

# Early initiation of extracorporeal life support in refractory out-of-hospital cardiac arrest

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# Early initiation of extracorporeal life support in refractory out-of-hospital cardiac arrest: Design and rationale of the INCEPTION trial

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**Background** Return of spontaneous circulation occurs in less than 10% of patients with cardiac arrest undergoing cardiopulmonary resuscitation (CPR) for more than 15 minutes. Studies suggest that extracorporeal life support during cardiopulmonary resuscitation (ECPR) improves survival rate in these patients. These studies, however, are hampered by their non-randomized, observational design and are mostly single-center. A multicenter, randomized controlled trial is urgently warranted to evaluate the effectiveness of ECPR.

**Hypothesis** We hypothesize that early initiation of ECPR in refractory out-of-hospital cardiac arrest (OHCA) improves the survival rate with favorable neurological status.

**Study design** The INCEPTION trial is an investigator-initiated, prospective, multicenter trial that will randomly allocate 110 patients to either continued CPR or ECPR in a 1:1 ratio. Patients eligible for inclusion are adults ( $\leq 70$  years) with witnessed OHCA presenting with an initial rhythm of ventricular fibrillation (VF) or ventricular tachycardia (VT), who received bystander basic life support and who fail to achieve sustained return of spontaneous circulation within 15 minutes of cardiopulmonary resuscitation by emergency medical services. The primary endpoint of the study is 30-day survival rate with favorable neurological status, defined as 1 or 2 on the Cerebral Performance Category score. The secondary endpoints include 3, 6 and 12-month survival rate with favorable neurological status and the cost-effectiveness of ECPR compared to CCPR.

**Summary** The INCEPTION trial aims to determine the clinical benefit for the use of ECPR in patients with refractory OHCA presenting with VF/VT. Additionally, the feasibility and cost-effectiveness of ECPR will be evaluated. (Am Heart J 2019;210:58-68.)

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## Background

Out-of-hospital cardiac arrest (OHCA) occurs approximately 275,000 times per year in Europe<sup>1</sup> and 350,000 times per year in the USA.<sup>2</sup> Two-thirds of these arrests have a primary cardiac origin.<sup>3,4</sup> In recent years, the survival of OHCA has significantly improved through public education in basic life support (BLS) and the widespread application of publicly accessible, automated electronic defibrillators (AED's).<sup>5,6</sup> These new measures especially benefit patients with an arrest of primary cardiac origin - typically presenting with ventricular fibrillation (VF) or ventricular tachycardia (VT) - since that the underlying cause is often reversible and that organ damage is limited due to the sudden onset of the arrest. Unfortunately, despite adequate cardiopulmonary resuscitation (CPR) and attempted defibrillation, only 42% of patients with VF/VT and OHCA survive to discharge.<sup>6,7</sup> After 15 minutes of CPR, the arrest can be considered to be refractory and the survival rate decreases dramatically to an estimated 8%.<sup>8-15</sup>

When the emergency medical services (EMS) fail to achieve return of spontaneous circulation (ROSC) on site, transportation to a hospital during CPR is an option. This strategy is increasingly utilized with the advent of mechanical chest compression devices, which ensure high-quality compressions during transport.<sup>16,17</sup> But care at the emergency department (ED) is in most instances a mere continuation of the CPR started by the EMS. Although a multidisciplinary medical team is present, no proven interventions are at hand that increase the chance of ROSC. To date, only high-quality chest compressions and defibrillation are of definite proven benefit in CPR.<sup>18</sup>

In an arrest of primary cardiac origin it is paramount to treat the underlying cause - in most cases coronary artery occlusion - but in the absence of ROSC, the possibilities to perform these life-saving interventions are limited. Extracorporeal cardiopulmonary resuscitation (ECPR) restores the circulation and provides a bridge to possible diagnosis and treatment. It has the potential to minimize (or even reverse) organ damage and to prevent re-arrest due to ischemia-triggered myocardial dysfunction. Several studies demonstrate that ECPR is a feasible option and may well increase survival up to 30%.<sup>8-15</sup> While this evidence is encouraging, it is hampered by the single center and non-randomized nature, as well as limited sample size. ECPR is a high-risk treatment and institutions need to invest not only financially but also logistically, both in-hospital and regionally, to ensure that potential candidates reach the center timely. Before large-scale introduction of ECPR, high-quality evidence is urgently warranted, as was also stipulated by the recent European Resuscitation Council (ERC) guidelines.<sup>16</sup>

The INCEPTION trial (early INitiation of extraCorporeal life suPporT In refractory Out of hospital cardiac arrest) compares continued cardiopulmonary resuscitation

(CCPR) to ECPR in the population that is expected to benefit the most from the intervention: patients in refractory cardiac arrest presenting with VF/VT. Additionally, this trial will provide data on the cost-effectiveness of this intervention, which to date is unavailable. Although the costs may prove to be high, the gain in quality-adjusted life years (QALY's) may be substantial given the fact that the patients are under 70 and the current alternative carries a poor prognosis. This trial aims to determine whether ECPR should be considered as a standard of care in patients with refractory OHCA.

## Methods

This work is funded by "The Netherlands Organization for Health Research and Development" (ZonMw-doelmatigheid, nr 80-84,300-98-71,040). The Gething Group (Göteborg, Sweden) supplies HLS advanced circuits for all patients undergoing ECPR in the ECPR arm of the trial and 4 loaner Cardiohelp systems to the three sites of the initial consortium for the duration of the trial. The industrial sponsor has no influence on study design, data analyses, interpretation and disclosure of data. The authors are solely responsible for the design and conduct of this study, the study analyses, the drafting and editing of the manuscript, and its final contents.

## Trial design

This is an investigator-initiated, multicenter, randomized controlled trial designed to evaluate the benefit of ECPR in patients with a refractory OHCA. The trial is registered at [clinicaltrials.gov](https://clinicaltrials.gov) (NCT03101787).

