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Review

Ethics of ECPR research



Martje M. Suverein^{a,*}, David Shaw^b, Roberto Lorusso^c, Thijs S.R. Delnoij^a, Brigitte Essers^d, Patrick W. Weerwind^c, David Townend^b, Marcel C.G. van de Poll^a, Jos G. Maessen^c

^a Department of Intensive Care, Maastricht University Medical Centre, Maastricht, the Netherlands

^b Department of Health, Ethics & Society, Maastricht University, Maastricht, the Netherlands

^c Department of Cardiothoracic Surgery, Maastricht University Medical Centre, Maastricht, the Netherlands

^d Department of Clinical Epidemiology and Medical Technical Assessment, Maastricht University Medical Centre, Maastricht, the Netherlands

Abstract

The design of emergency medicine trials can raise several ethical concerns – risks may be greater, and randomisation may have to occur before consent. Research in emergency medicine is thus an illuminating context to explore the interplay between risk and randomisation, and the consequences for consent. Using a currently running trial, we describe possible concerns, considerations, and solutions to reconcile the conflicting interests of scientific inquiry, ethical principles, and clinical reality in emergency medicine research.

Keywords: Extracorporeal cardiopulmonary resuscitation, Out-of-hospital cardiac arrest, Refractory cardiac arrest, Informed consent, Ethical issues

Introduction

As in all fields of medicine, the need for high-quality evidence in emergency medicine is of great importance. However, the circumstances in which to perform clinical research may prove to be more difficult: the risks may be greater, and randomisation may be necessary before consent. So while the same fundamental ethical principles apply,¹ they may collide with clinical reality, making it challenging to design an ethically sound study. In the present paper, we elaborate on the conflicting interests of scientific inquiry, ethical principles and clinical reality.

As an anchor, we use the INCEPTION trial, which has recently finished recruiting and was performed by the authors.² This multicentre, randomised controlled trial (RCT) studies the effectiveness of extracorporeal life support (ECLS) in patients with refractory cardiac arrest, a procedure also known as extracorporeal cardiopulmonary resuscitation (ECPR). The design of this study led the authors to this qualitative study into the methodological, ethical and legal considerations that can be faced when pursuing Level-I evidence in emergency medicine. This process yielded some valuable insights that may be useful for all who are designing randomised trials in this field. We describe the three main dilemmas concerning risk, randomisa-

Abbreviations: ACLS, Advanced Cardiac Life Support, APACAR2, A Comparative Study Between a Pre-hospital and an In-hospital Circulatory Support Strategy (ECMO) in Refractory Cardiac Arrest, BLS, Basic Life Support, CPR, CardioPulmonary Resuscitation, ECPB4OHCA, Emergency Cardiopulmonary Bypass for Cardiac Arrest, ECPR, Extracorporeal CardioPulmonary Resuscitation, ECLS, Extracorporeal Life Support, EFIC, Exception from Informed Consent, EMS, Emergency Medical Services, EROCA, ECPR for Refractory Out-Of-Hospital Cardiac Arrest, ICU, Intensive Care Unit, INCEPTION, Early Initiation of Extracorporeal Life Support in Refractory OHCA, IRB, Institutional Review Board, NCT, ClinicalTrials.gov registry, OCEBM, Oxford Centre of Evidence Based Medicine, OHCA, Out-of-Hospital Cardiac Arrest, PI, Principal Investigator, RCT, Randomised Controlled Trial

* Corresponding author at: Department of Intensive Care, Maastricht University Medical Centre, P.O. 5800, 6202 AZ Maastricht, the Netherlands.

E-mail address: martje.suverein@mumc.nl (M.M. Suverein).

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tion and consent, discuss the considerations and solutions as well as share the experience of fellow principal investigators.

The INCEPTION trial and ethical issues

INCEPTION trial design

The INCEPTION trial aims to randomise 110 patients with refractory out-of-hospital cardiac arrest to either continued cardiopulmonary resuscitation (CPR), which is the current gold standard, or extracorporeal cardiopulmonary resuscitation (ECPR).² ECPR is the rapid implementation of a heart–lung machine during cardiac arrest to temporarily take over the circulation as a bridge to diagnosis, treatment, and post-resuscitation support. Systematic reviews and meta-analyses of observational and retrospective studies on ECPR suggest a survival benefit.^{3–6} The INCEPTION trial aims to determine the benefit of ECPR in patients with refractory OHCA, defined as an arrest longer than 15 minutes, presenting with a shockable rhythm. The primary outcome is neurological survival at 30 days.

