. ETHICS REVIEW APPEALS BOARD

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Ö 62-2022/3.1

# Appellant

Region Stockholm

# Decision being appealed

The Swedish Ethical Review Authority’s decision of 19 September 2022, Ref. no. 2022-02446-01; see Appendix 1.

**Project title** PRINCESS2 - A Swedish-led, randomised, European multicentre study investigating the effect of ultra-early therapeutic hypothermia in the event of cardiac arrest

# The case

Examination under the Act (2003:460) concerning the Ethical Review of Research Involving Humans (the Ethical Review Act)

# Decision of the Appeals Board

The Ethics Review Appeals Board approves the research referred to in the application, subject to the following conditions regarding the information provided to research subjects:

* The term “Anonymised" is replaced by a correct description
* the term “Patient Ombudsman Manager” is replaced by the correct title, and contact details are provided.

# Background

Of people who suffer an out-of-hospital cardiac arrest, about a third are still living by the time they reach the hospital. Of these, more than half die due to severe brain damage caused by lack of oxygen in connection with the cardiac arrest. There are promising results from animal studies in which body temperature has been lowered very early after cardiac arrest; brain tissue is protected and survival is improved. In contrast, clinical treatment studies in which therapeutic hypothermia was induced later in the course of treatment have not been able to demonstrate clear beneficial effects. In the ethical approval application, the evidence for therapeutic hypothermia (targeted temperature management) following cardiac arrest is described as disputed, and clinical practice varies.

The research team behind this application, together with researchers in other countries, has developed a method by which therapeutic hypothermia treatment is administered via the nose by first-responding paramedics at the site of the cardiac arrest. The treatment has been evaluated in two small-scale, randomised trials. These have shown that the treatment concept is feasible. There has been what the researchers describe as a “signal” of better survival rates and better neurological function in the survivors.

In a large, multinational, and randomised clinical trial, the researchers now intend to compare the medical outcome for people treated with therapeutic hypothermia at the site of cardiac arrest, followed by therapeutic hypothermia in intensive care, with the outcome for patients who received conventional care. Therapeutic hypothermia is induced by delivering a combination of medical oxygen and coolant via the nose, through a device specially developed for this purpose. A total of 970 research subjects will be included in the study; out of 20 participating centres, four will

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be Swedish. The primary outcome measure is survival without severe neurological impairment 90 days after cardiac arrest. Quality of life at the 90-day follow-up and function after one year are also studied.

After receiving a response regarding the requested additional information, the Swedish Ethical Review Authority rejected the application. The Authority found that the conditions for research without consent under Section 21 of the Ethical Review Act were indeed met, but that the requirement for consultation with relatives, trustees or guardians before the research begins (Section 22) was not met.

In the appeal, the appellant refers to previous approvals for cardiac arrest research granted by the Ethical Review Authority and regional ethical review boards. This includes the two randomised trials that the research team previously conducted. In addition, reference is made to the EU Regulation on Clinical Trials and the Declaration of Helsinki. The appellant believes that the Ethical Review Authority’s decision involves an over-interpretation of the law and that it is questionable from a medical point of view.

The appellant has been represented by Per Nordberg and Fredrik Wersäll, legal advisors in the research project, who gave oral testimony at the Board’s meeting on 15 December 2022.

# Grounds for the decision

This application concerns a new treatment concept for cardiac arrest, wherein specific treatment is initiated by paramedics at the site of the cardiac arrest. In addition to the fact that the research subject is unable to give consent, it is obvious that there is no time for informed consultation with relatives.

The Ethical Review Act does not address situations arising in research on interventions in the event of cardiac arrest and similar life-threatening conditions where immediate action is required. Nor does the bill for the latest amendment to the law (Government Bill 2018/19:165), discuss the possibility of preemptive ethical approval and the deferred obtainment of informed consent or consultation with relatives when the subject is incapacitated due to very severe, acute illness. Moreover, the law provides no guidance on how to handle the situation when there are no relatives.

The Appeals Board’s assessment is that these gaps in the law allow for different legal interpretations regarding research on emergency interventions in the event of cardiac arrest. This is illustrated by the fact that in several cases, the Swedish Ethical Review Authority and the previous regional ethics committees have decided to grant ethical approval for deferred consent obtained from survivors competent to make decisions, or alternatively by informing relatives after treatment is provided (e.g., Ref. no. 2014/1170-31/1, 2017/1990-32, 2020-06906). On two previous occasions, the appellant’s research team has obtained ethical approval for projects that applied the same procedure for deferred consent and consultation with relatives as in the present

research project.

The Ethical Review Authority and the previous regional ethical review boards have usually rejected an application when the research subject’s acute condition did not allow for consent to be obtained and consultation with relatives was impossible. The Ethical Review Appeals Board has consistently rejected such applications. The Appeals Board has now re-examined the grounds for

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reconsidering this interpretation of the law. The Board’s starting point has been that an ethical review must take into account fundamental ethical values, the aims of the Ethical Review Act, and recent national and international legal developments.

Failing to take advantage of the possibility of scientific progress is - after taking risks into account - an active decision that may have negative ethical implications. Based on the principle of need, this applies to a particularly high degree to very serious conditions where potential knowledge gains include both survival and possible reduction of residual disability among survivors.