## Hypothesis

We hypothesize that early initiation of ECPR in refractory OHCA will improve 30-day survival rate with favorable neurological status.

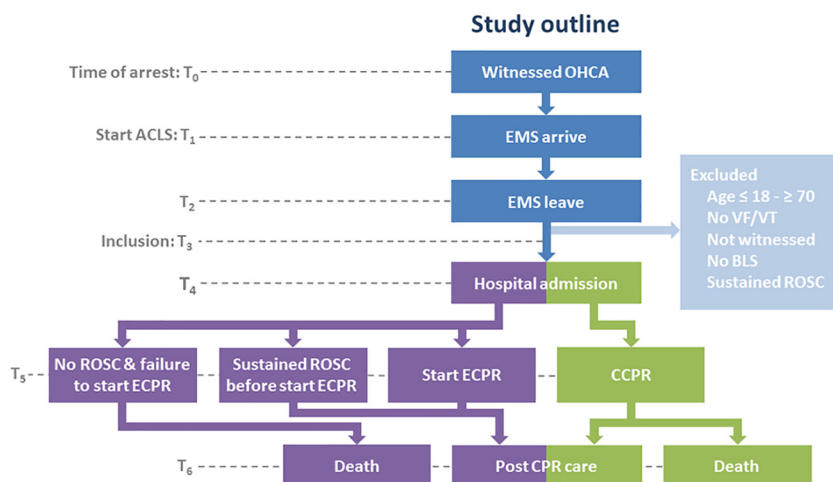
## Patient population

Adult patients under 70 years of age, with a witnessed OHCA, initially presenting with VF/VT or who have been administered an AED-shock, who have received bystander BLS and who fail to achieve sustained ROSC within 15 minutes, are eligible for inclusion. These criteria are designed to identify patients who are most likely to have an arrest with a primary cardiac origin. The exclusion criteria are: ROSC with sustained hemodynamic recovery within 15 minutes, terminal heart failure (NYHA III or IV), severe pulmonary disease (COPD Gold III or IV), oncological disease, pregnancy, bilateral femoral bypass surgery, pre-arrest Cerebral Performance Category (CPC) score of 3 or 4, multiple trauma (Injury Severity Score > 15) and an advance health care directive (Table 1). Patients are also excluded when it is estimated that cannulation will start

**Table I.** Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria (if known before randomization)
1. $\geq 18 - \leq 70$ years 2. Witnessed OHCA 3. Initial rhythm of VF/VT or AED-shock administered 4. Bystander BLS 5. No ROSC within 15 minutes	1. ROSC with sustained hemodynamic recovery within 15 minutes 2. Terminal heart failure (NYHA III or IV) 3. Severe pulmonary disease (COPD GIII of GIV) 4. Oncological disease 5. Pregnancy 6. Bilateral femoral vessel bypass surgery 7. Pre-arrest CPC score of 3 or 4 8. Multiple trauma (Injury Severity Score > 15) 9. Advance health care directive 10. Expected initiation of cannulation >60 min after arrest

**Figure 1**



Study outline. ACLS, Advanced Cardiac Life Support; BLS, Basic Life Support; CCPR, Continued CardioPulmonary Resuscitation; CPR, CardioPulmonary Resuscitation; ECPR, Extracorporeal CardioPulmonary Resuscitation; EMS, Emergency Medical Services; OHCA, Out-of-Hospital Cardiac Arrest; ROSC, Return Of Spontaneous Circulation; VF/VT, Ventricular Fibrillation/Tachycardia.

60 minutes after the initial arrest. Exclusion criteria are taken into account if they are known at the time of randomization and at the last check before start of treatment. (See Fig. 1.)

AED, Automated External Defibrillator; BLS, Basic Life Support; COPD, Chronic Obstructive Pulmonary Disease; CPC, Cerebral Performance Category; OHCA, Out-of-Hospital Cardiac Arrest; NYHA, New York Heart Association; ROSC, Return Of Spontaneous Circulation; VF/VT, Ventricular Fibrillation/Tachycardia.

**Trial consortium**

The original trial consortium consisted of one university hospital (Maastricht University Medical Center) and two cardiothoracic centers in the Netherlands (Catharina Hospital Eindhoven and Isala Clinics Zwolle). After public presentation of the trial protocol, the consortium has been expanded to include three additional university hospitals (Amsterdam University Medical Center location AMC, Leiden University Medical Center and University

Medical Center Utrecht) and one cardiothoracic center (St. Antonius Nieuwegein). Cardiothoracic surgery and management of veno-arterial extracorporeal membrane oxygenation (VA-ECMO) are restricted to 16 tertiary centers within the Netherlands. The 7 centers that participate in the trial are dispersed over six different regions and provide resuscitation care for a cumulative population of 5.586.565 inhabitants (see Table II).<sup>19</sup> Based on the EMS databases, we expect 10-20 eligible patients per center per year.

**Study protocol**

**Standard EMS care for OHCA.** Resuscitation care by EMS is protocolized for all patients with OHCA irrespective of study eligibility or participation. In the case of (suspected) OHCA, two ambulances are dispatched to the patient. Each ambulance is staffed with an ALS-trained paramedic and a BLS-trained chauffeur. The norm for the highest level of EMS alert (A1) is a maximal time-to-scene of

**Table II.** Population per region and average number of OHCA

Center	Population per region	Average number of OHCA per region per year
Maastricht UMC+	600.037	360
Isala Clinics Zwolle	520.478	250
UMC Utrecht and St. Antonius Hospital Nieuwegein	1.284.504	400
Amsterdam UMC location AMC	1.906.677	985
Leids UMC	786.818	350
Catharina Hospital Eindhoven	761.763	350
Total	5.586.565	2695

UMC, University Medical Center; AMC, Academic Medical Center.

