases of ECMO rewarming, we will evaluate the relationship between the information regarding ECMO and the prognosis.

**Ethics and dissemination:** This study received research ethics approval from Asahikawa Medical University (18194 & 19115). The study was approved by the institutional review board of each hospital, and the requirement for informed consent was waived due to the observational nature of the study.

**Trial registration number:** UMIN Clinical Trials Registry; UMIN000036132. Registered 1

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3 April 2019.  
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8 **Keywords:** accidental hypothermia, mortality, extracorporeal membrane oxygenation  
9 (ECMO), complication,  
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### Strengths and limitations of this study

1. This study will be the first large-scale, prospective study of ECMO rewarming for patients suffering from accidental hypothermia (AH).
2. This study will evaluate the efficacy of ECMO rewarming compared to non-ECMO rewarming for hypothermic patients with cardiac arrest or circulatory instability.
3. This study will also collect blood samples to determine the relationship between coagulation fibrinolysis and ECMO-related complications and identify optimal ECMO rewarming management approaches for hypothermic patients.
4. However, this study is not a randomized trial, which means that the adjustment for confounding factors is not complete.

## Introduction

Accidental hypothermia (AH) is a rare condition but can be life-threatening in severe cases<sup>1 2</sup>. Thanks to technological advances over the past few decades, veno-arterial extracorporeal membrane oxygenation (V-A ECMO) has become a viable rewarming treatment for patients with severe hypothermia with cardiac arrest or severe circulatory instability<sup>3 4 5 6</sup>. Recently, the resuscitation guidelines from both the European Resuscitation Council and the American Heart Association have recommend the use of ECMO in AH patients with cardiac arrest<sup>7 8</sup>. However, there has been limited evidence concerning the utility of ECMO rewarming in patients with AH because of the low frequency of eligible patients. In addition, ethical implications restrict the utility of randomized controlled trials. Thus, previous studies on patients with AH rewarmed by ECMO have been case reports or single-center retrospective analyses<sup>4 5 6</sup>.

A recent study using the nationwide Japanese Diagnosis Procedure Combination inpatients database showed that V-A ECMO was associated with a higher survival rate and more favorable neurological outcomes than conventional cardiopulmonary resuscitation (CPR) alone in hypothermic patients with cardiac arrest<sup>9</sup>. However, this study has several issues. First, whether or not ECMO should be initiated in hypothermic patients with circulatory instability remains unclear. Second, this study did not clarify whether ECMO or other warming methods should be used in patients with AH. At present, there are no clinical guidelines on this point. Third, this study did not describe the complications associated with ECMO rewarming in hypothermic patients. The use of ECMO for hypothermic patients with noncardiac arrest is highly debatable, as ECMO is a highly invasive treatment with potentially serious complications<sup>5</sup>. Therefore, a large-scale, nationwide, multicenter, prospective study is warranted to resolve these issues.



## Objectives

The primary objective of this study will be to clarify the efficacy of ECMO rewarming for hypothermic patients with cardiac arrest or circulatory instability. We hypothesized that the ECMO rewarming method is more beneficial in terms of survival than conventional rewarming methods. Our secondary objectives are to evaluate the incidence of adverse effects, such as bleeding, thrombosis, and infectious disease, during and after V-A ECMO rewarming for hypothermic patients with cardiac arrest or circulatory instability. The results will help identify the most appropriate management approach with ECMO for patients with AH.

## Methods and analyses

### *Study design and setting*

The Intensive Care with ExtraCorporeal membrane oxygenation Rewarming in Accidentally Severe Hypothermia (ICE-CRASH) study is a prospective, nationwide, observational study of patients with AH. The registry started in December 2019, with a planned three years of patient recruitment. The study is taking place at 35 tertiary emergency medical facilities that provide emergency and intensive care treatments to patients with AH in Japan.

### *Eligibility criteria*

- Inclusion criteria

The ICE-CRASH study consists of patients whose body temperature measured at the emergency department (ED) is less than 32 °C. Investigators will enroll consecutive patients  $\geq 18$  years old with AH, including those with cardiac arrest. We will include patients with AH who present to the ED from December 2019 to March 2022.

- Exclusion criteria

The following patients will be excluded: patients  $< 18$  years old and those with cardiac arrest who are not eligible for resuscitation, according to the judgment of the emergency physician at each institution.

### *Data collection and quality control*

A trained investigator or research assistant at each center will collect the following data: age, sex, any pre-existing conditions, activities of daily living (ADL), causes underlying the hypothermia, alcohol intake, anticoagulants, Charlson comorbidity index (CCI), Glasgow coma scale (GCS), Sequential Organ Failure Assessment (SOFA) score<sup>10</sup>, laboratory data,

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3 body temperature, blood pressure, heart rate, respiratory rate, electrocardiogram, cardiac arrest  
4 during pre-hospital, duration in the intensive-care unit (ICU), length of hospital stay, mortality  
5 and Cerebral Performance Category (CPC) score at discharge, event days (ventilator, renal  
6 replacement therapy, and catecholamine days), amount of transfusion, and mortality at 28 days  
7 after admission (Table 1). These data will be recorded in the electronic data capture system  
8 (NorthNet; <https://www.crmic-huhp.jp/northnet/edc/>).  
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17 Rewarming methods will be divided into active external rewarming (warmed blanket  
18 and warmed bath) and active internal rewarming (warmed fluid infusion, lavage, hemodialysis,  
19 intravascular catheter, and extracorporeal membrane oxygenation [ECMO]). The selection of  
20 the rewarming method will be decided based on the attending physician's judgement. When  
21 rewarming using ECMO is selected, the registry will also record additional information  
22 regarding ECMO as follows: the size of the ECMO cannula, the ECMO flow, presence of distal  
23 perfusion, usage and types of anticoagulants, patient status at the start of ECMO (CPA or non-  
24 CPA), time from the scene until ECMO initiation, duration using ECMO, and presence of  
25 weaning from ECMO.  
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38 In addition, registry data will be collected concerning the incidence of complications  
39 (ventricular fibrillation, bleeding, pneumonia, acute pancreatitis, acute kidney injury) and  
40 complications due to ECMO (infection or thrombosis of cannula). Complications will include  
41 events that occur within seven days after admission. Bleeding is defined as any amount  
42 requiring a transfusion. Pneumonia is defined as an obvious shadow on chest radiography or  
43 computed tomography (CT). Pancreatitis is defined as cases meeting at least two of the  
44 following conditions: 1) abdominal pain, 2) elevation of pancreatic enzyme levels in the blood,  
45 and 3) edema of the pancreas or peripancreatic effusion on ultrasound/CT. Acute kidney injury  
46 is defined as acute kidney injury network (AKIN) classification stage  $\geq 2$ .  
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58 Furthermore, the ICE-CRASH study will collect blood samples from patients with AH  
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3 at each participating institution and perform additional tests related to coagulation and  
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5 fibrinolysis.  
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## Outcomes

Our primary outcome is the comparison of the survival rate between the ECMO and non-ECMO (other treatments) groups for severe hypothermic patients. Our secondary outcomes are the examination of the incidence of complications in the ECMO group (ventricular fibrillation, bleeding, thrombosis, pneumonia, acute pancreatitis, lower limb ischemia, acute kidney injury) and the clarification of the relationship between the time to ECMO initiation and the prognosis in the ECMO group.