At its base, the Ethical Review Act is protective legislation. The Appeals Board finds that in the research project in question, the risk of significant physical or psychological harm is low. In the largest clinical trial to date of the use of this therapeutic hypothermia method in treating cardiac arrest, nosebleeds were the most common side effects that could be directly tied to the treatment. Treatment had to be discontinued in one per cent of subjects due to major nosebleeds (JAMA 2019; 321:677-85).

The integrity of the research subjects is respected if informed consent is obtained after the fact from survivors competent to make decisions, or if relatives are consulted as soon as they are available for longer conversations. The Appeals Board thus finds the protection of the research subjects in the research project in question to be sufficient. Animal experimental studies and early clinical trials of the current treatment concept have shown that the treatment concept is feasible and has some potential to provide beneficial effects to people who suffer from cardiac arrest. The Appeals Board considers the potential knowledge gains to be greater than the risks. There is also a certain possibility that research subjects who receive active treatment will directly benefit from theintervention.

While situations in which a research subject is unable to give consent due to severe acute illness are not regulated in the Ethical Review Act, they have been foreseen in other Swedish and international regulations.

In the Patient Act (2014:821), wherein great emphasis is placed on the patient’s consent to examination and treatment, the legislator foresaw situations in which the patient is unable to make decisions as a result of severe, acute illness.

Patients must be provided with the healthcare necessary to avert a danger that poses an acute and serious threat to their life or health, even if their will cannot be determined due to unconsciousness or for some other reason (The Patient Act, Chapter 4, Section 4).

In the government bill for the Ethical Review Act (2002/03:50), the section on informed consent is based entirely on the European Convention on Bioethics. Sweden is a signatory to the convention and has thereby undertaken to comply with it. An additional protocol to the Council of Europe’s Convention on Bioethics (“the Oviedo Convention”; CETS 195 - Human Rights and Biomedicine (Protocol), 25.1.2005) discusses Article 19 - “Research on persons in emergency clinical situations”. It sets out the specific situations that the legislation should cover. Regarding consent, it says:

Persons participating in the emergency research project or, if applicable, their representatives shall be provided with all the relevant information concerning their participation in the research project as soon as possible. Consent or authorisation for continued participation shall be requested as soon as reasonably possible.

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This additional protocol, which thus allows for deferred consent, was drafted after the Swedish Ethical Review Act 2002/03. However, Sweden has not fulfilled its international commitment to include the additional protocol in Swedish legislation.

The EU Clinical Trials Regulation (No. 536/2014) has been in force as Swedish law since 31 January 2022. Article 35 of the Regulation sets out the scope of clinical trials in emergency situations. It specifies the circumstances that must exist in order for an emergency drug trial to be permitted without the consent of the research participant; in such cases, consent must be obtained retrospectively (so-called “deferred subject consent”). The Appeals Board considers that similar circumstances exist in the study in question. However, the regulation only applies to clinical trials. Since its transposition into Swedish law, a contradictory situation has arisen: Research on acute interventions for treating cardiac arrest and similar acute conditions can be approved if it involves medications, but other types of interventions with similar potential knowledge gains and risks cannot gain approval.

The Appeals Board’s conclusion is that the legislation leaves room for different interpretations of the law, since the situation to which the application in question relates is not foreseen in the Ethical Review Act or in the government bill. The Appeal’s Board finds that applying the strictest possible interpretation of the law is contrary to fundamental ethical principles, the purpose of the Ethical Review Act (protective legislation), and legal developments as reflected in the positions adopted in the Swedish Patient Act,the Council of Europe’s Convention on Bioethics, and the EU Regulation on Clinical Trials.

The application includes information for research subjects. This is based on the EU Regulation’s provision on deferred consent. The information provided to the research subjects contains inaccuracies regarding the data being “anonymised” (a code key will be retained), as well as the term “Patient Ombudsman Manager". If the appellant is referring here to the Data Protection Officer, contact details must be provided.

Overall, the Appeals Board finds that the research can be approved, on the condition that the inaccuracies in the information provided to the research subjects are corrected.

According to Section 37 of the Ethical Review Act, a decision by the Appeals Board may not be appealed.

This decision has been taken by Carina Gunnarsson (dissenting; see Appendix 2), Yvonne Lundberg Giwercman, Kjell Asplund (rapporteur), Ingemar Engström, Ann Wennerberg, and Lena Näslund. The alternates Christina Eintrei, Johan Fritzell and Birgitta Hubinette, as well as Administrative Director Jörgen Sviden (special opinion; see Appendix 3), Administrative Secretary Katarina Gate Lundgren, and Legal Counsel Johanna Sjöcrona (special opinion) have also participated in the final processing of the case.

On behalf of the Appeals Board



Chairperson Carina Gunnarsson dissents and states: I agree with the majority’s assessment that the research in question is urgent. However, Section 22 of the Ethical Review Act affords no room to approve this research. Rather, it requires that consultation has taken place with the research participant’s next of kin, or where applicable with a trustee or administrator, before the research begins.

The Appeals Board, as well as other authorities, have on several occasions made requests to the Government for an amendment to the provision that would make it possible to carry out research projects of this kind. However, no change has been made. Thus, this application, which is based on the assumption that consultation cannot take place before the research begins, cannot be approved. In my view, the decision under appeal should therefore remain unaltered.

Special opinion by Permanent Secretary Jörgen Sviden and Legal Counsel Johanna Sjöcrona: For the reasons cited by the minority, we consider that the application cannot be approved.