15 minutes. In 2017 this was achieved in 92.4% of cases and on average the time-to-scene was 9:41 minutes.<sup>20</sup> Besides the EMS, first responders (policemen, firemen) and BLS/AED trained volunteers are notified when they are in the vicinity of the arrest.<sup>5</sup>

The EMS performs CPR according to the ERC guidelines with high-quality chest compressions, quick airway management and fast intravenous or intraosseous access. All ambulances are equipped with a mechanical chest compression device to facilitate transport. If no ROSC is present after a minimum of three resuscitation cycles, the patient is eligible for the study and transferred to hospital. One resuscitation cycle is defined as two minutes of CPR. With these three cycles added to the average time-to-scene, approximately 15 minutes since start of arrest will have passed. Upon departure from the scene, the EMS inform the hospital about the age and sex of the patient, presenting rhythm, administered AED-shocks, presence of ROSC, witnessed arrest, and known comorbidities to initiate randomization. En route, CPR is continued including mechanical chest compression, medication administration and defibrillation attempts.

**Randomization.** Based upon the information provided by the EMS, the resuscitation team leader assesses eligibility for study participation. When the patient meets the inclusion criteria and no exclusion criteria are known, randomization is performed.

Using concealed allocation, patients are randomly assigned to either CCPR or ECPR in a 1:1 ratio, stratified per center. A web-based system randomizes the patient using variable block randomization.

When the patient arrives in the hospital, a last check is performed to see if the patient fulfills the in- and exclusion criteria.

**a) Control group: CCPR.** In case of randomization to CCPR, no special preparations for the trial are needed before the patient's arrival.

Upon arrival, the standard of care, CCPR, is continued according to ERC guidelines.

**b) Intervention group: ECPR.** In case of randomization to ECPR, a physician skilled and qualified in peripheral femoral cannulation, a perfusionist and a

scrub nurse are called to the emergency department or the cath lab in addition to the routine response team.

Upon the patient's arrival, CPR is continued and the inguinal region is exposed and disinfected bilaterally. The choice between percutaneous or surgical cannulation is made according to the physician's preference. Cannulas are introduced into the femoral artery (15 F - 21 F) and vein (19 F - 25 F), and advanced into the iliac artery and inferior caval vein, respectively. Cannula size depends upon the estimated body size and flow requirements. Subsequently, these cannulas are connected to a portable heart-lung support system, according to local availability, and perfusion is initiated. During this phase, it is essential to continue chest compressions with minimal interruptions. Inserting a distal cannula for leg perfusion is encouraged, but not mandatory.

**Post-resuscitation care.** In both arms, post-resuscitation care and extracorporeal circulation management are executed according to current guidelines and local protocols. This entails targeted temperature management at 33–36 degrees Celsius for 24 hours, preventing hyperthermia for at least 72 hours, maintaining normoxia and normocapnia with protective ventilation, normoglycemia and optimizing hemodynamic parameters (i.e. rapid reduction of lactate levels, venous oxygen saturation > 65%, mean arterial pressure > 65–70 mmHg).<sup>21</sup> In most cases, a coronary angiography or CT-scan is performed to identify and possibly treat the cause of arrest. The decision to terminate treatment is left to the treating physician and is documented in the medical files and in the case report form (CRF).

### Follow-up

Follow-up assessments will be obtained by a structured interview at 30 days and 3, 6 and 12 months, at which time the CPC score and quality-of-life (EQ-5D-5 L, EuroQoL, Rotterdam, the Netherlands)<sup>22</sup> will be assessed. Additionally, the iMCQ<sup>23</sup> (medical consumption outside of the hospital) and the iPCQ<sup>24</sup> (productivity loss) are added to the interview at 3, 6 and 12-months.<sup>18,19</sup> At 12-months a predefined set of patient-reported outcome measures (PROMs) created by a patient panel will also be added to the interview (see below). Prevalence, incidence, and cause of repeated hospitalization will be recorded for both arms.

**Table III.** INCEPTION primary and secondary endpoints

Primary endpoint	Secondary endpoints
30-day survival rate with favorable neurological status (CPC 1 or 2)	QALY's at 1 year Costs of ECPR Costs of CCPR Costs per gained QALY Duration of CPR Duration to return of circulation Duration of ICU stay Duration of hospitalization Time to targeted temperature management Duration of mechanical ventilation Survival at 3, 6 and 12 months PROM's at 12 months after OHCA If applicable: reason for discontinuation of treatment If applicable: organ donation

CCPR, Continued CardioPulmonary Resuscitation; CPR, CardioPulmonary Resuscitation; CPC, Cerebral Performance Category; ECPR, Extracorporeal CardioPulmonary Resuscitation; ICU, Intensive Care Unit; OHCA, Out-of-Hospital Cardiac Arrest; PROM, Patient-Reported Outcome Measure; QALY, Quality-Adjusted Life Year.

### Study outcomes

The primary endpoint is the 30-day survival rate with favorable neurological status defined as a CPC score of 1 or 2. Secondary endpoints include survival with favorable neurological status and quality-of-life at 3, 6 and 12 months, cost-effectiveness expressed as the incremental costs per QALY gained at 12 months, duration to return of circulation, duration of mechanical ventilation, intensive care unit (ICU) and hospital stay, time to targeted temperature management, and reasons for discontinuation of treatment (Table III).

### Quality and safety assurance

A professional contract research organization (Clinical Trial Center Maastricht) monitors the study data, trial enrolment and conduct. Data is stored in a web-based case report system (MACRO, Elsevier, London, UK). An independent Data Safety Monitoring Board assesses the safety and efficacy of the intervention, to safeguard the interests of trial participants and the validity of the trial results.