## Statistical plan

### *Sample size estimation*

The sample size was calculated based on similar previous studies<sup>4 5 6</sup>. Based on the results of previous retrospective observational studies, we assumed proportions of surviving patients at 28 days after admission among patients with AH of 50% in the ECMO group and 85% in the non-ECMO group. For a power of 80% and a type 1 error of 5%, the number of patients required is at least 33 in each group. Taking into account the sample of patients who dropped out during the process, the total number needed was calculated to be 70 patients.

### *Statistical analyses*

Categorical variables will be presented as frequencies and percentages, and continuous variables will be presented as the means with the standard deviation or medians with the interquartile range (25<sup>th</sup> to 75<sup>th</sup> percentile). Intergroup comparisons will be carried out using Fisher's exact test for categorical data and the Mann-Whitney U test for continuous data. For the primary outcome, Kaplan-Meier curves in combination with the log-rank test and the multivariate Cox proportional hazard model, after adjusting for demographic and clinical variables, will be used to evaluate the association between ECMO rewarming and survival in patients with AH.

### *Ethics and dissemination*

This study will be conducted in accordance with the Declaration of Helsinki. It has received research ethics approval from Asahikawa Medical University (18194 & 19115) and is registered with the UMIN Clinical Trials Registry (UMIN000036132). It has also been approved by the Ethics Committee of each participating hospital. The need for informed consent will be waived due to the observational nature of the study. However, if blood samples

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3 are collected for additional studies, written informed consent will be obtained from each patient  
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5 as appropriate.  
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8 The results of the study will be disseminated to the participating hospitals, submitted to  
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10 peer-reviewed journals for publication, and presented at scientific congresses.  
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## Discussion

Since the successful use of ECMO for AH with cardiac arrest has been reported, many studies have reported the efficacy of ECMO rewarming in patients with AH<sup>3 4 5 6</sup>. In recent years, some studies have suggested the utility of predictive scores, such as the HOPE score<sup>11</sup> and ICE score<sup>12</sup>, for deciding to initiate ECMO rewarming in hypothermia patients. However, these scores were based on data obtained from retrospective studies and thus included significant issues, such as publication and selection bias. For example, few of these retrospective studies focused on complications associated with ECMO usage, especially hemorrhagic and thrombotic complications. Furthermore, even when they reported complications, the studies may have underestimated them.

Although previous studies have shown that deep hypothermia inhibited the platelet function and coagulation<sup>13 14</sup>, in the clinical application of ECMO, many centers routinely use anti-coagulants, such as heparin, to prevent thrombosis. However, no study has examined the appropriate use of heparin when performing ECMO for hypothermia. In the ICE-CRASH study, we will collect blood samples and perform additional coagulation and fibrinolysis tests to evaluate the relationship between thrombotic and bleeding complications during and after rewarming. In the future, these results may lead to the development of a new management approach for hypothermia specific to ECMO that differs from conventional ECMO management. If a safer and less-complicated method of ECMO management can be developed, ECMO may become the method of choice for hypothermic patients with non-cardiac arrest, in whom ECMO use has previously been discouraged due to its invasiveness.

According to studies regarding extracorporeal resuscitation (ECPR) for out-of-hospital cardiopulmonary arrest patients, the longer it takes to initiate ECPR, the poorer the neurological prognosis<sup>15 16</sup>. Some studies have shown that the optimal cut-off time from cardiac arrest to ECMO initiation is 40 to 59 minutes<sup>17 18</sup>. Recent review suggests that ECPR



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3 is not offered if the no-flow duration is unknown or prolonged to the extent that brain recovery  
4 is doubtful<sup>19</sup>. However, this did not apply to patients with AH resulting in cardiac arrest<sup>20 21</sup>.  
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6 Retrospective studies have shown that hypothermic patients with cardiac arrest or circulatory  
7 instability who required long-distance transport, resulting in a delayed introduction of ECMO,  
8 actually had a good neurological outcome<sup>20 21</sup>. Furthermore, a recent study showed that the  
9 parameter “un-witnessed cardiac arrest” was not associated with a worse outcome<sup>11</sup>. Although  
10 these results are very encouraging, the maximum permissible time until the initiation of ECMO  
11 remains unclear. In the ICE-CRASH study, we will collect data on the time to the initiation of  
12 ECMO and CPR to clarify the relationship between the time to ECMO and the prognosis. These  
13 results may provide strong evidence supporting the feasibility of long-distance transport for the  
14 introduction of ECMO for patients with AH in the future, even in remote areas where ECMO  
15 cannot be introduced immediately.  
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31 Furthermore, the ICE-CRASH study will collect data associated with the ECMO  
32 rewarming rate. A recent retrospective study showed that a slower ECMO rewarming rate was  
33 associated with a better survival rate<sup>22</sup>, while another study showed the opposite result<sup>23</sup>. The  
34 optimal ECMO rewarming rate thus remains unclear. Eventually, the ICE-CRASH study will  
35 be able to provide results that will help establish safer and more optimal ECMO management  
36 methods for patients with severe hypothermia.  
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#### 47 **Authors' contributions:**

48  
49 ST conceived and designed the ICE-CRASH study and is the principal investigator, MH  
50 developed the study protocol. ST and MH drafted and revised the manuscript, and all authors  
51 critically reviewed the content and approved the final manuscript.  
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### 8 **Competing interests**

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10 None declared.  
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### 14 **Patient and public involvement**

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17 No patient or public involvement.  
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### 20 **Patient consent for publication**

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39 2020/06/07]  
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Table 1. Variables collected in this study

