Supplementary Appendix

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This appendix has been provided by the authors to give readers additional information about the work.

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INCEPTION investigators

Martje M. Suverein, M.D.	Department of Intensive Care, Maastricht University Medical Center, Maastricht, the Netherlands
Thijs S.R. Delnoij, M.D.	Department of Intensive Care, Maastricht University Medical Center, Maastricht, the Netherlands
Roberto Lorusso, M.D., Ph.D.	Department of Cardiothoracic Surgery, Maastricht University Medical Center, Maastricht, the Netherlands
George J. Brandon Bravo Bruinsma, M.D., Ph.D.	Department of Cardiothoracic Surgery, Isala Clinics, Zwolle, the Netherlands
Luuk Otterspoor, M.D., Ph.D.	Department of Intensive Care, Catharina Hospital, Eindhoven, the Netherlands
Carlos V. Elzo Kraemer, M.D., Ph.D.	Department of Intensive Care, Leiden University Medical Center, Leiden, the Netherlands
Alexander P.J. Vlaar, M.D., Ph.D.	Department of Intensive Care, Amsterdam University Medical Center location AMC, Amsterdam, the Netherlands
Joris J. van der Heijden, M.D.	Department of Intensive Care, University Medical Center Utrecht, Utrecht, the Netherlands
Erik Scholten, M.D.	Department of Intensive Care, St. Antonius Hospital, Nieuwegein, the Netherlands
Corstiaan den Uil, M.D., Ph.D.	Department of Intensive Care, Erasmus Medical Center, Rotterdam, the Netherlands
Tim Jansen, M.D., Ph.D.	Department of Intensive Care, Haga Hospital, Den Hague, the Netherlands
Bas van den Bogaard, M.D., Ph.D.	Department of Intensive Care, OLVG, Amsterdam, the Netherlands
Marijn Kuijpers, M.D.	Department of Intensive Care, Isala Clinics, Zwolle, the Netherlands
Ka Yan Lam, M.D.	Department of Cardiothoracic Surgery, Catharina Hospital, Eindhoven, the Netherlands
José M. Montero Cabezas, M.D.	Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands

Antoine H.G. Driessen, M.D., Ph.D.	Department of Cardiothoracic Surgery, Amsterdam University Medical Center location AMC, Amsterdam, the Netherlands
Saskia Z.H. Rittersma, M.D., Ph.D.	Department of Cardiology, University Medical Center Utrecht, Utrecht, the Netherlands
Bram G. Heijnen, M.D.	Department of Intensive Care, St. Antonius Hospital, Nieuwegein, the Netherlands
Dinis Dos Reis Miranda, M.D., Ph.D.	Department of Intensive Care, Erasmus Medical Center, Rotterdam, the Netherlands
Gabe Bleeker, M.D., Ph.D.	Department of Cardiology, Haga Hospital, Den Hague, the Netherlands
Jesse de Metz, M.D., Ph.D.	Department of Intensive Care, OLVG, Amsterdam, the Netherlands
Renicus S. Hermanides, M.D., Ph.D.	Department of Cardiology, Isala Clinics, Zwolle, the Netherlands
Jorge Lopez Matta, M.D.	Department of Intensive Care, Leiden University Medical Center, Leiden, the Netherlands
Susanne Eberl, M.D., Ph.D.	Department of Anesthesia, Amsterdam University Medical Center location AMC, Amsterdam, the Netherlands
Dirk W. Donker, M.D., Ph.D.	Cardiovascular and Respiratory Physiology, TechMed Center, University of Twente, Enschede, the Netherlands Department of Intensive Care, University Medical Center Utrecht, Utrecht, the Netherlands
Robert J. van Thiel, M.D.	Department of Intensive Care, Erasmus Medical Center, Rotterdam, the Netherlands
Sakir Akin, M.D., Ph.D.	Department of Intensive Care, Haga Hospital, Den Hague, the Netherlands
Oene van Meer, M.D.	Department of Emergency Medicine, Leiden University Medical Center, Leiden, the Netherlands
José Henriques, M.D., Ph.D.	Department of Cardiology, Amsterdam University Medical Center location AMC, Amsterdam, the Netherlands
Karen C. Bokhoven, M.D.	Department of Intensive Care, Erasmus Medical Center, Rotterdam, the Netherlands

Loes Mandigers, M.D.	Department of Intensive Care, Erasmus Medical Center, Rotterdam, the Netherlands
Jeroen J.H. Bunge, M.D.	Department of Intensive Care, Erasmus Medical Center, Rotterdam, the Netherlands Department of cardiology, Thorax Center, Erasmus University Medical Center Rotterdam, the Netherlands
Martine E. Bol,	Department of Intensive Care, Maastricht University Medical Center, Maastricht, the Netherlands
Bjorn Winkens, Ph.D.	Department of Methodology & Statistics, Maastricht University, Maastricht, the Netherlands Care and Public Health Research Institute, Maastricht University, Maastricht, the Netherlands
Brigitte Essers, Ph.D.	Department of Clinical Epidemiology and Medical Technical Assessment, Maastricht University Medical Center, Maastricht, the Netherlands
Patrick W. Weerwind, CCP, Ph.D.	Department of Cardiothoracic Surgery, Maastricht University Medical Center, Maastricht, the Netherlands
Jos G. Maessen, M.D., Ph.D.	Department of Cardiothoracic Surgery, Maastricht University Medical Center, Maastricht, the Netherlands Cardiovascular Research Institute Maastricht, Maastricht University, Maastricht, the Netherlands
Marcel C.G. van de Poll, M.D., Ph.D.	Department of Intensive Care, Maastricht University Medical Center, Maastricht, the Netherlands School for Nutrition and Translational Research in Metabolism, Maastricht University, Maastricht, the Netherlands

Writing committee:

M.M. Suverein, M.C.G. van de Poll, B. Winkens.