Risk

Patients eligible for INCEPTION have a very high risk of dying with a survival of less than 8%, which ECPR may increase up to 30% with good neurological outcome.^{7–16} Nevertheless, ECPR is not a “nothing-to-lose” solution. The intervention carries the potential for severe complications, including ECLS related neurological events, bleeding, infection, and cannulation-related vascular complications.^{17,18} Furthermore, it could lead to a bridge-to-nowhere situation: a stable patient on ECLS who is ineligible for transplant or permanent assist device. It could also be an extra emotional burden for relatives, providing false hopes or futile intervention. While it does provide time to bid farewell, temporarily averting death burdens the family with several days of continued uncertainty and, in some instances, by having to ‘turn off’ the life support.¹⁹ Can such a high-risk study intervention be justified in a clinical trial?

Randomisation

A prerequisite for randomised research is clinical equipoise. But even if this is established, what is the influence of mortality on the adherence to randomisation? Despite a strong recommendation by the European Resuscitation Council to improve the quality of the evidence ECPR is increasingly used as a therapy for “back-against-the-wall” situations. When an intervention becomes a more standard practice, randomisation becomes increasingly difficult for the physician at the bedside. It risks cross-over to the arm with the more aggressive intervention, which reintroduces bias into the trial.

Consent

All patients in refractory cardiac arrest need treatment without any delay. In most cases, relatives are absent until after the start of treatment. This renders obtaining informed consent prior to inclusion nearly impossible. Even if present, they would have to decide immediately. One can speculate whether a decision made under such pressure and in a distressed state counts as truly ‘informed’ consent. Furthermore, in a situation where every minute counts, waiting for consent is harmful to the patient.

Despite adequate treatment, most patients die in the first hours after entering hospital. Do we ask informed consent of the relatives just after the news that their relative has passed? Do they have the right to sign for the use of data since their status as ‘active rep-

resentative’ has expired? A large part of the trial consists of data from these patients and it is thus vital for the internal validity.

Considerations

Risk

‘Can a high-risk study intervention, particularly without informed consent, be justified in a clinical trial?’

Risk is the combination of the probability and magnitude of future harm. The Belmont Report states that: “The requirement that research be justified on the basis of a favourable risk/benefit assessment bears a close relation to the principle of beneficence, just as the moral requirement that informed consent be obtained is derived primarily from the principle of respect for persons.”²⁰ While all studies applying for Institutional Review Board (IRB) approval conduct a risk/benefit assessment, no consensus exists on the best classification for risk in research. In general, two or three classifications are used, ranging from minimal to high risk. Each classification triggers different requirements from an IRB and monitor.

The classification is based on the study intervention’s added risk instead of the disease or standard treatment. All existing knowledge of the study intervention should be taken into account. For example, a new indication for a drug that has been in use for decades has a lower risk than a new drug with the same indication since the dosages, and side effects of the former are well-known.

Although mortality does not contribute to the classification, a direct relationship exists between the risk of a disease and the risk that is acceptable in therapeutic research. If the suspected benefits outweigh the potential disadvantages, it is more acceptable to impose risk on subjects entering a clinical trial. The acceptable risk directly relates to the anticipated benefit.

Since the beginning of the pandemic in 2020, physicians need to consider the risk to self and to the team, as well as the patient’s risk. Emergency patients might be contaminated with SARS-CoV-2, and performing ECPR puts a larger team at risk for transmission. Offering ECPR might be too great a risk during certain periods.

Randomisation

‘Is it ethical to randomise to a control arm in a population with extremely high mortality? Is there an increased risk of cross-over?’

On the other hand, the high mortality is an argument to question whether these patients should be randomised at all. Many patients are declared dead shortly after arrival to the hospital, and one might wonder if being in the control group harms patients.

New treatments are often enthusiastically embraced after some positive initial publications, despite the lack of proper evidence. Disproving this easily established faith in an intervention that ultimately turns out to be ineffective may take years and several high-quality randomised controlled trials.^{21,22} And the “no harm, no foul”-argument does not apply, as ECPR carries several risks and burdens. Moreover, a well-functioning ECPR program requires a substantial investment from institutions. Not randomising carries the risk that an ineffective, complex and expensive treatment is widely implemented based upon weak evidence.

