

# Ethical principles for medical research in Emergency Medicine\*

## *Princípios éticos para pesquisa médica na Medicina de Emergência*

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In between 1942 and 1945, several “medical experiments” were conducted on prisoners in Nazi concentration camps. All of these experiments are condemned and have no medical value. A 1990 review of the freezing experiments at Dachau concluded that the study had “all the ingredients of a scientific fraud,” and the data “do not advance science or save human lives.”<sup>1</sup> The doctors involved were tried in the case of *US v. Karl Brandt et al.* In their defense, the doctors argued that there was no international law on medical experimentation.

In response, Leo Alexander and Andrew Ivy, representing the American Medical Association, wrote a ten-point memorandum. This document became known as the Nuremberg Code, a collection of ethical principles for research in human experimentation.<sup>2</sup> In the section entitled “Permissible Human Experiments,” they state that “voluntary consent is absolutely essential”.<sup>2</sup> “The person involved must have the legal capacity to give consent, exercising his power of free choice without intervention of force, fraud, coercion, undue pressure, deception or any form of constraint, and having sufficient knowledge and comprehension of the elements involved in the matter to enable an understanding and enlightened choice”.<sup>2</sup>

This is a statement of human dignity in the face of the barbarity that had occurred.

The Declaration of Helsinki,<sup>3</sup> adopted in 1964, developed the ten principles of the Nuremberg Code and linked them to the Declaration of Geneva,<sup>4</sup> the modern version of the Hippocratic oath. The Declaration of Helsinki has undergone seven revisions, the most recent of which was held in Caucaia, in the metropolitan region of Fortaleza, in October 2013.

The evolution of the original code to the current declaration shows that consent has changed from “absolutely essential” to “always obtained if possible.” More specifically, paragraphs 28 and 30 of the declaration concern emergency medicine.<sup>3</sup> These paragraphs address research subjects who are unable to provide informed consent. In Article 28, the recommendation is to seek informed consent from the legally authorized representative, but this is not enough. It is also necessary that the research can only be approved if the research subject is part of the population that will benefit from the results; the nature of the research requires the involvement of individuals who cannot provide informed consent; the research brings only minimal risk. Many areas of emergency medicine meet these criteria – for example, research

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on cardiac arrest, orotracheal intubation, primary trauma care, stabilization and supportive treatment of the critically ill patient. The benefit of the research usually does not occur during the research, but at its end, finding or rejecting the hypothesis. Research subjects are part of the very population that will have this benefit at the end, meeting the first condition. There is no way to study cardiac arrest in conscious and consenting patients, fulfilling the second condition. Finally, when the declaration mentions that the research should bring minimal risk, it means that the additional risk brought by the research should be minimal. Although the situation of cardiac arrest is not low risk, the research intervention should add minimal risk.

Article 29 addresses research subjects who cannot provide informed consent but are able to express a refusal.<sup>3</sup> This refusal must be respected.

Article 30 requires that research involving subjects who are physically or mentally incapable of giving consent, such as unconscious subjects, can only take place if the mental or physical condition that impairs consciousness is a necessary characteristic of the group being studied. In this circumstance, the physician must obtain consent from the legally authorized representative.<sup>3</sup> However, there are cases where the research does not allow waiting. The declaration states that the study may proceed without informed consent provided that the situation is described in the research protocol and the study has been approved by an ethics research committee<sup>2</sup>. Consent to remain in the research must be obtained as soon as possible from the subject or his legally authorized representative.

There is a controversy over the term “consent to remain.” The declaration seems to dispense with the authorization to keep in the research what happened before obtaining late consent and only requests authorization to remain in the research. In general, in emergency medicine, the main intervention has already occurred at this point. The most correct thing would be to obtain authorization to keep the data already obtained and continue the follow-up in the research

These articles of the Declaration of Helsinki attempt to balance the need for progress in medical knowledge at the forefront of emergency medicine with respect for human dignity and the ethical principles of research in humans. The following are examples of how these guiding principles have been applied to state-of-the-art research in emergency medicine.

The PARAMEDIC 2 study investigated the benefit of adrenaline in out-of-hospital cardiac arrest.<sup>5</sup> The ethics committee determined that the study would take place with informed consent deferred until the patient’s improvement. The study was announced in Warwickshire, England, and researchers provided residents with bracelets inscribed with “no study”. Patients with this bracelet were not included in the study. Those without the bracelet were randomized to receive adrenaline or placebo. For survivors, informed consent was obtained later.

The AIRWAYS 2 study tested orotracheal intubation compared to the use of supraglottic devices in patients treated in the pre-hospital setting by paramedics in England.<sup>6</sup> In this study, all eligible patients were automatically included in the study under an ethics committee-approved waiver of consent.