Pre-hospital	In-hospital	Rewarming Time/Method	Outcome	Complications
Age, years	Body temperature	Time required for rewarming	Length of ICU stay	Bleeding/thrombosis
Sex	GCS	Active external rewarming	Length of hospital stay	Pneumonia
Time from EMS alert to ED arrival	CPA or non-CPA	Warmed blanket	Mortality at discharge	Pancreatitis
Location (indoor or outdoor)	Blood pressure	Warmed bath	CPC	Acute kidney injury
Causes underlying the hypothermia	Heart rate	Active internal rewarming	Event days	
ADL	ECG	Warmed fluid infusion	Ventilator	
Charlson comorbidity index	Respiratory rate	Lavage	Renal replacement therapy	
	Laboratory tests	Hemodialysis	catecholamine	
	Arterial blood gas analysis	Intravascular catheter	Transfusion	
	SOFA score	ECMO (Cannula size, flow, distal perfusion, anticoagulant, time to initiate ECMO, duration, weaning)	Mortality at 28 days after admission	

EMS, emergency medical service; ED, Emergency department; ADL, Activities of daily living; GCS, Glasgow Coma Scale; CPA, Cardiopulmonary Arrest; ECG, Electrocardiogram; SOFA, Sequential Organ Failure Assessment; ECMO, Extracorporeal membrane oxygenation; CPC, Cerebral Performance Category;

# Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
<b>Administrative information</b>			
Title	<a href="#">#1</a>	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	P1
Trial registration	<a href="#">#2a</a>	Trial identifier and registry name. If not yet registered, name of intended registry	P3
Trial registration: data set	<a href="#">#2b</a>	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	<a href="#">#3</a>	Date and version identifier	P3
Funding	<a href="#">#4</a>	Sources and types of financial, material, and other support	P14
Roles and responsibilities: contributorship	<a href="#">#5a</a>	Names, affiliations, and roles of protocol contributors	P14



1	Roles and	<a href="#">#5b</a>	Name and contact information for the trial sponsor	n/a
2	responsibilities:			
3	sponsor contact			
4	information			
5				
6				
7				
8	Roles and	<a href="#">#5c</a>	Role of study sponsor and funders, if any, in study design;	n/a
9	responsibilities:		collection, management, analysis, and interpretation of data;	
10	sponsor and funder		writing of the report; and the decision to submit the report for	
11			publication, including whether they will have ultimate authority	
12			over any of these activities	
13				
14				
15				
16	Roles and	<a href="#">#5d</a>	Composition, roles, and responsibilities of the coordinating centre,	n/a
17	responsibilities:		steering committee, endpoint adjudication committee, data	
18	committees		management team, and other individuals or groups overseeing the	
19			trial, if applicable (see Item 21a for data monitoring committee)	
20				
21				
22				
23	<b>Introduction</b>			
24				
25	Background and	<a href="#">#6a</a>	Description of research question and justification for undertaking	P5
26	rationale		the trial, including summary of relevant studies (published and	
27			unpublished) examining benefits and harms for each intervention	
28				
29				
30	Background and	<a href="#">#6b</a>	Explanation for choice of comparators	n/a
31	rationale: choice of			
32	comparators			
33				
34				
35				
36	Objectives	<a href="#">#7</a>	Specific objectives or hypotheses	P6
37				
38	Trial design	<a href="#">#8</a>	Description of trial design including type of trial (eg, parallel	P7
39			group, crossover, factorial, single group), allocation ratio, and	
40			framework (eg, superiority, equivalence, non-inferiority,	
41			exploratory)	
42				
43				
44				
45	<b>Methods:</b>			
46	<b>Participants,</b>			
47	<b>interventions, and</b>			
48	<b>outcomes</b>			
49				
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51				
52	Study setting	<a href="#">#9</a>	Description of study settings (eg, community clinic, academic	n/a
53			hospital) and list of countries where data will be collected.	
54			Reference to where list of study sites can be obtained	
55				
56				
57	Eligibility criteria	<a href="#">#10</a>	Inclusion and exclusion criteria for participants. If applicable,	P7
58			eligibility criteria for study centres and individuals who will	
59				
60				