### Patient panel

A panel of patients and a family member with personal experience in CCPR or ECPR is composed for this trial. This panel created patient-reported outcome measures (PROMs) to reflect the outcomes they themselves believe to be important for this patient population. The panel has also judged information for patients and relatives on clarity.

## Statistical considerations

### Sample size

The study is powered for the primary endpoint of 30-day survival with favorable neurological outcome. Sample size is based on an uncorrected two-sided Chi-square test,

accepting a power of 80% and a level of significance of 5%. Based on recent studies<sup>8-15</sup> and our own center's experience, we estimate the chances of survival with good neurological outcome to increase from 8% to 30%. Including a dropout of 10%, this results in 55 study subjects per arm. Additionally, the study has an adaptive design to allow for a change in sample size if the survival benefit is substantial but different from the 22% increase mentioned above.

### Interim analysis

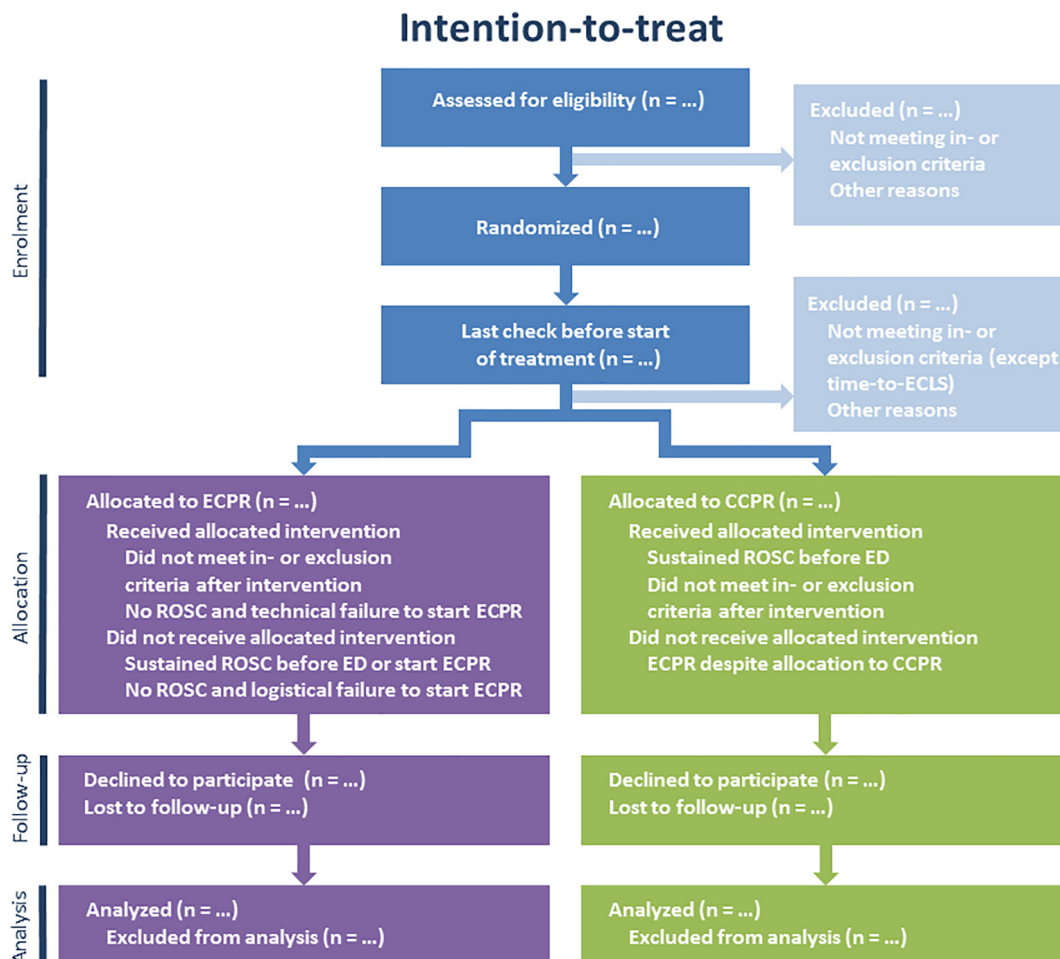
An interim analysis will be performed after the CPC score has been established for the 40th patient at 30 days after the OHCA. In this interim analysis, the percentage of survival with good neurological outcome will be calculated for both treatment groups. Analysis of the primary outcome will be blinded. All analyses will be performed by an independent blinded statistician. These percentages will be used to estimate the chance of a type II error. In case of an imminent type II error, a new sample size calculation will be performed which may result in an advice to increase the sample size. Any increase in sample size shall be submitted to the Ethics Committee for approval.

### Data analysis

Data will be analyzed primarily on an intention-to-treat basis (Figure 2), but two additional analyses will also be performed (Figures 3 and 4).

In the as-treated analysis, the ECPR-arm will consist of all patients who received ECPR or ECPR was initiated, regardless of allocation. The CCPR-arm will consist of all patients who were treated conventionally, e.g. patients who achieved ROSC in hospital before start of ECPR and patients who did not receive ECPR due to logistical failure to start treatment. Patients meeting the in- or exclusion criteria before the start of the intervention or who

**Figure 2**



Intention-to-treat analysis. CCPR, Continued CardioPulmonary Resuscitation; ECLS, ExtraCorporeal Life Support; ECPR, Extracorporeal CardioPulmonary Resuscitation; ED, Emergency Department; ROSC, Return Of Spontaneous Circulation.

achieve ROSC before arrival in the hospital will be excluded. The exception is the exclusion criterion ‘expected initiation of cannulation > 60 min after arrest’ since this could lead to bias (e.g. exclusion of late randomization in the ECPR-arm).