Trial steering committee:

M.C.G. van de Poll, J.G. Maessen, R. Lorusso, P.W. Weerwind, T.S.R. Delnoij, M.M. Suverein.

Data Safety Monitoring Board

Chair of the DSMB

Dr. D.A. van Waardenburg, Head of the Pediatric Intensive Care Unit at Maastricht University Medical Center, Maastricht, the Netherlands.

Members

Dr. J. Vainer, interventional cardiologist, interventional cardiologist at Maastricht University Medical Center, Maastricht, the Netherlands.
Dr. S. van Kuijk, clinical epidemiologist, Clinical Epidemiology & Medical Technology Assessment (KEMTA), Maastricht University Medical Center, Maastricht, the Netherlands.

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Legal and ethical considerations

Legal considerations

The study was performed in accordance with the Dutch law on Medical Research Involving Human Subjects (WMO), issued on February 26th, 1998, most recently revised on July 1st, 2022. The legal frameworks for the informed consent process are described in Article 6.[1] The basic principle is that a patient can only participate in medical research after written informed consent by the patient themselves or a legal representative when under-aged or incapacitated (proxy consent). Moreover, a reflection period before providing informed consent is mandatory to carefully consider the burden, risks, and benefits of study participation. Consequently, obtaining informed consent is a process that warrants care and time under normal circumstances.

During emergencies, there is no time to adhere to the abovementioned principles and study actions may be initiated without prior consent under strict regulations as outlined in the WMO article 6, paragraph 4. The primary prerequisite to obtaining permission for such deferred consent is that the patient suffering from a medical emergency may benefit from study participation. When deferred consent is allowed, study actions may be initiated and continued until circumstances prohibiting a thorough informed consent procedure have been resolved. After which, (proxy) informed consent should be sought without undue delay.

In emergency research – and particularly in resuscitation research – the situation may arise where a patient entered in a study by deferred consent passes away before (proxy) informed consent could be sought. Under Dutch law, there is no obligation to obtain proxy consent to use study data from these patients after their passing since legal representation ends after death. The Central Committee on Research Involving Human Subjects has issued a memorandum “flowcharts deferred consent for medical research in emergency situations,” which is used as a practical guideline to deal with issues where legislation is not conclusive.

Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki and approved by the joint institutional committee on ethics of human investigation of the University Hospital Maastricht and Maastricht University.

Randomization and deferred consent

Fundamental to the study design was the absolute uncertainty whether the broad implementation of extracorporeal CPR (ECPR) in out-of-hospital cardiac arrest (OHCA) would lead to better, worse, or unaltered outcomes compared to usual care, the sole application of conventional CPR. Based on the available literature, we hypothesized that ECPR could lead to better outcomes and that patients could potentially benefit from study participation, particularly when assigned to ECPR. The true equipoise underlying the study and the potential benefit of study participation were prerequisites to obtain permission to apply a randomized study design and a deferred consent procedure.

Timing of proxy consent

In resuscitation research, study participants often remain incapacitated for a prolonged time, meaning proxy consent is accepted as the standard procedure. As mentioned above, the law (WMO) clearly states that after application of deferred consent, (proxy) informed consent should be sought without undue delay after resolving circumstances prohibiting a thorough informed consent procedure. However, the question of when these circumstances actually have been resolved, is not unequivocally answered when there is an acute life-threatening condition. A prerequisite of the informed consent process is that the researcher seeking consent from the proxy must be convinced that the provided information is fully understood. However, during the acute phase of critical illness, it is very probable that relatives and other next-of-kin are emotionally overwhelmed by the sudden life-threatening situation of their loved one and are unable to engage in a conversation about study participation or are unable or unwilling to consider the information provided rationally. Despite resolving the actual medical emergency that initially warranted the deferred consent procedure, these circumstances may prohibit a thorough informed consent procedure. This notion has also been acknowledged by the Central Committee on Research Involving Human Subjects in their abovementioned memorandum that states that it is “acceptable, in cases where the legal representatives are not immediately approachable due to the acute situation, to give them some time to get used to the situation of their relative.”

In our study, the earliest appropriate moment to engage in the proxy consent procedure was left to the personal judgment of the local study coordinators in consultation with the attending physicians with a maximum period of seven days. Members of the study team performed all informed consent conversations. In all cases, where subjects regained consciousness at any point in time, confirmation of the proxy consent was sought from the subject self.

Use of data of subjects deceased prior to informed consent

Given the high initial mortality of refractory cardiac arrest, we anticipated a very high proportion of patients that would come to pass away before proxy consent could be obtained. Since legal representation ends after death, there is no legal obligation to ask permission from relatives or next of kin to use study data. In addition, from a methodological point of view, it is very undesirable to exclude patients who die early during study participation since this could lead to bias and incorrect conclusions. However, the Central Committee on Research Involving Human Subjects emphasizes the importance of transparency and ethical awareness and warrants informing the relatives or next-of-kin about study participation and the importance of using the data for the proper completion of the study. Although from a legal standpoint, the objection of relatives or next-of-kin to use data from deceased subjects may be ignored, The Central Committee suggests “depending on the circumstances - consider honoring this objection.”