The European Resuscitation Council guidelines underlined the pressing need to improve the evidence regarding ECPR.²³ The best-known grading system is developed by the Oxford Centre of Evidence Based Medicine (OCEBM).²⁴ This system objectively grades evidence with an increasing level inverse to the chance of bias of

a given type of research. Level-I is reserved for systematic reviews of high-quality RCTs, producing comparable groups and eliminating selection bias. Furthermore, RCTs follow a predetermined protocol with monitoring of adherence, have better long-term follow-up and clinical endpoint data than retrospective studies. A notable exception in the OCEBM grading system is the so-called “all-or-nothing” study when case series of a novel treatment consistently show a positive or negative outcome in all included patients. Such is considered to be Level-I evidence in the latest revision by the OCEBM. However, care must be taken not to abuse this regulation to defend “no-gain, no-loss” treatments.

Randomisation relies on the attending physician. Withholding a potentially life-saving (or temporarily life-extending) treatment to a succumbing patient may feel frustrating or unethical to a physician. Even despite lacking evidence for the procedure. In studies where the main outcome is hidden (e.g., myocardial damage on an MRI), both arms do not yield a direct and visible clinical outcome. This sharply contrasts with INCEPTION, where at least 70 to 90% of patients die during resuscitation, and that outcome is irreversible. The physician’s urge to intervene in an individual patient is understandable and could invoke cross-over to the arm with the more aggressive intervention.

This is a slippery slope; switching a patient from control to intervention seems to put patient interest above randomisation. However, it does remove some of the lustres from the gold standard of randomisation. Randomisation eliminates selection bias; it maintains objectivity to generate the best evidence. But if it is modified based on clinical judgment, are the results of a randomised controlled trial better than those of a retrospective study? This is the paradox of randomisation, evidence, and risk: randomisation removes bias but can increase individual risk, and when protocols permit re-assignment of participants to different arms, it reintroduces bias.

However, the clinical reality is that preparation for ECPR takes time, and the protocol for ECPR gives a team time to organize the effort before arrival of the patient. Since every minute counts in a resuscitation, one can argue that a cross-over is not a “true” per protocol cross-over. The delay in start of ECPR in case of cross-over blunts the potential survival benefit.

Consent

‘How should the informed consent procedure be handled when the majority of patients die shortly after arrival at the hospital?’

Informed consent is the ethical cornerstone of medical research in humans: investigators must obtain informed consent prior to subjecting a patient to study interventions. In emergency medicine, however, the very nature of the condition and situation may negate the ability to make a well-informed, autonomous decision. This means that the mechanisms of the consent process need to be modified, to preserve the integrity of this contract between researcher and study patient.

Deferred consent

The INCEPTION trial uses both deferred and a waiver of consent. If the patient survives, deferred consent to participation is sought, first from the relatives and when possible from the patient itself. This is a widely accepted form of informed consent in emergency medicine.

The term ‘deferred consent’ can, strictly speaking, be misrepresentative when the patient already underwent the intervention or

control treatment of the trial. Instead, the patient is informed about his or her participation in the treatment phase of the trial. They can then decide to consent to the use of their data and whether to participate in follow-up. In essence, deferred consent to the intervention is impossible; it is only deferred in the sense that the consent question for data use follows at a later stage. The patient needs to be aware that the choice before him or her only concerns the use of data and participation in follow-up. When a patient survives with good health, this is a relatively simple decision. But when, for example, left with a seriously disabling complication, it might be a burden knowing they were unknowingly a trial participant.

Waiver of consent

As abovementioned, most patients die quickly after hospital admission. In these cases, how can we do justice to the informed consent procedure? The gathered data is invaluable; it represents the ‘worst’ part of the population and is therefore essential for the internal validity of the study. Removing the data introduces selection bias, which not only affects the study results – possibly harming future patients –, but also undervalues the contribution made by the other participating patients.²⁵ So, should proxy consent be asked from grieving relatives? Confronting grieving relatives can be seen as harm or burden. Adopting policies that prevent seeking deferred consent from grieving relatives seems morally more correct. One option would be to extend the time to seek consent, but this brings new practical problems: do we inform directly but ask consent later? What if relatives do not want to come back into the hospital? Can this be done over the phone? Or should we simply inform the relatives of the participation?²⁶