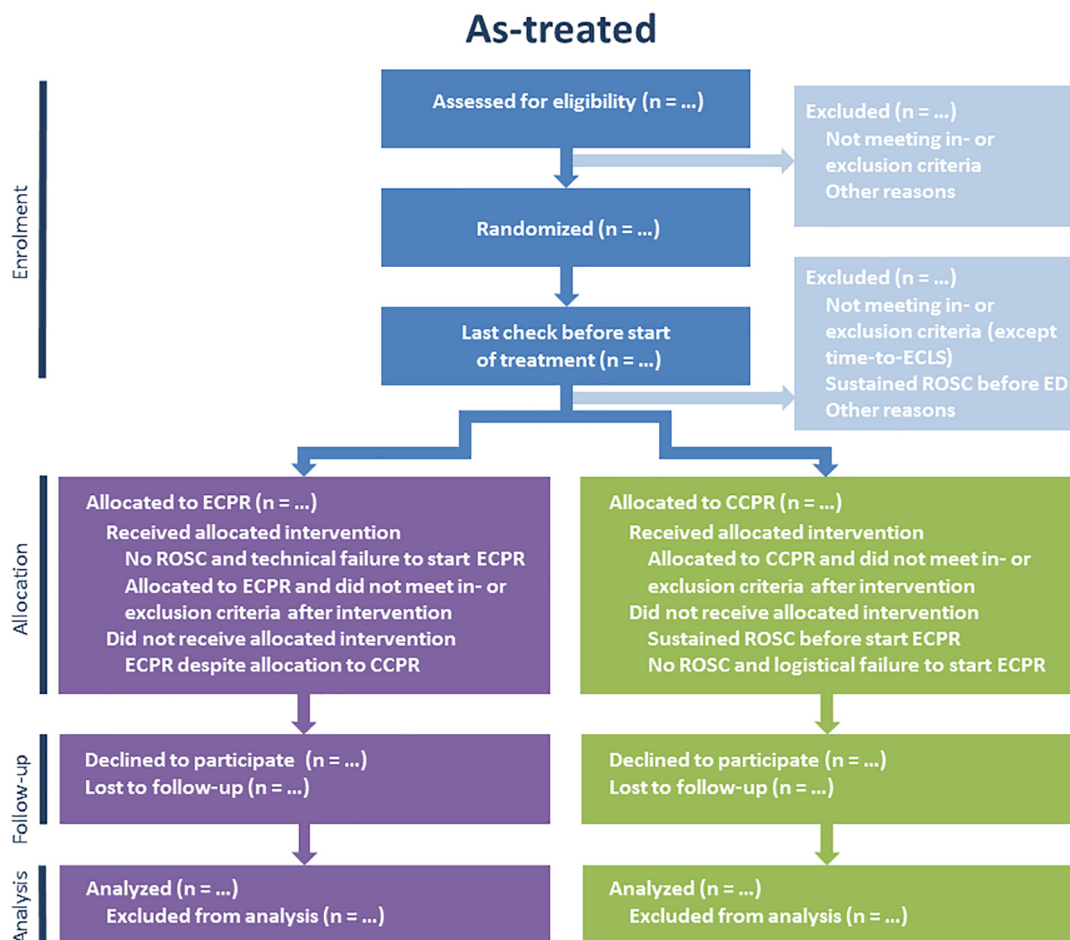
The per-protocol analysis will consist of patients in whom the allocated protocol was strictly adhered to. Thus the patients who did not meet the in- or exclusion criteria after the start of the intervention will be excluded, this will eliminate all procedures started 60 minutes after the arrest. In the ECPR-arm, ROSC after arrival in the hospital and before start of ECPR will be seen as part of the protocol. All crossovers will be excluded to avoid a time-effect bias. ECPR despite allocation to CCPR and CCPR despite allocation to ECPR due to logistical failure to start treatment are seen as crossovers. Initiation of ECLS post-resuscitation (e.g. for cardiac failure after sustained ROSC) is not regarded as crossover, but as part of regular post-resuscitation care.

Numerical values will be reported as mean ± standard deviation or median (Interquartile range (IQR), i.e. 25th to 75th percentile). Categorical variables will be reported as frequency with percentage.

**Primary endpoint.** At 30-days after the OHCA, an independent neurologist, blinded to the intervention will perform an evaluation of the CPC score. These scores will be reported as frequency with percentage. For the analysis between treatment groups a logistic mixed regression analysis will be used, which is described in more detail below, correcting for the stratification variable (center). No missing outcome data will be imputed since a likelihood approach will be used. For the primary outcome, we focus only on the treatment effect measured at 30 days after OHCA. A complete case analysis (CCA) will be used to perform a sensitivity analysis.

**Secondary endpoints.** For numerical and categorical variables linear and logistic mixed effects model will be

Figure 3



As-treated analysis. CCPR, Continued CardioPulmonary Resuscitation; ECPR, Extracorporeal CardioPulmonary Resuscitation; ECLS, Extracorporeal Life Support; ED, Emergency Department; ROSC, Return Of Spontaneous Circulation.