Fully agreeing with this notion, we dedicated ourselves to informing the next-of-kin of study participants who died before proxy consent could be sought to the best of our abilities, particularly for patients who died immediately after inclusion due to an unsuccessful resuscitation attempt. Information provided in the latter situation differs substantially from patients dying after hospital admission since there is customarily only one conversation with relatives or next-of-kin in these very early deaths. In this brief interaction, the sudden, unexpected death of a loved one is announced,

almost invariably leaving the relatives devastated and unable to receive and process any other information whatsoever. Nonetheless, study information had to be provided during this highly emotional conversation. Since patients could be admitted 24 hours a day and a study team member was not always present at the time of the family conversation, all resuscitation team leaders, who could encounter an eligible patient, were trained to provide minimal essential information during the conversation with the relatives or next-of-kin. This minimal essential information included the announcement of study participation and a brief description of both study arms. All relatives were given a letter containing information about the study, a telephone number of the study coordinator, and an invitation for a follow-up appointment after three months. It was emphasized that both ECPR and conventional CPR are applied as standard care in varying settings and that the subject had not been exposed to “experimental medicine.” Finally, it was emphasized that there was true equipoise between both arms.

System description

The trial included 12 of the 25 ambulance regions in the Netherlands:

- RAV Zuid Limburg (region 24)
- RAV IJsselland (region 4)
- RAV Brabant-Zuidoost (region 22)
- RAV Utrecht (region 9)
- Ambulance Rotterdam-Rijnmond (region 17)
- RAV Haaglanden - Witte Kruis Haaglanden (region 15)
- RAV Hollands Midden (region 16)
- RAV Amsterdam-Amstelland (region 11)
- RAV Zaanstreek-Waterland (region 13)
- RAV Kennemerland - Witte Kruis Kennemerland (region 12)
- RAV Gooi en Vechtstreek (region 14)
- RAV Flevoland (region 25)

These ambulance services serve a mix of urban and rural locations in the Netherlands, covering 8.5 million people over an area of 9,572 km^2. Approximately 4,000 cardiac arrests per year are attended by the ambulance service in a region of this size in the Netherlands.

The Ambulance Services activate through the national emergency number (112) which directs the caller to the geographically relevant dispatch center. Calls are received and processed by trained personnel.

The Netherlands has a two-tiered emergency medical service system: the first tier includes first responders (i.e., police, firefighters) equipped with automated external defibrillators, the second tier includes two ambulances, each staffed with a driver with CPR skills and a paramedic who is competent to administer advanced life support according to European Resuscitation Guidelines. Cases identified as cardiac arrest are assigned the highest priority response (A1), and two ambulances are dispatched simultaneously. In most of the participating regions ambulances are equipped with automatic chest compression devices. Thirdly, there is a nation-spanning network of trained volunteers (HartslagNu) who are alerted if a cardiac arrest is nearby via SMS or a smartphone app. Some of these nearby volunteers are instructed to go to the nearest AED that are widely accessible in public spaces and others proceed directly to the location of the arrest. In December 2021, 1.4% of the population in the Netherlands was actively connected to this network (245.000 people on a population of 17.591.045).[2,3] Apart from this network, a high proportion of Dutch residents are BLS-trained.

The Dutch Heart Association (Hartstichting) pooled all national data in 2016 and found an overall survival rate in the Netherlands after out-of-hospital cardiac arrest is 23%. For patients with an initially shockable rhythm, the survival rate is 44%.[4]

There are 16 centers for cardiothoracic surgery in the Netherlands, together performing 15,000 cardiac surgeries per year. Of these 16 centers, 10 participated in this trial. All centers are

experienced in cannulating and managing veno-arterial extracorporeal membrane oxygenation in hemodynamically compromised patients. The original trial consortium consisted of one university hospital (Maastricht University Medical Centre) and two large teaching hospitals in the Netherlands (Catharina Hospital Eindhoven and Isala Clinics Zwolle). After public presentation of the trial protocol, the consortium was expanded to include seven additional hospitals (Amsterdam University Medical Centre, Leiden University Medical Centre, University Medical Centre Utrecht, Haga Hospital Den Haag, OLVG Hospital Amsterdam, Erasmus MC University Rotterdam, and St. Antonius Hospital Nieuwegein).