But putting ethical and practical issues aside, there is the added question of the right of the relatives to give informed consent. During life, while the patient is incapacitated, the family members are the legal representatives. But are they still after death? Their only concern can be the privacy of the patient, but careful handling and confidential use of data do not harm these interests. In the age of well-regulated research governed by IRB’s, monitoring by an independent Clinical Research Associate, and regular evaluation of patient safety by a Data Safety Monitoring Board, it is not entirely clear that consent is always required. Because of these safeguards, there is very little risk of abuse, additional costs, or unnecessary risk – and consent may not be required. Faden and colleagues suggest that informing the patient community that comparative effectiveness research is routinely conducted is the most that can be done in terms of consent in many such cases²⁷ – and maybe the same applies to emergency medicine research?

In the INCEPTION trial, relatives are informed of trial participation post resuscitation; they receive an information letter containing contact details and the offer to consult with the attending physician and a research team member for any lingering questions. This decision is underpinned by Dutch legislation that states that proxies’ legal representation ends after death; thus, proxy consent can only be pursued for living patients. To qualify for a waiver of consent, three conditions need to be met:

1. Patients should receive the standard treatment or a new treatment with a possible benefit.
2. The gathered data can be used to improve the health of the population.
3. During life, patients have not explicitly stated their objection against participation.

When relatives turn out to be adamantly opposed to the study after explanation, it is seen as an expression of the patient's objection, and the data is withdrawn from the analysis.

Experiences of other trials

Concurrent with the INCEPTION trial, five other randomised controlled trials on ECPR have been recruiting patients, summarized in Table 1. We contacted the principal investigators (PI's) to learn from their research experience in this setting.

IRB approval process

The PI's reported various discussions with the Institutional Review Board. The three main topics were: difficulty getting approval for a study without consent, lengthy approval process to get a waiver of consent, and difficulty using CCPR as a control.

In Prague, the IRB did not have much prior experience with randomisation before consent.²⁸ Only with the TTM trial, which randomised at the hospital with two physicians' consent.²⁹ The main point of discussion for the current study was that randomisation was even earlier – on the street by the EMS. The approval process took two years and eventually was approved based on the latest revision of the declaration of Helsinki that research is allowed if the patient is unconscious; providing that the trial concerns the condition preventing the person from consenting, the treatment is at least equal to the standard one, and proxy consent is obtained as soon as possible. The IRB in Vienna approved the intervention, but they did state concerns regarding the recruitment frequency. This turned out to be valid as they have had recruitment problems and are currently on hold.

In Ann Arbor and Minneapolis,^{30,31} the IRB had experience with the Exception From Informed Consent (EFIC). However, under the FDA and local IRB regulations, approval for EFIC is a lengthy process of community consultation and public disclosure of the study. Community consultation entails face-to-face meetings, focus groups, and presence at events in the municipality. An added value of these meetings was the opportunity to discuss cardiac arrest with the public. Once a majority of the consulted public has agreed a trial should ensue, the IRB can approve, and the trial is advertised in social media advertisements and flyers. If, after public disclosure, members of the public do not want to participate, they have the option to prospectively opt-out by wearing a bracelet or adding "EROCA or ARREST study declined" to their File of Life card. A card commonly used in the USA, often placed in the wallet or on the refrigerator, holding emergency contacts and advanced health care directives. Both were available via the trial website but are rarely requested.

Some of the research groups have been performing and publishing on ECPR for several years. Having seen positive results from past trials has made it difficult for some to establish equipoise. While the intervention has not proven superior in international literature, the local results can make the control arm seem unethical. The current trial in Paris compares in-hospital with pre-hospital ECPR, which brings the intervention to the patient on the street. Changing the location to shorten delays was quickly approved. However, while designing the trial, they intended to include three arms: pre-hospital, in-hospital, and conventional. Because of their published previous success with ECPR, the IRB judged it unethical to have a control arm. Minneapolis has been performing and fine-tuning their ECPR process for years and with a high survival - but not in a randomised setting. They designed an adaptive trial in which the ran-

domisation could be altered to a different ratio, not exceeding 3:1, in either direction. After each DSMB meeting, the randomisation could be adjusted; this method assured that a larger group of patients could benefit from the superior treatment than standard randomisation. However, this did not turn out to be necessary; the trial was terminated early by the DSMB since, after 30 patients, the interventional arm had proven to be superior.