		perform the interventions (eg, surgeons, psychotherapists)	
1			
2	Interventions:	<a href="#">#11a</a> Interventions for each group with sufficient detail to allow	P8
3	description	replication, including how and when they will be administered	
4			
5	Interventions:	<a href="#">#11b</a> Criteria for discontinuing or modifying allocated interventions for a	n/a
6	modifications	given trial participant (eg, drug dose change in response to harms,	
7		participant request, or improving / worsening disease)	
8			
9	Interventions:	<a href="#">#11c</a> Strategies to improve adherence to intervention protocols, and any	n/a
10	adherence	procedures for monitoring adherence (eg, drug tablet return;	
11		laboratory tests)	
12	Interventions:	<a href="#">#11d</a> Relevant concomitant care and interventions that are permitted or	n/a
13	concomitant care	prohibited during the trial	
14			
15	Outcomes	<a href="#">#12</a> Primary, secondary, and other outcomes, including the specific	P10
16		measurement variable (eg, systolic blood pressure), analysis metric	
17		(eg, change from baseline, final value, time to event), method of	
18		aggregation (eg, median, proportion), and time point for each	
19		outcome. Explanation of the clinical relevance of chosen efficacy	
20		and harm outcomes is strongly recommended	
21	Participant timeline	<a href="#">#13</a> Time schedule of enrolment, interventions (including any run-ins	n/a
22		and washouts), assessments, and visits for participants. A	
23		schematic diagram is highly recommended (see Figure)	
24			
25	Sample size	<a href="#">#14</a> Estimated number of participants needed to achieve study	P11
26		objectives and how it was determined, including clinical and	
27		statistical assumptions supporting any sample size calculations	
28			
29	Recruitment	<a href="#">#15</a> Strategies for achieving adequate participant enrolment to reach	n/a
30		target sample size	
31			
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45	<b>Methods: Assignment</b>		
46	<b>of interventions (for</b>		
47	<b>controlled trials)</b>		
48			
49			
50	Allocation: sequence	<a href="#">#16a</a> Method of generating the allocation sequence (eg, computer-	n/a
51	generation	generated random numbers), and list of any factors for	
52		stratification. To reduce predictability of a random sequence,	
53		details of any planned restriction (eg, blocking) should be provided	
54		in a separate document that is unavailable to those who enrol	
55		participants or assign interventions	
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1	Allocation concealment	<a href="#">#16b</a>	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	n/a
2	mechanism			
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8	Allocation:	<a href="#">#16c</a>	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	n/a
9	implementation			
10				
11	Blinding (masking)	<a href="#">#17a</a>	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
12				
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16				
17	Blinding (masking):	<a href="#">#17b</a>	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
18	emergency unblinding			
19				
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21				
22	<b>Methods: Data</b>			
23	<b>collection,</b>			
24	<b>management, and</b>			
25	<b>analysis</b>			
26				
27				
28				
29	Data collection plan	<a href="#">#18a</a>	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	n/a
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39	Data collection plan:	<a href="#">#18b</a>	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	n/a
40	retention			
41				
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43				
44	Data management	<a href="#">#19</a>	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	P8
45				
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51	Statistics: outcomes	<a href="#">#20a</a>	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	P11
52				
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56	Statistics: additional	<a href="#">#20b</a>	Methods for any additional analyses (eg, subgroup and adjusted analyses)	n/a
57	analyses			
58				
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1	Statistics: analysis	<a href="#">#20c</a>	Definition of analysis population relating to protocol non-	n/a
2	population and missing		adherence (eg, as randomised analysis), and any statistical methods	
3	data		to handle missing data (eg, multiple imputation)	
4				
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6	<b>Methods: Monitoring</b>			
7				
8	Data monitoring:	<a href="#">#21a</a>	Composition of data monitoring committee (DMC); summary of its	n/a
9	formal committee		role and reporting structure; statement of whether it is independent	
10			from the sponsor and competing interests; and reference to where	
11			further details about its charter can be found, if not in the protocol.	
12			Alternatively, an explanation of why a DMC is not needed	
13				
14	Data monitoring:	<a href="#">#21b</a>	Description of any interim analyses and stopping guidelines,	n/a
15	interim analysis		including who will have access to these interim results and make	
16			the final decision to terminate the trial	
17				
18	Harms	<a href="#">#22</a>	Plans for collecting, assessing, reporting, and managing solicited	n/a
19			and spontaneously reported adverse events and other unintended	
20			effects of trial interventions or trial conduct	
21				
22	Auditing	<a href="#">#23</a>	Frequency and procedures for auditing trial conduct, if any, and	n/a
23			whether the process will be independent from investigators and the	
24			sponsor	
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33	<b>Ethics and</b>			
34	<b>dissemination</b>			
35				
36	Research ethics	<a href="#">#24</a>	Plans for seeking research ethics committee / institutional review	P11
37	approval		board (REC / IRB) approval	
38				
39				
40	Protocol amendments	<a href="#">#25</a>	Plans for communicating important protocol modifications (eg,	n/a
41			changes to eligibility criteria, outcomes, analyses) to relevant	
42			parties (eg, investigators, REC / IRBs, trial participants, trial	
43			registries, journals, regulators)	
44				
45				
46				
47	Consent or assent	<a href="#">#26a</a>	Who will obtain informed consent or assent from potential trial	P11
48			participants or authorised surrogates, and how (see Item 32)	
49				
50				
51	Consent or assent:	<a href="#">#26b</a>	Additional consent provisions for collection and use of participant	n/a
52	ancillary studies		data and biological specimens in ancillary studies, if applicable	
53				
54				
55	Confidentiality	<a href="#">#27</a>	How personal information about potential and enrolled participants	n/a
56			will be collected, shared, and maintained in order to protect	
57			confidentiality before, during, and after the trial	
58				
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1	Declaration of interests	<a href="#">#28</a>	Financial and other competing interests for principal investigators for the overall trial and each study site	P15
2				
3				
4				
5	Data access	<a href="#">#29</a>	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	n/a
6				
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10	Ancillary and post trial care	<a href="#">#30</a>	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
11				
12				
13				
14	Dissemination policy: trial results	<a href="#">#31a</a>	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	P12
15				
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20				
21	Dissemination policy: authorship	<a href="#">#31b</a>	Authorship eligibility guidelines and any intended use of professional writers	n/a
22				
23				
24	Dissemination policy: reproducible research	<a href="#">#31c</a>	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
25				
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28	<b>Appendices</b>			
29				
30				
31	Informed consent materials	<a href="#">#32</a>	Model consent form and other related documentation given to participants and authorised surrogates	n/a
32				
33				
34				
35	Biological specimens	<a href="#">#33</a>	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a
36				
37				
38				
39				

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# BMJ Open

## Intensive care with extracorporeal membrane oxygenation rewarming in accident severe hypothermia (ICE-CRASH) study: A protocol for a multicenter prospective, observational study in Japan

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Manuscript ID	bmjopen-2021-052200.R1
Article Type:	Protocol
Date Submitted by the Author:	15-Sep-2021
Complete List of Authors:	Takauji, Shuheji; Asahikawa Medical University Hospital, Department of Emergency Medicine Hayakawa, Mineji; Hokkaido University Hospital, Department of Emergency Medicine
<b>Primary Subject Heading</b>:	Emergency medicine
Secondary Subject Heading:	Intensive care
Keywords:	ACCIDENT & EMERGENCY MEDICINE, Adult intensive & critical care < INTENSIVE & CRITICAL CARE, Cardiology < INTERNAL MEDICINE

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3 1 **Title:** Intensive care with extracorporeal membrane oxygenation rewarming in accident severe  
4  
5 2 hypothermia (ICE-CRASH) study: A protocol for a multicenter prospective, observational  
6  
7 3 study in Japan  
8  
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12 5 **Authors and Institutions:** Shuhei Takauji<sup>1)</sup>, Mineji Hayakawa<sup>2)</sup>  
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1  
2  
3 **1 Abstract**  
4

5 **2 Introduction:** Accidental hypothermia (AH) is a rare but critical disease, leading to death in  
6  
7 severe cases. In recent decades, extracorporeal membrane oxygenation (ECMO) has been  
8  
9 successfully used to rewarm hypothermic patients with cardiac arrest or circulation instability.  
10  
11 However, data on the efficacy of rewarming using ECMO for patients with AH are limited.  
12  
13 Therefore, a large-scale, multicenter, prospective study is warranted. The primary objective of  
14  
15 this study will be to clarify the effectiveness of rewarming using ECMO for patients with AH.  
16  
17 Our secondary objectives will be to compare the incidence of adverse effects between ECMO  
18  
19 rewarming and non-ECMO rewarming and to identify the most appropriate management of  
20  
21 ECMO for AH.  
22  
23  
24