Figure S1. Enrollment duration per participating center

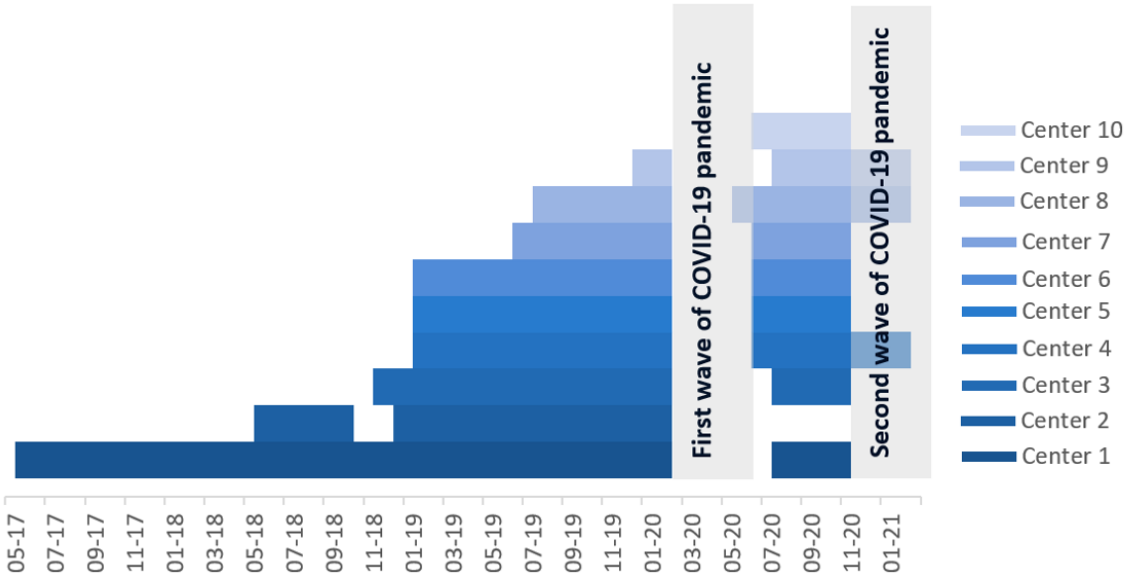

Figure S1. Enrollment duration per participating center.

Each bar indicates active enrollment of patients. All centers paused inclusion during the first wave of the COVID-19 pandemic; some centers continued to enroll patients during the second wave of the COVID-19 pandemic. The bars do not represent the number of patients enrolled per site.

Figure S2. Sample screening flowchart of five participating hospitals

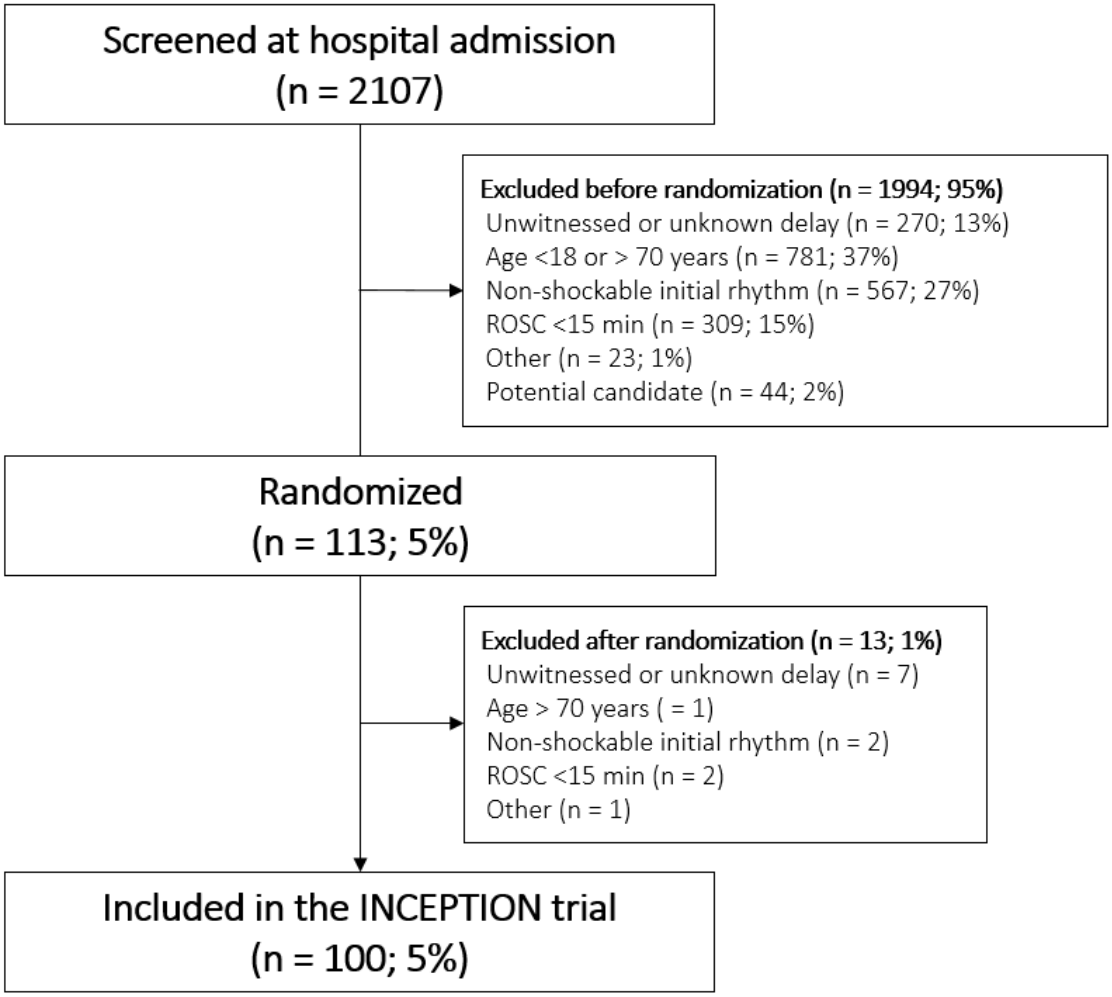

Figure S2. Sample screening flowchart of five participating hospitals

The study flow chart that includes data from 5 of 10 centers in the study shows the screening, exclusion, randomization, and exclusion after randomization for INCEPTION patients. Potential candidates denotes individuals that fulfilled inclusion criteria but were not included due to logistical reasons (e.g., team unavailable) or because an eligible patient was not recognized during screening due to misinterpretation of selection criteria.

ROSC denotes return of spontaneous resuscitation.