Cross-over

Outside of the research team, colleagues often have a preference for one arm over the other. When the investigators are not present, this can lead to cross-overs. Most centres describe that there is an evident preference for the intervention arm. Prague and Vienna allow for cross-over if the clinician decides this favours the patient; this occurred in 17 cases in Prague. The switch from control to intervention is usually based on age and is often initiated by the EMS, which prefer the invasive arm. Their protocol also allows the physician not to continue to ECPR when there are signs of death or irreversible organ damage. In Paris, the EMS appear to have a preference for pre-hospital ECPR over in-hospital. However, cross-over is impossible since it would entail changing the entire location. The preference is based on the assumption that the shorter delay is the reason for better results. However, the pre-hospital protocol is possibly also better developed than the in-hospital logistics, by necessity, since all equipment needs to be present and easily accessible. In Ann Arbor, the option of ECPR was open for all patients, but the patients in the expedited transport arm were transported earlier to see if this would result in more ECPR candidates. Minneapolis sidestepped the issue of cross-over by having an investigator present at all randomisations.

Consent

Three RCTs – Prague, Vienna and Ann Arbor – continue on-site resuscitation for the control arm. In Prague and Vienna, when the patient dies on scene, consent is waived, and since there is no contact with the family, they are not informed. In Ann Arbor and Minneapolis, family members receive a letter of notification. When a patient in the interventional arm dies in the hospital, Prague will always ask for proxy consent from the family, leading to 7 exclusions out of 247 patients. In Paris, the family is informed of study participation but not asked for consent. In Ann Arbor and Minneapolis, passing before consent falls under the EFIC guidelines, and data can be used. The family member can no longer consent as the participation ends at the death. Vienna does not ask for informed consent from the family but will inform them openly about the study.

After ICU admission, Prague, Minneapolis, Ann Arbor, and Paris asked the relatives for informed consent for the use of data and continued study participation. In Minneapolis, this has to be done within 24 hours and face-to-face. If a family member withdraws consent, the gathered data thus far can still be used. In Vienna, during this time, the family is informed but not asked for consent. In all centres, patients are asked for consent when they regain consciousness.

Conclusions and recommendations

When considering risk in research, two types of risk are important: the added risk of the trial intervention and the baseline risk of the disease. The first should always be as low as possible, but the higher the disease's baseline risk, the more acceptable it becomes to study a high-risk treatment.

Table 1 – Overview of currently recruiting ECPR trials.

	Hyperinvasive Approach in Cardiac Arrest	ARREST	EROCA	ECPB4OHCA	APACAR2	INCEPTION
	Prague, Czech Republic	Minneapolis, Minnesota, United States	Ann Arbor, Michigan, United States	Vienna, Austria	Paris, France	The Netherlands
Study						
Recruitment status (n) [#]	250/250 completed	30/30 completed early	15/30 completed early	4/40 terminated early	68/210 terminated early	134/134 completed
NCT	01511666	03880565	03065647	01605409	02527031	03101787
Treatment						
Intervention	Hyperinvasive arm	In-hospital ECPR	Expedited transport with mechanical CPR for in-hospital ECPR	In-hospital ECPR	Pre-hospital vs. in-hospital ECPR	In-hospital ECPR
Control	On-site ACLS	Transport to hospital for ACLS	On-site ACLS	On-site ACLS	Not allowed	Transport to hospital for ACLS
Cross-over allowed	Yes	No	Yes	Yes	No	Yes
Consent						
Proxy deferred consent	Yes	Yes	Yes	No	Yes	Yes
Waiver of consent	No	Yes	Yes	Yes	Yes	Yes

[#]as per February 2021; ACLS: Advanced Cardiac Life Support, CPR: Cardiopulmonary Resuscitation, ECPR: Extracorporeal Cardiopulmonary Resuscitation, EROCA: ECPR for Refractory Out-Of-Hospital Cardiac Arrest; ECPB4OHCA: Emergency Cardiopulmonary Bypass for Cardiac Arrest, APACAR2: A Comparative Study Between a Pre-hospital and an In-hospital Circulatory Support Strategy (ECMO) in Refractory Cardiac Arrest, INCEPTION: Early Initiation of Extracorporeal Life Support in Refractory OHCA; NCT: ClinicalTrials.gov registry.