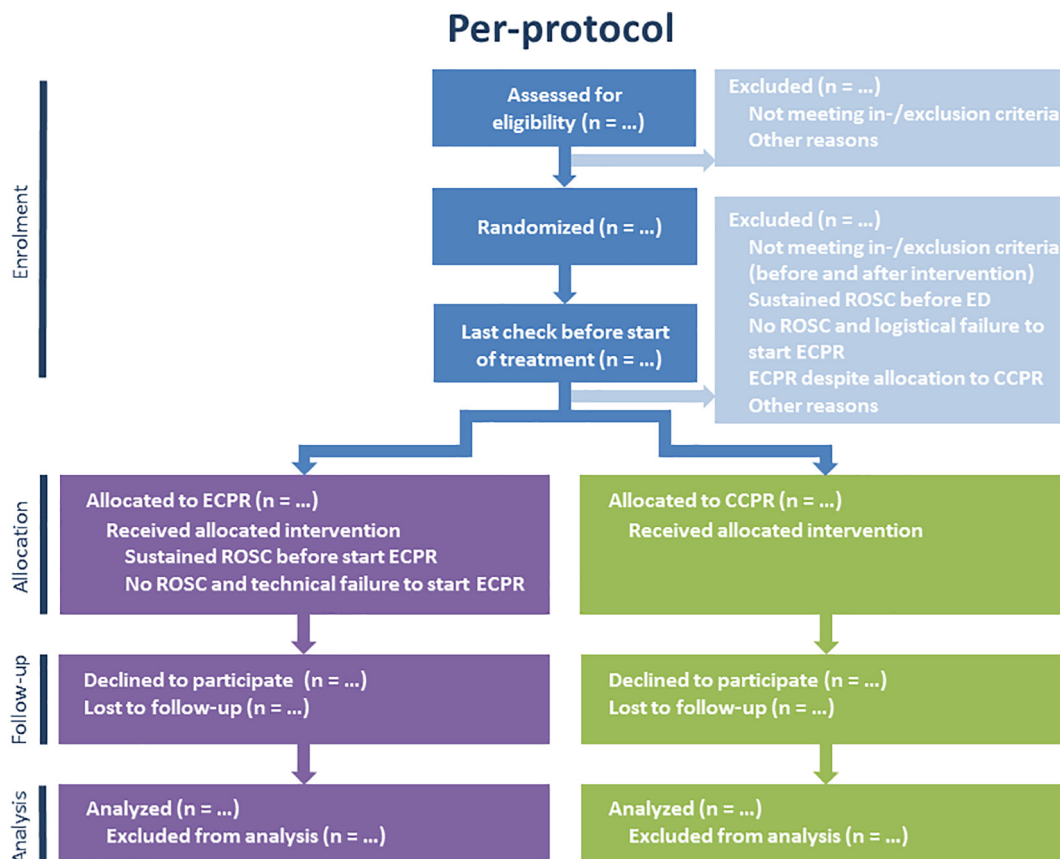
used, where the fixed factors include group (ECPR vs. CCPR), time (30 days, 3, 6 and 12 months), group-time, and center. As for the random part, a random intercept model, a random intercept and slope (variance components) model, or a random intercept and slope (unstructured) model will be assessed, where the one with the smallest Akaike's information criterion (AIC) will be reported. To check whether center is an effect-modifier, the interaction terms group-center, time-center and group-time-center will be added to the model. No missing outcome data will be imputed since a likelihood approach will be used, where patient characteristics related to missing values will be included in the model. Parameters will be estimated based on restricted maximum likelihood (REML). A CCA will be used to perform a sensitivity analysis. For time to return of circulation Cox regression analysis will be used, where the fixed factors include group and center.

### Cost-effectiveness

We will perform a cost-utility analysis from a societal perspective to address cost-effectiveness of ECPR compared to CCPR. Health care costs are collected by registering the use of hospital resources and the medical consumption outside the hospital using the iMCQ.<sup>23</sup> Productivity loss will be registered using iPCQ.<sup>24</sup> Health-related quality-of-life will be assessed with the EQ-5D-5 L. As most volumes of resources follow a skewed distribution, differences in costs between the two groups will be analyzed with non-parametric bootstrap analysis. In addition, bootstrap analysis will be used to quantify the uncertainty surrounding the incremental cost-effectiveness ratio.<sup>25</sup> Results of this analysis will be presented in cost-effectiveness planes and acceptability curves. Missing data will be imputed by a multiple imputation approach. Uncertainty related to the impact of different parameters on the incremental cost-



**Figure 4**



Per-protocol analysis. CCPR, Continued CardioPulmonary Resuscitation; ECPR, Extracorporeal CardioPulmonary Resuscitation; ED, Emergency Department; ELS, Extracorporeal Life Support; ROSC, Return Of Spontaneous Circulation.

effectiveness ratio will be assessed with uni- and multivariate sensitivity analysis.

### Ethical considerations

The study is conducted according to the Declaration of Helsinki, in accordance with the Medical Research Involving Human Subjects Act and the statements of the Dutch Central Committee on Research Involving Human Subject addressing deferred consent in unresponsive patients.<sup>26</sup> The study is approved by the Medical Ethics Committee at the Maastricht University Medical Center, Maastricht, the Netherlands and by the Ethics Committees of all participating centers.

#### Prior informed consent

The study intervention fulfills the ethical requirement of clinical equipoise. Patients can benefit from the intervention, but up to now, a state of honest, professional uncertainty exists in the community of expert practitioners as to the outcome perspective of

ECPR. Since the study intervention concerns an emergency intervention, it has to be applied without delay. Patients eligible for inclusion are unconscious, unable to consent and have an extremely high risk of dying. Legal representatives are either absent or distressed by circumstances and not in a state of mind to make a well-considered decision. This renders obtaining informed consent prior to inclusion impossible. In research in a time-sensitive setting when the patient or proxy is unable to provide consent, the use of a deferred consent is an accepted method.

#### Deferred (proxy) consent

If and when the patient regains consciousness, the investigator will inform the patient about the study and ask informed consent (deferred consent). When the patient remains unable to communicate, the legal representative will be asked for deferred proxy consent between day one and seven. In the case of deferred proxy consent, the patient will also be asked for consent if and when his consciousness recovers.

## Waiver of consent

Due to the nature of the study population, we expect that a substantial number of patients will be declared dead before informed consent can be obtained. Deferred proxy consent can no longer be pursued, since, according to Dutch legislation, legal representation ends after death.<sup>26,27</sup> It is essential for the validity of the study to use the data of these patients, to avoid a large risk of inclusion- or “consent”-bias.