Figure S3. Survival with a favorable neurologic outcome at 30 days

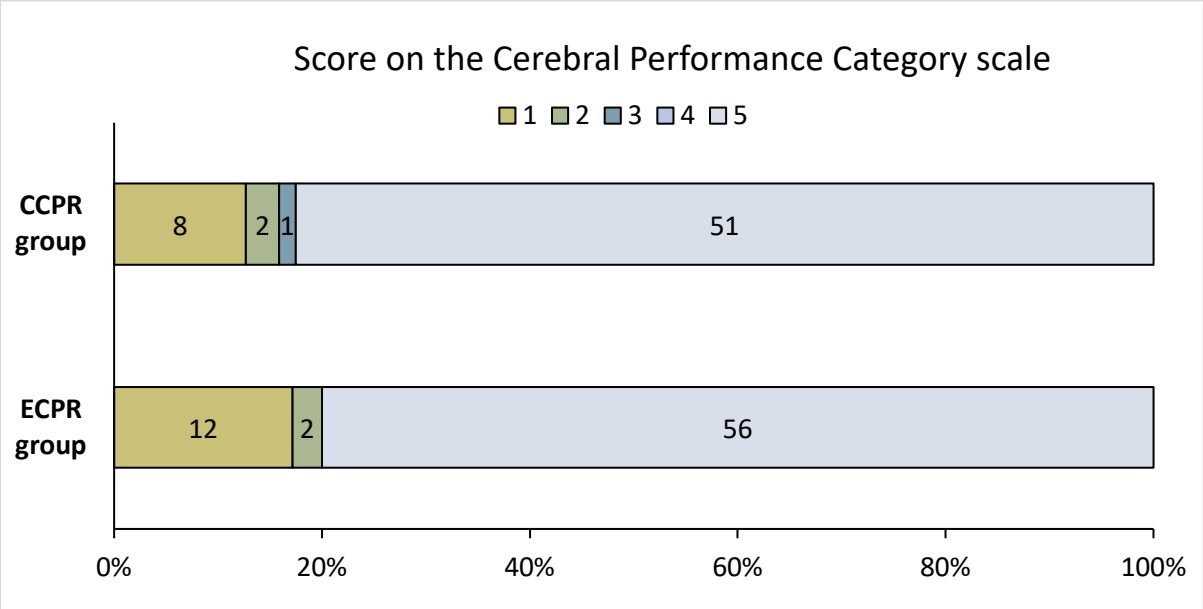

Figure S3. Survival with a favorable neurologic outcome at 30 days

The distribution of patients' scores on the Cerebral Performance Category scale, which ranges from 0 (no symptoms) to 5 (death). Survival at 30 days with a favorable neurologic outcome, as indicated by a score of 1 or 2, occurred in 14 of 70 patients (20%) in the extracorporeal CPR group (ECPR) and in 10 of 62 patients (16%) in the conventional CPR (CCPR) group. The patients who died within 30 days are indicated by a score of 5 on the scale.