25  
26 **11 Methods and analyses:** The ICE-CRASH study is taking place in 35 tertiary emergency  
27  
28 medical facilities in Japan. The inclusion criteria are patients  $\geq 18$  years old with a body  
29  
30 temperature  $\leq 32$  °C. We will include patients with AH who present to the ED from December  
31  
32 2019 to March 2022. The research personnel at each hospital will collect several variables,  
33  
34 including patient demographics, rewarming method, ECMO data, and complications. Our  
35  
36 primary outcome is to compare the 28-day survival rate between the ECMO and non-ECMO  
37  
38 (other treatments) groups among patients with severe AH. Our secondary outcomes are to  
39  
40 compare the following values between the ECMO and non-ECMO groups: length of stay in  
41  
42 the intensive-care unit and complications. Furthermore, in patients with cardiac arrest, the CPC  
43  
44 score at discharge will be compared between both groups.  
45  
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49 **21 Ethics and dissemination:** This study received research ethics approval from Asahikawa  
50  
51 Medical University (18194 & 19115). The study was approved by the institutional review  
52  
53 board of each hospital, and the requirement for informed consent was waived due to the  
54  
55 observational nature of the study.  
56  
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58 **25 Trial registration number:** UMIN Clinical Trials Registry; UMIN000036132. Registered 1  
59  
60

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3 1 April 2019.  
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8 3 **Keywords:** accidental hypothermia, mortality, extracorporeal membrane oxygenation  
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10 4 (ECMO), complication,  
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For peer review only

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2  
3 **1 Strengths and limitations of this study**  
4

- 5  
6 2 1. This study will be the first large-scale, prospective study of ECMO rewarming for patients  
7  
8 3 suffering from accidental hypothermia (AH).  
9  
10 4 2. This study will evaluate the effectiveness of ECMO rewarming compared to non-ECMO  
11  
12 5 rewarming for hypothermic patients with cardiac arrest or circulatory instability.  
13  
14 6 3. This study will also collect blood samples to determine the relationship between coagulation  
15  
16 7 fibrinolysis and ECMO-related complications and identify optimal ECMO rewarming  
17  
18 8 management approaches for hypothermic patients.  
19  
20 9 4. However, this study is not a randomized trial, which means that the adjustment for  
21  
22 10 confounding factors is not complete.  
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## 1 Introduction

2 Accidental hypothermia (AH) is a rare condition but can be life-threatening in severe cases <sup>1 2</sup>.  
3 Thanks to technological advances over the past few decades, veno-arterial extracorporeal  
4 membrane oxygenation (V-A ECMO) has become a viable rewarming treatment for patients  
5 with severe hypothermia with cardiac arrest or severe circulatory instability <sup>3 4 5 6</sup>. Recently,  
6 the resuscitation guidelines from both the European Resuscitation Council and the American  
7 Heart Association have recommend the use of ECMO in AH patients with cardiac arrest <sup>7 8</sup>.  
8 However, there has been limited evidence concerning the utility of ECMO rewarming in  
9 patients with AH because of the low frequency of eligible patients. In addition, ethical  
10 implications restrict the utility of randomized controlled trials. Thus, previous studies on  
11 patients with AH rewarmed by ECMO have been case reports or single-center retrospective  
12 analyses <sup>4 5 6</sup>.

13 A recent study using the nationwide Japanese Diagnosis Procedure Combination  
14 inpatients database showed that V-A ECMO was associated with a higher survival rate and  
15 more favorable neurological outcomes than conventional cardiopulmonary resuscitation (CPR)  
16 alone in hypothermic patients with cardiac arrest <sup>9</sup>. However, this study has several issues. First,  
17 whether or not ECMO should be initiated in hypothermic patients with circulatory instability  
18 remains unclear. Second, this study did not clarify whether ECMO or other rewarming methods  
19 should be used in patients with AH. At present, there are no clinical guidelines on this point.  
20 Third, this study did not describe the complications associated with ECMO rewarming in  
21 hypothermic patients. The use of ECMO for hypothermic patients with noncardiac arrest is  
22 highly debatable, as ECMO is a highly invasive treatment with potentially serious  
23 complications <sup>5</sup>. Therefore, a large-scale, multicenter, prospective study is warranted to resolve  
24 these issues.

25

## 1 **Objectives**

2 The primary objective of this study will be to clarify the effectiveness of ECMO rewarming  
3 for hypothermic patients with cardiac arrest and those with unstable circulation. We  
4 hypothesized that the ECMO rewarming method is more beneficial in terms of survival than  
5 conventional rewarming methods. Our secondary objectives are to compare the incidence of  
6 adverse effects, such as bleeding, thrombosis, and infectious disease between ECMO  
7 rewarming and non-ECMO rewarming. Furthermore, in this study, we will collect blood  
8 samples and perform additional tests related to coagulation and fibrinolysis to investigate the  
9 relationship between bleeding or thrombotic complications and anticoagulant use.

10 The results will help identify the most appropriate management approach with ECMO  
11 for patients with AH.

12

## 1 **Methods and analyses**

### 2 *Study design and setting*

3 The Intensive Care with ExtraCorporeal membrane oxygenation Rewarming in Accidentally  
4 Severe Hypothermia (ICE-CRASH) study is a prospective, multicenter, observational study of  
5 patients with AH. The registry started in December 2019, with a planned three years of patient  
6 recruitment. The study is taking place at 35 tertiary emergency medical facilities that provide  
7 emergency and intensive care treatments to patients with AH in Japan.

### 8 *Eligibility criteria*

#### 9 • Inclusion criteria

10 The ICE-CRASH study consists of patients whose core body temperature measured at the  
11 emergency department (ED) is less than 32 °C. Investigators will enroll consecutive patients  
12  $\geq 18$  years old with AH, including those with cardiac arrest. We will include patients with AH  
13 who present to the ED from December 2019 to March 2022.

#### 14 • Exclusion criteria

15 The following patients will be excluded: patients  $< 18$  years old and those with cardiac arrest  
16 who are not eligible for resuscitation, according to the judgment of the emergency physician at  
17 each institution.

### 18 *Data collection and quality control*

19 A trained investigator or research assistant at each center will collect the following data: age,  
20 sex, any pre-existing conditions, activities of daily living (ADL), causes underlying the  
21 hypothermia, alcohol intake, anticoagulants, Charlson comorbidity index (CCI), Glasgow  
22 coma scale (GCS), Sequential Organ Failure Assessment (SOFA) score<sup>10</sup>, laboratory data,  
23  
24  
25

1  
2  
3 1 core body temperature, temperature measurement site, blood pressure, heart rate, respiratory  
4  
5 2 rate, electrocardiogram, cardiac arrest during pre-hospital, duration in the intensive-care unit  
6  
7 3 (ICU), length of hospital stay, mortality and Cerebral Performance Category (CPC) score at  
8  
9 4 discharge, event days (ventilator, renal replacement therapy, and catecholamine days), amount  
10  
11 5 of transfusion, and mortality at 28 days after admission (Table 1). The laboratory data consist  
12  
13 6 of the following: an arterial blood gas analysis, including the lactate level, blood count,  
14  
15 7 biochemical tests, and coagulation test. Measurement of the body temperature is based on the  
16  
17 8 core body temperature. If for some reason the core body temperature cannot be measured, the  
18  
19 9 peripheral body temperature will be measured, and data on the measurement site (bladder,  
20  
21 10 rectum, esophagus, axilla, and others) will be collected. These data will be recorded in the  
22  
23 11 electronic data capture system (NorthNet; <https://www.crmic-huhp.jp/northnet/edc/>).