This introduces the difficult ethical and juridical situation in which we need to use data without any informed consent. Dutch legislation allows the use of data for statistics or scientific research in the field of public health without consent when the following three conditions are met: 1) the research is in the public interest, 2) the research cannot be conducted without the information in question, and 3) the patient in question has not explicitly objected to the possibility that information will be provided for this purpose (BW 7:458:2). The ethical board deemed this trial, after careful deliberation, to be in line with these conditions.

If a participant deceases before consent is obtained, the leader of the resuscitation team will inform the legal representatives that the patient participated in the study.

## Discussion

An essential factor for the success of ECPR is the chain of survival – without excellent pre-hospital care, ECPR has no possible benefit. The Dutch pre-hospital resuscitation care is very well-organized – with a high coverage of AED's and BLS trained volunteers<sup>5,6</sup> and ALS-trained EMS with a short time-to-arrival ( $\pm$  9:41 minutes<sup>20</sup>), who aim at rapid transfer to the hospital using mechanical compressions. To optimally incorporate the ECPR-link into the chain, a well-prepared ECPR-team is mobilized while the patient is still en route to the hospital. This minimizes the delay between cardiac arrest and initiation of ECPR and maximizes the chance of a positive outcome.

At present, there are four other ECPR trials recruiting patients in Prague, Paris, Vienna and Michigan (NCT01511666, NCT02527031, NCT01605409, NCT03065647). These studies differ from the INCEPTION trial, in the respect that they are typically performed in large, multimillion cities by high-volume single centers that have teams exclusively dedicated to ECPR. This situation is not representative for less densely populated areas where the full-time assignment of an ECPR-team is not feasible. The number of eligible patients per center is simply too small to make this cost-effective. Thus ECPR needs to be implemented within the existing resuscitation infrastructure. This trial will provide a picture of the broader feasibility outside these high-volume, expertise centers.

In line with this, the trial is designed pragmatically. We have not changed the local ACLS protocol, nor the local

ECPR and ECLS protocol. Each site has a different procedure, based on their infrastructure and own experience. The resuscitation leader will be the fellow intensive care, anesthesiologist, emergency physician or cardiology resident. ECPR is performed in either the emergency department or the cath lab, by either the cardiothoracic surgeon, intervention cardiologist and/or ECLS-intensivist. With the current level of evidence, it is not yet known what is the most effective way to perform ECPR, so experience and expediency are more likely contribute to a successful procedure than one uniform protocol. While there will be a difference within the ECPR arm, the difference when comparing to the control arm will be much larger. To minimize this confounder we stratify per site in the randomization.

Since little information is available during an out-of-hospital cardiac arrest; we have chosen inclusion criteria that are easy to interpret. We decided not to use etCO<sub>2</sub> to select patients because 1) etCO<sub>2</sub> is a dynamic value and the EMS might report multiple values; 2) there could be technical problems preventing the etCO<sub>2</sub> from being measured; 3) leakage with a supraglottic airway device might lead to unreliable measurements. In these cases, it is unclear which value should be used for randomization or if the patient should be randomized without the measurement. While we would prefer to use more parameters to base the decision on (e.g. lactate and pH), we have chosen to use those most easily interpreted and readily available.

Recently, there has been a growing awareness that centralization of OHCA care to hospitals with percutaneous coronary intervention facilities, cardiothoracic surgery, and specialized neuromonitoring facilities can improve outcome.<sup>28,29</sup> A proven benefit of ECPR over CCPR would be a further argument to centralize resuscitation care. However, in an era where budget control in health care is increasingly important, it is essential to evaluate the costs accompanying a clinical benefit. This trial is therefore not only designed to determine the clinical benefit of ECPR but also to provide data on the cost-effectiveness of this intervention.

Because of the difficult ethical considerations, we feel it crucial to involve the patients in this trial. Therefore, we have instated a patient panel during the design of the study, consisting of people with personal experience with CCPR and ECPR. The panel has shared their opinion on trial design, patient information letters, and consent procedures. We feel that the active involvement of patients in this phase of trial conception will strongly contribute to warrant public support for the study background and execution. Furthermore, they have defined PROM's to reflect the outcomes they themselves have experienced and deem to be important. Because of this, the questionnaire is not validated, but we hope to gain more knowledge on the experience of our patients. These PROM's provide unique qualitative data on

outcomes that can bridge the gap between clinical reality and the patient perspective.

## Summary

The INCEPTION trial is the first multicenter, randomized controlled trial to explore ECPR in patients in refractory OHCA presenting with VF/VT. It aims to determine the effect of ECPR on survival rate and neurological outcome, and to evaluate its feasibility and cost-effectiveness. The trial will provide valuable data for solid evidence-based recommendations on the application of ECPR in future resuscitation guidelines.

## Current status of trial

As of mid-October 2018, 33 patients have been recruited by the initiating center (Maastricht University Medical Center) and the Isala Clinics Zwolle, the other participating centers will start enrolling later this year.

## Disclosures

Martine E. Bol, MSc: Declarations of interest: none.

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Roberto Lorusso, MD, PhD: Declarations of interest: none.

