Review

Ethics of ECPR research

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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, 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. 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-

References

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

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

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). 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. 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. 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. 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. 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 representative’ 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.” 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. 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. The best-known grading system is developed by the Oxford Centre of Evidence Based Medicine (OCEBM). This system objectively grades evidence with an increasing level inverse to the chance of bias of
The INCEPTION trial uses both deferred and a waiver of consent. If the patient already underwent the intervention or the patient survives, deferred consent to participation is sought, first to preserve the integrity of this contract between researcher and participant when the patient community that comparative effectiveness research is routinely conducted is the most that can be done in terms of consent in many such cases 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. Only with the TTM trial, which randomised at the hospital with two physicians’ consent. 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, 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 gathered data thus far can still be used. In Vienna, during this time, the family is informed but not asked for consent. 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 ask the relatives for informed consent for the use of data and continuation of cross-over. In Minneapolis, family members receive a letter of notification. When a patient in the interventional arm dies in the hospital, Prague will ask the relatives for informed consent for the use of data and continuation of cross-over. In Minneapolis, family members receive a letter of notification. When a patient in the interventional arm dies in the hospital, Prague will ask the relatives for informed consent for the use of data and continuation of cross-over. In Minneapolis, family members receive a letter of notification. When a patient in the interventional arm dies in the hospital, Prague will ask the relatives for informed consent for the use of data and continuation of cross-over. In Minneapolis, family members receive a letter of notification. When a patient in the interventional arm dies in the hospital, Prague will ask the relatives for informed consent for the use of data and continuation of cross-over.

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>
<thead>
<tr>
<th>Study</th>
<th>Recruitment status (n)</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>Hyperinvasive</td>
<td></td>
<td>In-hospital ECPR / Expedited transport with mechanical CPR for in-hospital CPR</td>
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<td>Approach in Cardiac Arrest</td>
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<td>Pre-hospital vs. in-hospital ECPR</td>
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<td>ARREST</td>
<td>30/30 completed early</td>
<td>In-hospital ECPR</td>
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<td>EROCA</td>
<td>15/30 completed early</td>
<td>On-site ACLS</td>
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<tr>
<td>ECPB4OHCA</td>
<td>4/40 terminated early</td>
<td>Transport to hospital for ACLS</td>
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<tr>
<td>APACAR2</td>
<td>68/210 terminated early</td>
<td>On-site ACLS</td>
</tr>
<tr>
<td>INCEPTION</td>
<td>134/134 completed</td>
<td>On-site ACLS</td>
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#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 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. Thijis 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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