24  
25 12 Rewarming methods will be divided into active external rewarming (warmed blanket  
26  
27 13 and warmed bath) and active internal rewarming (warmed fluid infusion, lavage, hemodialysis,  
28  
29 14 intravascular catheter, and extracorporeal membrane oxygenation [ECMO]). The selection of  
30  
31 15 the rewarming method will be decided based on the attending physician's judgement. When  
32  
33 16 rewarming using ECMO is selected, the registry will also record additional information  
34  
35 17 regarding ECMO as follows: the ECMO setting (venous-arterial or venous-venous), the size of  
36  
37 18 the ECMO cannula, the ECMO flow, presence of distal perfusion, usage and types of  
38  
39 19 anticoagulants, patient status at the start of ECMO (CPA or non-CPA), time from the scene  
40  
41 20 until ECMO initiation, duration using ECMO, and presence of weaning from ECMO.

42  
43 21 In addition, registry data will be collected concerning the incidence of complications  
44  
45 22 (ventricular fibrillation, bleeding, pneumonia, acute pancreatitis, acute kidney injury) and  
46  
47 23 complications due to ECMO (infection or thrombosis of cannula). Complications will include  
48  
49 24 events that occur within seven days after admission. Bleeding is defined as any amount  
50  
51 25 requiring a transfusion. Pneumonia is defined as an obvious shadow on chest radiography or  
52  
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2  
3 1 computed tomography (CT). Pancreatitis is defined as cases meeting at least two of the  
4  
5 2 following conditions: 1) abdominal pain, 2) elevation of pancreatic enzyme levels in the blood,  
6  
7 3 and 3) edema of the pancreas or peripancreatic effusion on ultrasound/CT. Acute kidney injury  
8  
9 4 is defined as acute kidney injury network (AKIN) classification stage  $\geq 2$ .

10  
11  
12 5 Furthermore, the ICE-CRASH study will collect blood samples from patients with AH  
13  
14 6 at each participating institution and perform additional tests related to coagulation and  
15  
16 7 fibrinolysis.  
17  
18  
19 8



## 1 **Outcomes**

2 Our primary outcome is the comparison of the survival rate between the ECMO and non-  
3 ECMO (other treatments) groups for severe hypothermic patients. Our secondary outcomes are  
4 to compare the CPC score at discharge between the ECMO and non-ECMO groups for  
5 hypothermic patients with cardiac arrest; to compare the incidence of complications  
6 (ventricular fibrillation, bleeding, thrombosis, pneumonia, acute pancreatitis, lower limb  
7 ischemia, acute kidney injury) between the ECMO and non-ECMO groups; and to clarify the  
8 relationship between the time to ECMO initiation and the prognosis in the ECMO group.

## 1 **Statistical plan**

### 2 *Sample size estimation*

3 The sample size was calculated based on similar previous studies <sup>4 5 6</sup>. Based on the results of  
4 previous retrospective observational studies, we assumed proportions of surviving patients at  
5 28 days after admission among hypothermic patients with cardiac arrest of 50% in the ECMO  
6 group and 15% in the non-ECMO group <sup>4 5</sup>. For a power of 80% and a type 1 error of 5%, the  
7 number of patients required is at least 33 in each group. Taking into account the sample of  
8 patients who dropped out during the process, the total number needed was calculated to be 70  
9 patients. Similarly, we assumed proportions of surviving patients at 28 days after admission  
10 among hypothermic patients with circulatory instability (non-cardiac arrest) of 85% in the  
11 ECMO group and 55% in the non-ECMO group <sup>5</sup>. Based on the same calculation, the number  
12 of patients required was determined to be at least 43 in each group, and the total number needed  
13 was calculated to be 90 patients.

14 This study is a registry study, so it will be conducted until at least March 2022, after  
15 which enrollment may continue in order to increase the number of cases.

### 17 *Statistical analyses*

18 Categorical variables will be presented as frequencies and percentages, and continuous  
19 variables will be presented as the means with the standard deviation or medians with the  
20 interquartile range (25<sup>th</sup> to 75<sup>th</sup> percentile). Intergroup comparisons will be carried out using  
21 Fisher's exact test for categorical data and the Mann-Whitney U test for continuous data. We  
22 will use propensity matching between the ECMO and non-ECMO groups to adjust for the  
23 patient background as much as possible for statistical analyses. We will then compare the  
24 survival rates of the ECMO and non-ECMO groups.

1  
2  
3 1 *Ethics and dissemination*  
4

5 2 This study will be conducted in accordance with the Declaration of Helsinki. It has received  
6  
7 3 research ethics approval from Asahikawa Medical University (18194 & 19115) and is  
8  
9 4 registered with the UMIN Clinical Trials Registry (UMIN000036132). It has also been  
10  
11 5 approved by the Ethics Committee of each participating hospital. The need for informed  
12  
13 6 consent will be waived due to the observational nature of the study. However, if blood samples  
14  
15 7 are collected for additional studies, written informed consent will be obtained from each patient  
16  
17 8 as appropriate.  
18  
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21 9 The results of the study will be disseminated to the participating hospitals, submitted to  
22  
23 10 peer-reviewed journals for publication, and presented at scientific congresses.  
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## 1 Discussion

2 Since the successful use of ECMO for AH with cardiac arrest has been reported, many studies  
3 have reported the efficacy of ECMO rewarming in patients with AH<sup>3 4 5 6</sup>. In recent years, the  
4 resuscitation guidelines from both the European Resuscitation Council and the American Heart  
5 Association have recommend the use of ECMO in AH patients with cardiac arrest<sup>7 8</sup>. However,  
6 at present, there are no global guidelines concerning the use of ECMO in AH patients with  
7 circulatory instability. The present findings may support the creation of guidelines concerning  
8 the use of ECMO in AH patients with circulatory instability.

9 Previous studies have shown that severe hypothermia inhibited the platelet function and  
10 coagulation<sup>11 12</sup>. However, few retrospective studies have focused on complications associated  
11 with ECMO usage, especially hemorrhagic and thrombotic complications. Thus, the incidence  
12 of these complications from using ECMO rewarming in patients with AH remains unclear. In  
13 this study, we will collect blood samples and perform additional coagulation and fibrinolysis  
14 tests to evaluate the relationship between thrombotic and bleeding complications during and  
15 after rewarming. These results may lead to the development of a new management approach  
16 for hypothermia specific to ECMO.