The TROICA study, which tested the use of thrombolytics in cardiac arrest in 66 countries, had informed consent waived.<sup>7</sup> The ACORN randomized clinical trial, which compared cefepime to piperacillin-tazobactam in septic patients with an indication for anti-pseudomonas antibiotic, also had informed consent waived by the ethics committee.<sup>8</sup> The DOSE-VF study, which tested sequential double defibrillation in refractory ventricular fibrillation, also obtained a waiver of informed consent from the ethics committee.<sup>9</sup>

In 2024, the Brazilian law on research with human beings (14.874/2024) was enacted.<sup>10</sup> The law determines that research must guarantee voluntary participation, through informed consent of the participant. In its article 18, paragraph 6, it states: “The inclusion of a participant in research

in an emergency situation and without their prior consent will follow the provisions of the approved protocol, and the participant or their legal representative must be informed of the fact as soon as possible. and collect the decision regarding their permanence in the research”. In Article 24, on vulnerability, paragraph II, the inclusion of participants in vulnerable situations in research is conditioned to: the research being essential for the population represented by the participant in a vulnerable situation and it not being possible to obtain comparable data from adult individuals capable of giving consent or through other research methods. However, it adds a requirement in the second paragraph: “The responsible researcher and the representative of the incapable person will co-sign a communication to the Public Prosecutor’s Office, informing the route of participation of the incapable person in the research”.

The law brings advances in recognizing emergencies and vulnerabilities in emergency medicine research. However, it is crucial that the requirement for communication to the Public Prosecutor’s Office has clarity and an efficient and transparent mechanism, so that there is no burden on emergency medicine research. For example, what is the procedure when there is no legal representative who can be found?

In short, emergency medicine research is constantly being ethically refined. The search for a balance between advancing knowledge and respecting the human dignity of patients is an ongoing challenge that requires constant dialogue between researchers, ethics committees, authorities and

civil society. Through critical reflection, consensus building and the implementation of transparent and efficient mechanisms, we can ensure human dignity in research with human beings and ensure that emergency medicine research continues to contribute to saving lives and improving people’s quality of life.

## REFERENCES

1. Berger RL. Nazi science - the Dachau hypothermia experiments. *NEJM* 1990;332:1435-40.
2. The Nuremberg Code (1947). *BMJ*. 1996;313:1448.
3. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013 Nov 27;310(20):2191-4.
4. Parsa-Parsi RW. The Revised Declaration of Geneva: A Modern-Day Physician’s Pledge. *JAMA*. 2017;318(20):1971-2.
5. Perkins GD, Ji C, Deakin CD, Quinn T, Nolan JP, Scopinari C, et al.; PARAMEDIC2 Collaborators. A Randomized Trial of Epinephrine in Out-of-Hospital Cardiac Arrest. *N Engl J Med*. 2018;379(8):711-21.
6. Bengler JR, Kirby K, Black S, Brett SJ, Clout M, Lazaroo MJ, et al. Effect of a Strategy of a Supraglottic Airway Device vs Tracheal Intubation During Out-of-Hospital Cardiac Arrest on Functional Outcome: The AIRWAYS-2 Randomized Clinical Trial. *JAMA*. 2018;320(8):779-91.
7. Böttiger BW, Arntz HR, Chamberlain DA, Bluhmki E, Belmans A, Danays T, et al.; TROICA Trial Investigators; European Resuscitation Council Study Group. Thrombolysis during resuscitation for out-of-hospital cardiac arrest. *N Engl J Med*. 2008;359(25):2651-62.
8. Qian ET, Casey JD, Wright A, Wang L, Shotwell MS, Siemann JK, et al.; Vanderbilt Center for Learning Healthcare and the Pragmatic Critical Care Research Group. Cefepime vs Piperacillin-Tazobactam in Adults Hospitalized With Acute Infection: The ACORN Randomized Clinical Trial. *JAMA*. 2023 Oct 24;330(16):1557-67.
9. Cheskes S, Verbeek PR, Drennan IR, McLeod SL, Turner L, Pinto R, et al. Defibrillation Strategies for Refractory Ventricular Fibrillation. *N Engl J Med*. 2022;387(21):1947-56.
10. Brasil. Presidência da República. Casa Civil. Secretaria Especial para Assuntos Jurídicos. Lei no 14.874, de 28 de maio de 2024. Dispõe sobre a pesquisa com seres humanos e institui o Sistema Nacional de Ética em Pesquisa com Seres Humanos. Brasília, DF: Diário Oficial da União; 2024 [citado 2024 Jul 24]. Disponível em: [https://www.planalto.gov.br/ccivil\\_03/\\_ato2023-2026/2024/lei/L14874.htm#:~:text=Esta%20Lei%20dispõe%20sobre%20princípios,e m%20Pesquisa%20com%20Seres%20Humanos](https://www.planalto.gov.br/ccivil_03/_ato2023-2026/2024/lei/L14874.htm#:~:text=Esta%20Lei%20dispõe%20sobre%20princípios,e m%20Pesquisa%20com%20Seres%20Humanos)