Figure S4. Patient flow during the trial from recruitment to hospital discharge

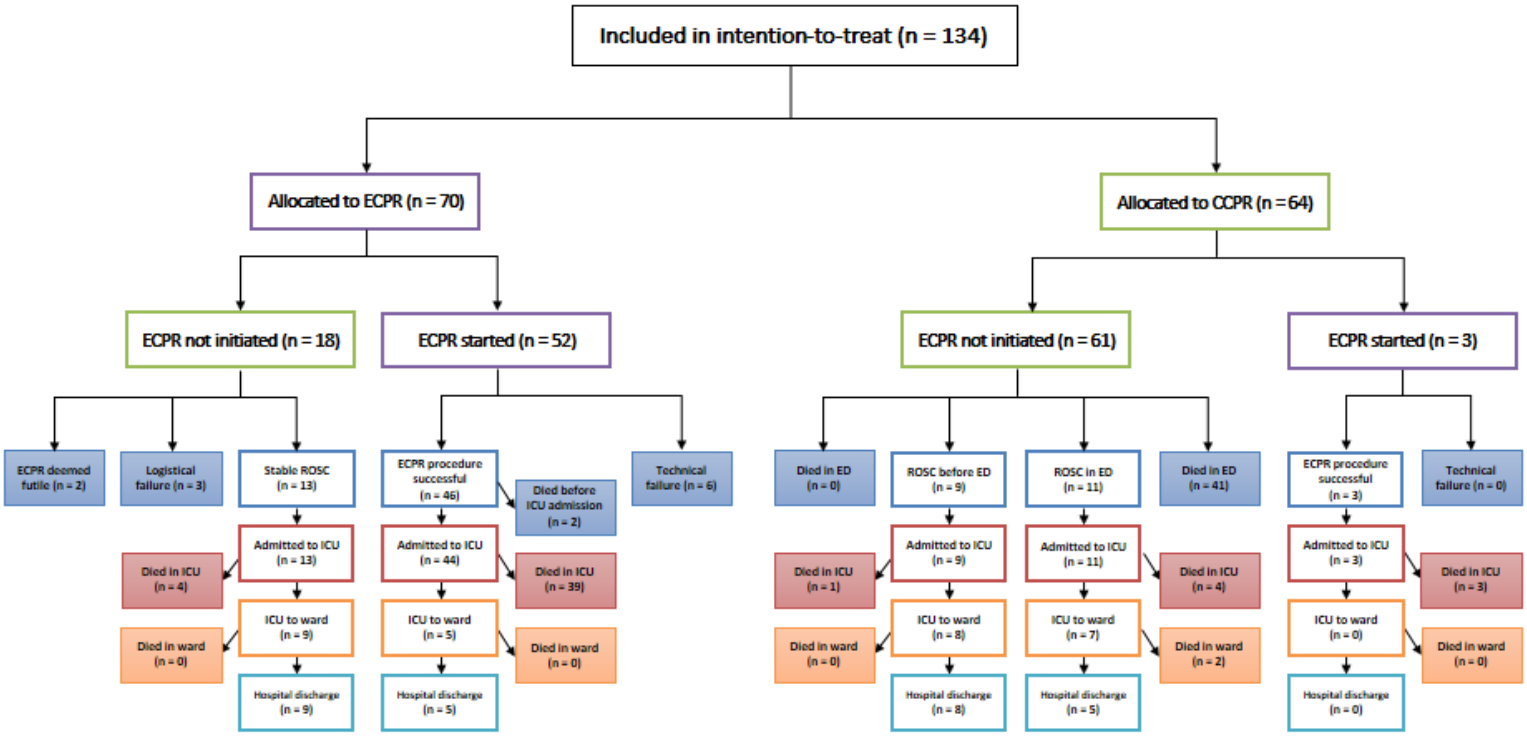

Figure S4. Patient flow during the trial from recruitment to hospital discharge

The study flow chart demonstrates enrollment, treatment allocation and outcomes of INCEPTION patients from the start to the end of the study.

CCPR denotes conventional cardiopulmonary resuscitation, ECPR extracorporeal cardiopulmonary resuscitation, ED emergency department, ICU intensive care unit, ROSC return of spontaneous circulation.

Table S1. Inclusion and exclusion criteria

INCLUSION CRITERIA	EXCLUSION CRITERIA
Age ≥ 18 - ≤ 70 years	ROSC within 15 minutes of conventional CPR with sustained hemodynamic recovery
Witnessed OHCA (by bystanders)	Terminal heart failure (NYHA III or IV)
Initial rhythm of VF/VT or AED administered	Severe pulmonary disease (COPD GOLD stage III or IV)
Bystander BLS	Disseminated oncological disease
	Obvious or suspected pregnancy
	Bilateral femoral bypass surgery
	Known contraindications for extracorporeal CPR
	Known pre-arrest CPC score 3 or 4
	Known Advanced Directive
	Multi-trauma (Injury Severity Score > 15) *
	Expected time-to-start cannulation > 60 min **

AED denotes automated external defibrillator, COPD GOLD chronic obstructive pulmonary disease Global Initiative for Chronic Obstructive Lung Disease, CPC Cerebral Performance Category, NYHA New York Heart Association, OHCA out-of-hospital cardiac arrest, ROSC return of spontaneous circulation, VF/VT ventricular fibrillation/ventricular tachycardia.

* The Injury Severity Score standardizes the severity of traumatic injury for patients with multiple injuries for 6 body regions. The highest score in each body region is used. The score ranges from 0 to 75. Scores above 15 are classified as severe.

** Expected time-to-start cannulation of more than 60 minutes from the start of the cardiac arrest.

Table S2. Center description

Table S2. Center description				
	Number of patients	**Median time to ECMO flow (min)**	**Location of Extracorporeal CPR**	**Cannulation**
Center 1	43	66 (44-75)	Emergency department	Cardiothoracic surgeon
Center 2	10	95 *	Cath lab	Cardiothoracic surgeon, Interventional cardiologist
Center 3	14	63 (37-80)	Cath lab	Interventional cardiologist
Center 4	13	77 (36-89)	Emergency department	Cardiothoracic surgeon
Center 5	6	43 **	Cath lab	Interventional cardiologist
Center 6	3	41 *	Emergency department	Cardiothoracic surgeon, Intensivist
Center 7	8	53 (25-108)	Cath lab	Interventional cardiologist
Center 8	32	69 (54-75)	Emergency department	Intensivist
Center 9	3	69 *	Cath lab	Cardiothoracic surgeon
Center 10	1	NA	Emergency department	Cardiothoracic surgeon, Intensivist

ECMO denotes extracorporeal membrane oxygenation.

* n = 1

** n = 2 (18 and 68 minutes)

Table S3. Prespecified secondary objectives

Table S3. Overview of prespecified secondary objectives and if applicable reason for not including in the manuscript.	
Prespecified secondary objectives	**Reason for not including in this manuscript**
Outcome evaluation	
Does ECPR improve the neurological outcome at 30 days, 3 months, 6 months and 12 months on the CPC scale?	30-day, 3- and 6-month outcome is reported in this manuscript. 12-month outcome is being collected and analyzed and will be reported separately.
Does ECPR improve the amount of Quality Adjusted Life Years (QALY's) at 30 days, 3 months, 6 months and 12 months?	Will be reported in a future publication.
Is there a difference in reason for discontinuation of treatment between the treatment groups?	Reported in this manuscript.
What is the time to return of circulation?	Reported in this manuscript.
Economic evaluation	
What are the additional costs of ECPR with respect to CCPR?	Will be reported in a future publication.
What are the costs per gained QALY for ECPR vs. CCPR?	Will be reported in a future publication.
Temporal evaluation	
Is there a difference in length of stay at the ICU between the treatment groups?	Reported in this manuscript.
Is there a difference in length of stay at the hospital between the treatment groups?	Reported in this manuscript.
Is there a difference in the duration of clinical rehabilitation time?	Very few patients underwent clinical rehabilitation; sample size too small for data analysis.
Organ support evaluation	
Is there a difference in the duration of mechanical ventilation between treatment groups?	Reported in this manuscript.
Is there a difference in need for renal replacement therapy between the treatment groups?	Reported in this manuscript.
Is there a difference in acute kidney injury according to the RIFLE criteria?	Reported in this manuscript.
Is there a difference in time to target hypothermia between the treatment groups?	Too many missing values for publication.
Metabolic evaluation	
Is there a difference in metabolic markers such as (1) pH, (2) etCO2, (3) ScVO2 and (4) lactate at arrival at the ED, right after initialization of circulation (either by ROSC or ECPR), 1, 2, 3, 4, 5 and 6 hours after return of circulation and at 1, 2, 3, 4, 5 and 6 days after the OHCA between the treatment groups?	Lactate is reported in this manuscript: pH, etCO2, ScVO2 have too many missing values for publication.