17 According to studies regarding extracorporeal resuscitation (ECPR) for out-of-hospital  
18 cardiopulmonary arrest patients, the longer it takes to initiate ECPR, the poorer the  
19 neurological prognosis<sup>13 14</sup>. However, this did not apply to patients with AH resulting in  
20 cardiac arrest<sup>15 16</sup>. A recent study showed that the parameter “un-witnessed cardiac arrest” was  
21 not associated with a worse outcome<sup>17</sup>. However, the maximum permissible time until the  
22 initiation of ECMO remains unclear. In the present study, we will collect data on the time to  
23 the initiation of ECMO and CPR to clarify the relationship between the time to ECMO and the  
24 prognosis. These results may provide evidence supporting the feasibility of long-distance  
25 transport for the introduction of ECMO for patients with AH in the future.

1  
2  
3 1 Furthermore, a recent retrospective study showed that a slower ECMO rewarming rate  
4  
5 2 was associated with a better survival rate<sup>18</sup>, while another study showed the opposite result<sup>19</sup>.  
6  
7  
8 3 The optimal ECMO rewarming rate thus remains unclear. The present study will collect data  
9  
10 4 associated with the ECMO rewarming rate. The results may help establish safer and more  
11  
12 5 optimal ECMO management methods for patients with severe hypothermia.  
13  
14  
15 6

16  
17 7 **Authors' contributions:**

18  
19 8 ST conceived and designed the ICE-CRASH study and is the principal investigator, MH  
20  
21 9 developed the study protocol. ST and MH drafted and revised the manuscript, and all authors  
22  
23  
24 10 critically reviewed the content and approved the final manuscript.  
25  
26  
27 11

28 12 **Funding statement:**

29  
30 13 This work was supported by the Japanese Association for Acute Medicine (Approval No.0005).  
31  
32  
33 14

34  
35 15 **Competing interests**

36  
37 16 None declared.  
38  
39  
40 17

41  
42 18 **Patient and public involvement**

43  
44 19 No patient or public involvement.  
45  
46  
47 20

48  
49 21 **Patient consent for publication**

50  
51 22 Not required  
52  
53  
54 23

55  
56 24 **Provenance and peer review**

57  
58 25 Not commissioned; externally peer reviewed.  
59  
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8

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Table 1. Variables collected in this study

Pre-hospital	In-hospital	Rewarming Time/Method	Outcome	Complications
Age, years	Core body temperature (measurement site)	Time required for rewarming	Length of ICU stay	Bleeding/thrombosis
Sex	GCS	Active external rewarming	Length of hospital stay	Pneumonia
Time from EMS alert to ED arrival	CPA or non-CPA	Warmed blanket	Mortality at discharge	Pancreatitis
Location (indoor or outdoor)	Blood pressure	Warmed bath	CPC score at discharge	Acute kidney injury
Causes underlying the hypothermia	Heart rate	Active internal rewarming	Event days	
ADL	ECG	Warmed fluid infusion	Ventilator	
Charlson comorbidity index	Respiratory rate	Lavage	Renal replacement therapy	
	Laboratory tests (blood counts, biochemical tests, and coagulation test)	Hemodialysis	catecholamine	
	Arterial blood gas analysis (including lactate)	Intravascular catheter	Transfusion	
	SOFA score	ECMO	Mortality at 28 days after admission	
		(Venous-Arterial or Venous-Venous, Cannula size, flow, distal perfusion, anticoagulant, time to initiate ECMO, duration, weaning)		

EMS, emergency medical service; ED, Emergency department; ADL, Activities of daily living; GCS, Glasgow Coma Scale; CPA, Cardiopulmonary Arrest; ECG, Electrocardiogram; SOFA, Sequential Organ Failure Assessment; ECMO, Extracorporeal membrane oxygenation; CPC, Cerebral Performance Category;

# Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

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		Reporting Item	Page Number
<b>Administrative information</b>			
Title	<a href="#">#1</a>	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	P1
Trial registration	<a href="#">#2a</a>	Trial identifier and registry name. If not yet registered, name of intended registry	P3
Trial registration: data set	<a href="#">#2b</a>	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	<a href="#">#3</a>	Date and version identifier	P3
Funding	<a href="#">#4</a>	Sources and types of financial, material, and other support	P14
Roles and responsibilities: contributorship	<a href="#">#5a</a>	Names, affiliations, and roles of protocol contributors	P14

1	Roles and	<a href="#">#5b</a>	Name and contact information for the trial sponsor	n/a
2	responsibilities:			
3	sponsor contact			
4	information			
5				
6				
7	Roles and	<a href="#">#5c</a>	Role of study sponsor and funders, if any, in study design;	n/a
8	responsibilities:		collection, management, analysis, and interpretation of data;	
9	sponsor and funder		writing of the report; and the decision to submit the report for	
10			publication, including whether they will have ultimate authority	
11			over any of these activities	
12				
13				
14				
15	Roles and	<a href="#">#5d</a>	Composition, roles, and responsibilities of the coordinating centre,	n/a
16	responsibilities:		steering committee, endpoint adjudication committee, data	
17	committees		management team, and other individuals or groups overseeing the	
18			trial, if applicable (see Item 21a for data monitoring committee)	
19				
20				
21				
22				
23	<b>Introduction</b>			
24				
25	Background and	<a href="#">#6a</a>	Description of research question and justification for undertaking	P5
26	rationale		the trial, including summary of relevant studies (published and	
27			unpublished) examining benefits and harms for each intervention	
28				
29				
30	Background and	<a href="#">#6b</a>	Explanation for choice of comparators	n/a
31	rationale: choice of			
32	comparators			
33				
34				
35	Objectives	<a href="#">#7</a>	Specific objectives or hypotheses	P6
36				
37				
38	Trial design	<a href="#">#8</a>	Description of trial design including type of trial (eg, parallel	P7
39			group, crossover, factorial, single group), allocation ratio, and	
40			framework (eg, superiority, equivalence, non-inferiority,	
41			exploratory)	
42				
43				
44				
45	<b>Methods:</b>			
46	<b>Participants,</b>			
47	<b>interventions, and</b>			
48	<b>outcomes</b>			
49				
50				
51	Study setting	<a href="#">#9</a>	Description of study settings (eg, community clinic, academic	n/a
52			hospital) and list of countries where data will be collected.	
53			Reference to where list of study sites can be obtained	
54				
55				
56				
57	Eligibility criteria	<a href="#">#10</a>	Inclusion and exclusion criteria for participants. If applicable,	P7
58			eligibility criteria for study centres and individuals who will	
59				
60				