The first step towards randomisation should always be the establishment of equipoise, based on existing literature and guideline recommendations. Yet even with established equipoise randomisation, it might be morally difficult for an attending physician to randomise, which underlines the importance of performing a trial before widespread implementation of a treatment. If the risk of cross-over is considered to be high, one should always consider whether randomisation is really better than retrospective studies. Yet, in some interventions, for example the MR CLEAN trial and COACT trial,^{32,33} time plays such an important role that cross-over is not comparable to the original intervention. In these complex cases, a close eye should be kept on the current status of evidence. If there is a preponderance of evidence that a new intervention is efficacious, equipoise may be lost, and randomisation to the control arm could be unethical.

It is justified to include patients as participants without consent where they lack capacity and seeking it would be impractical or even harmful. Surviving patients must then be informed to decide whether they allow their data to be used for research and whether they are willing to participate in follow-up. They should not be asked for consent for the intervention retroactively because that would be meaningless, and the same applies to their relatives.

Ethical approval and consent to participate

Not applicable.

Consent for publication

All authors have approved the manuscript and agree with its submission to Resuscitation.

Availability of supporting data

Not applicable.

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Declaration of Competing Interest

Professor JG Maessen is a member of the Medical Ethical Review Board of Maastricht University Medical Centre. He has not been involved in any part of the review and approval process of the protocol of the INCEPTION trial.

CRedit authorship contribution statement

Martje M. Suverein: Conceptualization, Investigation, Data curation, Writing – original draft, Writing – review & editing. **David Shaw:** Conceptualization, Investigation, Writing – original draft, Writing – review & editing. **Roberto Lorusso:** Conceptualization, Writing – review & editing, Supervision. **Thijs S.R. Delnoij:** Conceptualization, Writing – review & editing. **Brigitte Essers:** Conceptualization, Writing – review & editing. **Patrick W. Weerwind:** Conceptualization, Writing – review & editing. **David Townend:** Conceptualization, Writing – review & editing, Supervision. **Marcel C.G. van de Poll:** Conceptualization, Writing – review & editing, Supervision. **Jos G. Maessen:** Conceptualization, Writing – review & editing, Supervision.