Is there a difference in metabolic markers such as (1) pH, (2) etCO2, (3) ScVO2 and (4) lactate at arrival at the ED, right after initialization of circulation (either by ROSC or ECPR), 1, 2, 3, 4, 5 and 6 hours after return of circulation and at 1, 2, 3, 4, 5 and 6 days after the OHCA between the survivors and non-survivors?	Will be reported in a future publication.
Subgroup analyses	
Sex, women/men	Will be reported in a future publication.
Age	Will be reported in a future publication.
As-treated analysis	Will be reported in a future publication.
Per-protocol analysis	Will be reported in a future publication.

CCPR denotes conventional CPR, CPC Cerebral Performance Category, ECPR extracorporeal cardiopulmonary resuscitation, ECMO extracorporeal membrane oxygenation, ED emergency department, EtCO2 end-tidal carbon dioxide, OHCA out-of-hospital cardiac arrest, ROSC return of spontaneous circulation, ScVO2 central venous oxygen saturation.

Table S4. Prehospital characteristics and treatments

Table S4. Prehospital characteristics and treatments				
Characteristics	**Patients with data**	**Extracorporeal CPR (n = 70)**	**Patients with data**	**Conventional CPR (n = 64)**
Witnessed by civilians – no. (%)	70	57 (81)	62	55 (89)
Witnessed by first responders – no. (%)	70	4 (6)	62	1 (2)
Witnessed by EMS – no. (%)	70	9 (13)	62	5 (8)
BLS started by civilians – no. (%)	70	48 (69)	62	40 (65)
BLS started by first responders– no. (%)	70	7 (10)	62	9 (15)
BLS started by medical professional – no. (%)	70	6 (9)	62	3 (5)
BLS started by EMS – no. (%)	70	9 (13)	62	10 (16)
AED used – no. (%)	68	36 (53)	64	40 (63)
Number of AED shocks	36	1.7±1.1	39	1.9±0.9
Epinephrine dose – mg	63	9±4	60	9±4
Amiodarone dose – mg	70	321±193	62	346±162
Transport distance – km	68	17±10	63	16±11
Mask ventilation – no. (%)	69	9 (13)	63	5 (8)
Manual chest compression – no. (%)	70	8 (11)	62	6 (10)
LUCAS* – no. (%)	70	31 (44)	62	22 (35)
AutoPulse* – no. (%)	70	28 (40)	62	30 (48)
Corpuls* – no. (%)	70	3 (4)	62	4 (6)
Signs of ischemia on the initial ECG – no. (%)	66	33 (50)	64	16 (25)

Values are means ±SD. Percentages are rounded and may not add up to 100. AED denotes automated external defibrillator, BLS basic life support, CCPR conventional cardiopulmonary resuscitation, CPR cardiopulmonary resuscitation, ECPR extracorporeal cardiopulmonary resuscitation, EMS emergency medical services, LUCAS Lund university cardiopulmonary assist system.

*Mechanical chest compression devices.

Table S5. In-hospital treatments and clinical outcomes

Table S5. In-hospital treatments and clinical outcomes				
Outcome	**Patients with data**	**Extracorporeal CPR (n = 70)**	**Patients with data**	**Conventional CPR (n = 64)**
Laboratory values at hospital admission				
pH – arterial	43	6.97±0.16	37	6.88±0.16
Lactic acid	58	13±5	48	14±4
Median partial pressure of oxygen – kPa (IQR)	64	8 (3-18)	53	6 (3-9)
Lactic acid at ICU admission	47	14±5	20	12±4
First hour	53	8±4	23	8±6
Second hour	44	7±4	14	7±5
Third hour	46	7±4	16	4±3
Fourth hour	39	7±4	18	4±3
Fifth hour	35	6±5	12	3±2
Sixth hour	37	6±5	13	4±3
Lactic acid on day two	42	4±3	17	3±3
Lactic acid on day third	25	3±2	16	2±1
RIFLE classification – no. (%)	53		22	
Normal		10 (19)		3 (14)
Risk		9 (17)		8 (36)
Injury		21 (40)		6 (27)
Failure		13 (25)		5 (23)
Duration of ventilation – days	55	3±6	22	9±21
Revascularization treatment – no. (%)	58	34 (59)	23	14 (61)
LAD – no. (%)		18 (31)		9 (39)
LM – no. (%)		7 (12)		1 (4)
RCX – no. (%)		6 (10)		2 (9)
RCA – no. (%)		8 (14)		4 (17)
RPDA – no. (%)		1 (2)		1 (4)
Graft – no. (%)		0 (0)		0 (0)
IABP or Impella – no. (%)	70	20 (29)	64	2 (3)
Duration of ventilation – days	55	3±6	22	9±21

Values are means ±SD. Percentages are rounded and may not add up to 100. IQR denotes interquartile range. IABP intra-aortic balloon pump, ICU intensive care unit, LAD left anterior descending artery, LM left main artery, RCA right coronary artery, RCX ramus circumflex artery, RPDA right posterior descending artery, RIFLE classification risk, injury, failure, loss of kidney function, and end-stage kidney disease.