		perform the interventions (eg, surgeons, psychotherapists)	
1			
2	Interventions:	<a href="#">#11a</a> Interventions for each group with sufficient detail to allow	P8
3	description	replication, including how and when they will be administered	
4			
5	Interventions:	<a href="#">#11b</a> Criteria for discontinuing or modifying allocated interventions for a	n/a
6	modifications	given trial participant (eg, drug dose change in response to harms,	
7		participant request, or improving / worsening disease)	
8			
9	Interventions:	<a href="#">#11c</a> Strategies to improve adherence to intervention protocols, and any	n/a
10	adherence	procedures for monitoring adherence (eg, drug tablet return;	
11		laboratory tests)	
12	Interventions:	<a href="#">#11d</a> Relevant concomitant care and interventions that are permitted or	n/a
13	concomitant care	prohibited during the trial	
14			
15	Outcomes	<a href="#">#12</a> Primary, secondary, and other outcomes, including the specific	P10
16		measurement variable (eg, systolic blood pressure), analysis metric	
17		(eg, change from baseline, final value, time to event), method of	
18		aggregation (eg, median, proportion), and time point for each	
19		outcome. Explanation of the clinical relevance of chosen efficacy	
20		and harm outcomes is strongly recommended	
21	Participant timeline	<a href="#">#13</a> Time schedule of enrolment, interventions (including any run-ins	n/a
22		and washouts), assessments, and visits for participants. A	
23		schematic diagram is highly recommended (see Figure)	
24			
25	Sample size	<a href="#">#14</a> Estimated number of participants needed to achieve study	P11
26		objectives and how it was determined, including clinical and	
27		statistical assumptions supporting any sample size calculations	
28			
29	Recruitment	<a href="#">#15</a> Strategies for achieving adequate participant enrolment to reach	n/a
30		target sample size	
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45	<b>Methods: Assignment</b>		
46	<b>of interventions (for</b>		
47	<b>controlled trials)</b>		
48			
49			
50	Allocation: sequence	<a href="#">#16a</a> Method of generating the allocation sequence (eg, computer-	n/a
51	generation	generated random numbers), and list of any factors for	
52		stratification. To reduce predictability of a random sequence,	
53		details of any planned restriction (eg, blocking) should be provided	
54		in a separate document that is unavailable to those who enrol	
55		participants or assign interventions	
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1	Allocation concealment	<a href="#">#16b</a>	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	n/a
2	mechanism			
3				
4				
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8	Allocation:	<a href="#">#16c</a>	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	n/a
9	implementation			
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11	Blinding (masking)	<a href="#">#17a</a>	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
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17	Blinding (masking):	<a href="#">#17b</a>	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
18	emergency unblinding			
19				
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22	<b>Methods: Data</b>			
23	<b>collection,</b>			
24	<b>management, and</b>			
25	<b>analysis</b>			
26				
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29	Data collection plan	<a href="#">#18a</a>	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	n/a
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39	Data collection plan:	<a href="#">#18b</a>	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	n/a
40	retention			
41				
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43				
44	Data management	<a href="#">#19</a>	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	P8
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51	Statistics: outcomes	<a href="#">#20a</a>	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	P11
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56	Statistics: additional	<a href="#">#20b</a>	Methods for any additional analyses (eg, subgroup and adjusted analyses)	n/a
57	analyses			
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1	Statistics: analysis	<a href="#">#20c</a>	Definition of analysis population relating to protocol non-	n/a
2	population and missing		adherence (eg, as randomised analysis), and any statistical methods	
3	data		to handle missing data (eg, multiple imputation)	
4				
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6	<b>Methods: Monitoring</b>			
7				
8	Data monitoring:	<a href="#">#21a</a>	Composition of data monitoring committee (DMC); summary of its	n/a
9	formal committee		role and reporting structure; statement of whether it is independent	
10			from the sponsor and competing interests; and reference to where	
11			further details about its charter can be found, if not in the protocol.	
12			Alternatively, an explanation of why a DMC is not needed	
13				
14	Data monitoring:	<a href="#">#21b</a>	Description of any interim analyses and stopping guidelines,	n/a
15	interim analysis		including who will have access to these interim results and make	
16			the final decision to terminate the trial	
17				
18	Harms	<a href="#">#22</a>	Plans for collecting, assessing, reporting, and managing solicited	n/a
19			and spontaneously reported adverse events and other unintended	
20			effects of trial interventions or trial conduct	
21				
22	Auditing	<a href="#">#23</a>	Frequency and procedures for auditing trial conduct, if any, and	n/a
23			whether the process will be independent from investigators and the	
24			sponsor	
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28	<b>Ethics and</b>			
29	<b>dissemination</b>			
30				
31	Research ethics	<a href="#">#24</a>	Plans for seeking research ethics committee / institutional review	P11
32	approval		board (REC / IRB) approval	
33				
34	Protocol amendments	<a href="#">#25</a>	Plans for communicating important protocol modifications (eg,	n/a
35			changes to eligibility criteria, outcomes, analyses) to relevant	
36			parties (eg, investigators, REC / IRBs, trial participants, trial	
37			registries, journals, regulators)	
38				
39	Consent or assent	<a href="#">#26a</a>	Who will obtain informed consent or assent from potential trial	P11
40			participants or authorised surrogates, and how (see Item 32)	
41				
42	Consent or assent:	<a href="#">#26b</a>	Additional consent provisions for collection and use of participant	n/a
43	ancillary studies		data and biological specimens in ancillary studies, if applicable	
44				
45	Confidentiality	<a href="#">#27</a>	How personal information about potential and enrolled participants	n/a
46			will be collected, shared, and maintained in order to protect	
47			confidentiality before, during, and after the trial	
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1	Declaration of interests	<a href="#">#28</a>	Financial and other competing interests for principal investigators for the overall trial and each study site	P15
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4	Data access	<a href="#">#29</a>	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	n/a
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10	Ancillary and post trial care	<a href="#">#30</a>	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
11				
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14	Dissemination policy: trial results	<a href="#">#31a</a>	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	P12
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21	Dissemination policy: authorship	<a href="#">#31b</a>	Authorship eligibility guidelines and any intended use of professional writers	n/a
22				
23				
24	Dissemination policy: reproducible research	<a href="#">#31c</a>	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
25				
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28	<b>Appendices</b>			
29				
30				
31	Informed consent materials	<a href="#">#32</a>	Model consent form and other related documentation given to participants and authorised surrogates	n/a
32				
33				
34	Biological specimens	<a href="#">#33</a>	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a
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