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REFERENCES

1. World Medical Association Declaration of Helsinki. ethical principles for medical research involving human subjects. *JAMA* 2013;310:2191–4.
2. Bol ME, Suverein MM, Lorusso R, et al. Early initiation of extracorporeal life support in refractory out-of-hospital cardiac arrest: Design and rationale of the INCEPTION trial. *Am Heart J* 2019.
3. Kim SJ, Kim HJ, Lee HY, Ahn HS, Lee SW. Comparing extracorporeal cardiopulmonary resuscitation with conventional cardiopulmonary resuscitation: A meta-analysis. *Resuscitation* 2016;103:106–16.
4. Xie A, Phan K, Tsai Y-C, Yan TD, Forrest P. Venous arterial extracorporeal membrane oxygenation for cardiogenic shock and cardiac arrest: a meta-analysis. *J Cardiothorac Vasc Anesth* 2015;29:637–45.
5. Ouweneel DM, Schotborgh JV, Limpens J, et al. Extracorporeal life support during cardiac arrest and cardiogenic shock: a systematic review and meta-analysis. *Intensive Care Med* 2016;42:1922–34.
6. Wang G-N, Chen X-F, Qiao LI, et al. Comparison of extracorporeal and conventional cardiopulmonary resuscitation: A meta-analysis of 2 260 patients with cardiac arrest. *World J Emerg Med* 2017;8:5. <https://doi.org/10.5847/wjem.j.1920-8642.2017.01.001>.
7. 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.
8. 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.
9. 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.
10. Bellezzo JM, Shinar Z, Davis DP, et al. Emergency physician-initiated extracorporeal cardiopulmonary resuscitation. *Resuscitation* 2012.
 11. 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.
 12. Le Guen M, Nicolas-Robin A, Carreira S, et al. Extracorporeal life support following out-of-hospital refractory cardiac arrest. *Crit Care* 2011.
 13. Maekawa K, Tanno K, Hase M, et al. Extracorporeal cardiopulmonary resuscitation for patients with out-of-hospital cardiac arrest of cardiac origin: A propensity-matched study and predictor analysis. *Crit Care Med* 2013.
 14. Shin SD, Suh GJ, Ahn KO, Song KJ. Cardiopulmonary resuscitation outcome of out-of-hospital cardiac arrest in low-volume versus high-volume emergency departments: An observational study and propensity score matching analysis. *Resuscitation* 2011;82: 32–9.
 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.
 16. Fjølner J, Greisen J, Jørgensen MRS, et al. Extracorporeal cardiopulmonary resuscitation after out-of-hospital cardiac arrest in a Danish health region. *Acta Anaesthesiol Scand* 2017;61:176–85.
 17. Cheng R, Hachamovitch R, Kittleson M, et al. Complications of extracorporeal membrane oxygenation for treatment of cardiogenic shock and cardiac arrest: a meta-analysis of 1,866 adult patients. *Ann Thorac Surg* 2014;97:610–6.
 18. Kreibich M, Benk C, Leitner S, et al. Local and Lower Limb Complications during and after Femoral Cannulation for Extracorporeal Life Support. *Thorac Cardiovasc Surg* 2019;67:176–82.
 19. Riggs KR, Becker LB, Sugarman J. Ethics in the use of extracorporeal cardiopulmonary resuscitation in adults. *Resuscitation* 2015;91:73–5.
 20. BB F: Belmont Report. SAGE Encycl Educ Res Meas Eval; 2018.
 21. Heyland DK, Dhaliwal R, Day AG, et al. REducing Deaths due to OXidative Stress (The REDOX Study): Rationale and study design for a randomized trial of glutamine and antioxidant supplementation in critically-ill patients. *Proc Nutr Soc* 2006;65:250–63.
 22. Soeters P, Bozzetti F, Cynober L, et al. Meta-analysis is not enough: The critical role of pathophysiology in determining optimal care in clinical nutrition. *Clin Nutr* 2016;35:748–57.
 23. Soar J, Nolan JP, Böttiger BW, et al. European Resuscitation Council Guidelines for Resuscitation 2015: Section 3. Adult advanced life support. *Resuscitation* 2015;95:100–47.
 24. Durieux N, Pasleau F. OCEBM Levels of Evidence Working Group. *Oxford Levels Evid* 2011.
 25. Jansen TC, Kompanje EJO, 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;33:894–900.
 26. Perkins GD, Ji C, Deakin CD, et al. A Randomized Trial of Epinephrine in Out-of-Hospital Cardiac Arrest [Internet]. *N Engl J Med* 2018;379:711–21. <https://doi.org/10.1056/NEJMoa1806842>.
 27. Biros MH, Runge JW, Lewis RJ, et al. Emergency medicine and the development of the Food and Drug Administration's final rule on informed consent and waiver of informed consent in emergency research circumstances. *Acad Emerg Med Off J Soc Acad Emerg Med* 1998;5:359–68.
 28. Belohlavek J, Kucera K, Jarkovsky J, et al. Hyperinvasive approach to out-of hospital cardiac arrest using mechanical chest compression device, prehospital intraarrest cooling, extracorporeal life support and early invasive assessment compared to standard of care. A randomized parallel groups comp. *J Transl Med* 2012;10:163.
 29. Nielsen N, Wetterslev Jørn, Cronberg T, et al. Targeted temperature management at 33°C versus 36°C after cardiac arrest. *N Engl J Med* 2013;369:2197–206.
 30. Hsu CH, Meurer WJ, Domeier R, et al. Extracorporeal Cardiopulmonary Resuscitation for Refractory Out-of-Hospital Cardiac Arrest (EROCA): Results of a Randomized Feasibility Trial of Expedited Out-of-Hospital Transport. *Ann Emerg Med* 2021;78:92–101.
 31. Yannopoulos D, Bartos J, Raveendran G, et al. Advanced reperfusion strategies for patients with out-of-hospital cardiac arrest and refractory ventricular fibrillation (ARREST): a phase 2, single centre, open-label, randomised controlled trial. *Lancet* 2020.
 32. Lemkes JS, Janssens GN, van der Hoeven NW, et al. Coronary Angiography After Cardiac Arrest Without ST Segment Elevation: One-Year Outcomes of the COACT Randomized Clinical Trial. *JAMA Cardiol* 2020;5:1358. <https://doi.org/10.1001/jamacardio.2020.3670>.
 33. Berkhemer OA, Fransen PSS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med* 2015;372:11–20.