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## References

1. Atwood C, Eisenberg MS, Herlitz J, et al. Incidence of EMS-treated out-of-hospital cardiac arrest in Europe. *Resuscitation* 2005;67(1):75-80.
2. Benjamin EJ, Virani SS, Callaway CW, et al. Heart Disease and Stroke Statistics-2018 Update: A Report From the American Heart Association. *Circulation* 2018;137(12):e67-e492.
3. Dumas F, Cariou A, Manzo-Silberman S, et al. Immediate percutaneous coronary intervention is associated with better survival after out-of-hospital cardiac arrest: insights from the PROCAT (Parisian Region Out of hospital Cardiac Arrest) registry. *Circ Cardiovasc Interv* 2010;3(3):200-7.
4. de Vreede-Swagemakers JJ, Gorgels AP, Dubois-Arbouw WI, et al. Out-of-hospital cardiac arrest in the 1990's: a population-based study in the Maastricht area on incidence, characteristics and survival. *J Am Coll Cardiol* 1997;30(6):1500-5.
5. Pijls RW, Nelemans PJ, Rahel BM, et al. A text message alert system for trained volunteers improves out-of-hospital cardiac arrest survival. *Resuscitation* 2016;105:182-7.
6. Blom MT, Beesems SG, Homma PC, et al. Improved survival after out-of-hospital cardiac arrest and use of automated external defibrillators. *Circulation* 2014;130(21):1868-75.
7. Beesems SG, Zijlstra JA, Stieglis R, et al. *Reanimatie buiten het ziekenhuis in Noord-Holland en Twente: resultaten ARREST- onderzoek over 2006-2011, Hart- en vaatziekten in Nederland*. 2012.
8. Sakamoto T, Morimura N, Nagao K, et al. Extracorporeal cardiopulmonary resuscitation versus conventional cardiopulmonary resuscitation in adults with out-of-hospital cardiac arrest: a prospective observational study. *Resuscitation* 2014;85(6):762-8.
9. Chen YS, Lin JW, Yu HY, et al. Cardiopulmonary resuscitation with assisted extracorporeal life-support versus conventional cardiopulmonary resuscitation in adults with in-hospital cardiac arrest: an observational study and propensity analysis. *Lancet* 2008;372(9638):554-61.
10. Kagawa E, Inoue I, Kawagoe T, et al. Assessment of outcomes and differences between in- and out-of-hospital cardiac arrest patients treated with cardiopulmonary resuscitation using extracorporeal life support. *Resuscitation* 2010;81(8):968-73.
11. Bellezzo JM, Shinar Z, Davis DP, et al. Emergency physician-initiated extracorporeal cardiopulmonary resuscitation. *Resuscitation* 2012;83(8):966-70.
12. Haneya A, Phillip A, Diez C, et al. A 5-year experience with cardiopulmonary resuscitation using extracorporeal life support in non-postcardiotomy patients with cardiac arrest. *Resuscitation* 2012;83(11):1331-7.
13. Lamhaut L, Jouffroy R, Soldan M, et al. Safety and feasibility of prehospital extra corporeal life support implementation by non-surgeons for out-of-hospital refractory cardiac arrest. *Resuscitation* 2013;84(11):1525-9.
14. Le Guen M, Nicolas-Robin A, Carreira S, et al. Extracorporeal life support following out-of-hospital refractory cardiac arrest. *Crit Care* 2011;15(1):R29.
15. Wang CH, Chou NK, Becker LB, et al. Improved outcome of extracorporeal cardiopulmonary resuscitation for out-of-hospital cardiac arrest—a comparison with that for extracorporeal rescue for in-hospital cardiac arrest. *Resuscitation* 2014;85(9):1219-24.
16. Soar J, Nolan JP, Bottinger BW, et al. European Resuscitation Council Guidelines for Resuscitation 2015: Section 3. Adult advanced life support. *Resuscitation* 2015;95:100-47.
17. Slattery DE, Silver A. The hazards of providing care in emergency vehicles: an opportunity for reform. *Prehosp Emerg Care* 2009;13(3):388-97.

18. Wallace SK, Abella BS, Becker LB. Quantifying the effect of cardiopulmonary resuscitation quality on cardiac arrest outcome: a systematic review and meta-analysis. *Circ Cardiovasc Qual Outcomes* 2013;6(2):148-56.
19. Data from the Dutch National Institute for Public Health and the Environment (RIVM). 2017.
20. AmbulancezorgNederland. *Tabellenboek ambulancezorg 2017*. 2017:17.
21. Nolan JP, Soar J, Cariou A, et al. European Resuscitation Council and European Society of Intensive Care Medicine Guidelines for Post-resuscitation Care 2015: Section 5 of the European Resuscitation Council Guidelines for Resuscitation 2015. *Resuscitation* 2015;95:202-22.
22. Versteegh MM, Vermeulen KM, Evers SMAA. Dutch Tariff for the Five-Level Version of EQ-5D. *Value Health* 2016;19(4):343-52.
23. Bouwmans C, Hakkaart-van Rooijen L, Koopmanschap M, et al. *Manual of the iMTA Medical Cost Questionnaire (iMCQ)*. Rotterdam: iMTA, Erasmus University, Rotterdam. 2013.
24. Bouwmans C, Hakkaart-van Rooijen L, Koopmanschap M, et al. *Manual of the iMTA Productivity Cost Questionnaire (iPCQ)*. Rotterdam: iMTA, Erasmus University Rotterdam. 2013.
25. Efron B, Tibshirani RJ. *An introduction to the bootstrap*. Chapman and Hall. 1993.
26. Kompanje EJ, Jansen TC, Le Noble JL, et al. Deferred consent for inclusion of patients unable to give their consent in studies in the field of emergency medicine. *Ned Tijdschr Geneesk* 2008;152(38):2057-61.
27. Jansen TC, Kompanje EJ, Druml C, et al. Deferred consent in emergency intensive care research: what if the patient dies early? Use the data or not? *Intensive Care Med* 2007;33(5):894-900.
28. Tranberg T, Lippert FK, Christensen EF, et al. Distance to invasive heart centre, performance of acute coronary angiography, and angioplasty and associated outcome in out-of-hospital cardiac arrest: a nationwide study. *Eur Heart J* 2017;38:1645-52.
29. Soholm H, Kjaergaard J, Bro-Jeppesen J, et al. Prognostic Implications of Level-of-Care at Tertiary Heart Centers Compared With Other Hospitals After Resuscitation From Out-of-Hospital Cardiac Arrest. *Circ Cardiovasc Qual Outcomes* 2015;8(3):268-76.