The RIFLE classification defines three levels of acute kidney injury of increasing severity: risk, injury, and failure.

Table S6. Serious adverse events

Table S6. Serious adverse events		
	Extracorporeal CPR (n = 70)	**Conventional CPR (n = 64)**
Mean number of SAEs per patient	1.4±0.9	1±0.6
Patients with more than one event – no. (%)	33 (47)	14 (22)
Death before ICU admission – no. (%)	13 (19)	41 (64)
Cardiogenic shock or multi-organ failure – no. (%)	15 (21)	5 (8)
Recurrent arrest – no. (%)	2 (3)	3 (5)
Major bleeding – no. (%)	11 (16)	2 (3)
Infection – no. (%)	4 (6)	2 (3)
Post-anoxic encephalopathy – no. (%)	24 (34)	3 (5)
Limb ischemia – no. (%)	4 (6)	0 (0)
Cannulation dislocation – no. (%)	4 (6)	0 (0)
ECMO circulation failure – no. (%)	9 (13)	0 (0)
Other	8 (11)	6 (9)

Values are means ±SD. Percentages are rounded and may not add up to 100. ECMO denotes extracorporeal membrane oxygenation, ICU intensive care unit, SAE serious adverse event.

Table S7. Representativeness of study participants

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Category	
Disease, problem, or condition under investigation	Out-of-hospital cardiac arrest due to ventricular arrhythmia.
Special considerations related to	
Sex and gender	Out-of-hospital cardiac arrest due to ventricular arrhythmia affects men more than women (ratio of 4:1 to 5:1). Men affected by this condition are on average younger than women. Men are more likely to experience an out-of-hospital cardiac arrest in a public place and tend to experience a witnessed arrest and receive bystander CPR more frequently than women.
Age	The peak incidence of out of hospital cardiac arrest due to ventricular arrhythmia is around age 60-65 years, with the majority of the cases occurring between the age of 50 and 75 years.
Race or ethnic group.	The relation between race and incidence of out-of-hospital cardiac arrest due to ventricular arrhythmia remains uncertain. Based on recent data from the United States it appears that the incidence of out-of-hospital cardiac arrest (of any cause) is similar in non-Hispanic Whites and Hispanics. The incidence in non-Hispanic Blacks is slightly higher and in Asians somewhat lower. The age distribution is not dependent on race. The percentage of out-of-hospital cardiac arrest patients presenting with a ventricular arrhythmia was lower in Asians. Inhabitants of predominantly Black areas have lower chances of surviving out-of-hospital cardiac arrest due to ventricular arrhythmia than inhabitants of predominantly White areas.
Geography	The median age of patients affected by out-of-hospital cardiac arrest due to ventricular arrhythmia is similar across North America, Europe and Japan.
Other considerations	The prognosis of out-of-hospital cardiac arrest is very much dependent on early recognition and treatment. A ventricular arrhythmia may rapidly progress to asystole, especially if there are no responding witnesses to initiate

	CPR. Risk factors for a delayed bystander response include female sex, age and social, educational and economic status of the environment where the arrest occurs.
Overall representativeness of this trial	This trial only included patients in the Netherlands. The maximum age or enrollment was 70 years, excluding some of the elderly population affected by out-of-hospital cardiac arrest due to ventricular arrhythmias, as age is a known risk factor for poor outcome after extracorporeal CPR. A witnessed cardiac arrest and performance of bystander basic life support were additional inclusion criteria; both were considered mandatory criteria for a favorable extracorporeal CPR attempt. Many citizens are trained to perform basic life support and to apply an automated external defibrillator. The number of patients receiving immediate and adequate bystander treatment in case of a cardiac arrest is higher in The Netherlands than in other western societies. These inclusion criteria and the quality of bystander treatment (mostly applied to men) may have resulted in a lower mean age of the study population in comparison to the general population that is affected by out-of-hospital cardiac arrest due to a ventricular arrhythmia. It also may have increased the male: female ratio, which is already extremely skewed in the general population affected by out-of-hospital cardiac arrest due to ventricular arrhythmia. Social and educational status in The Netherlands is very evenly distributed and every inhabitant has mandatory health care insurance so that race or economic status of a patient should not affect medical treatment in case of emergencies.

References

1. Rijksoverheid. Wet medisch-wetenschappelijk onderzoek met mensen: artikel 6. 2022 [cited 2022 Oct 11];Available from: https://wetten.overheid.nl/BWBR0009408/2022-07-01#Paragraaf2

2. HartslagNu: Mijlpaal: in heel Nederland kan binnen 6 minuten worden gestart met reanimeren. HartslagNu. [cited 2022 Oct 13];Available from: https://hartslagnu.nl/nieuws/mijlpaal-in-heel-nederland-kan-binnen-6-minuten-worden-gestart-met-reanimeren/#:~:text=245.000 burgerhulpverleners,minuten kan starten met reanimeren.

3. StatLine: Bevolkingsontwikkeling; maand en jaar [Internet]. CBS. [cited 2022 Oct 13];Available from: https://opendata.cbs.nl/statline/#/CBS/nl/dataset/83474NED/table?ts=1665594989858

4. Zijlstra JA, Radstok A, Pijls R, et al. Overleving na een reanimatie buiten het ziekenhuis: vergelijking van de resultaten van 6 verschillende Nederlandse regio's. In: Reanimatie in Nederland. Hartstichting; 2016. p. 9–24.