Ethics of data-driven innovation in the treatment and prevention of sudden cardiac arrest

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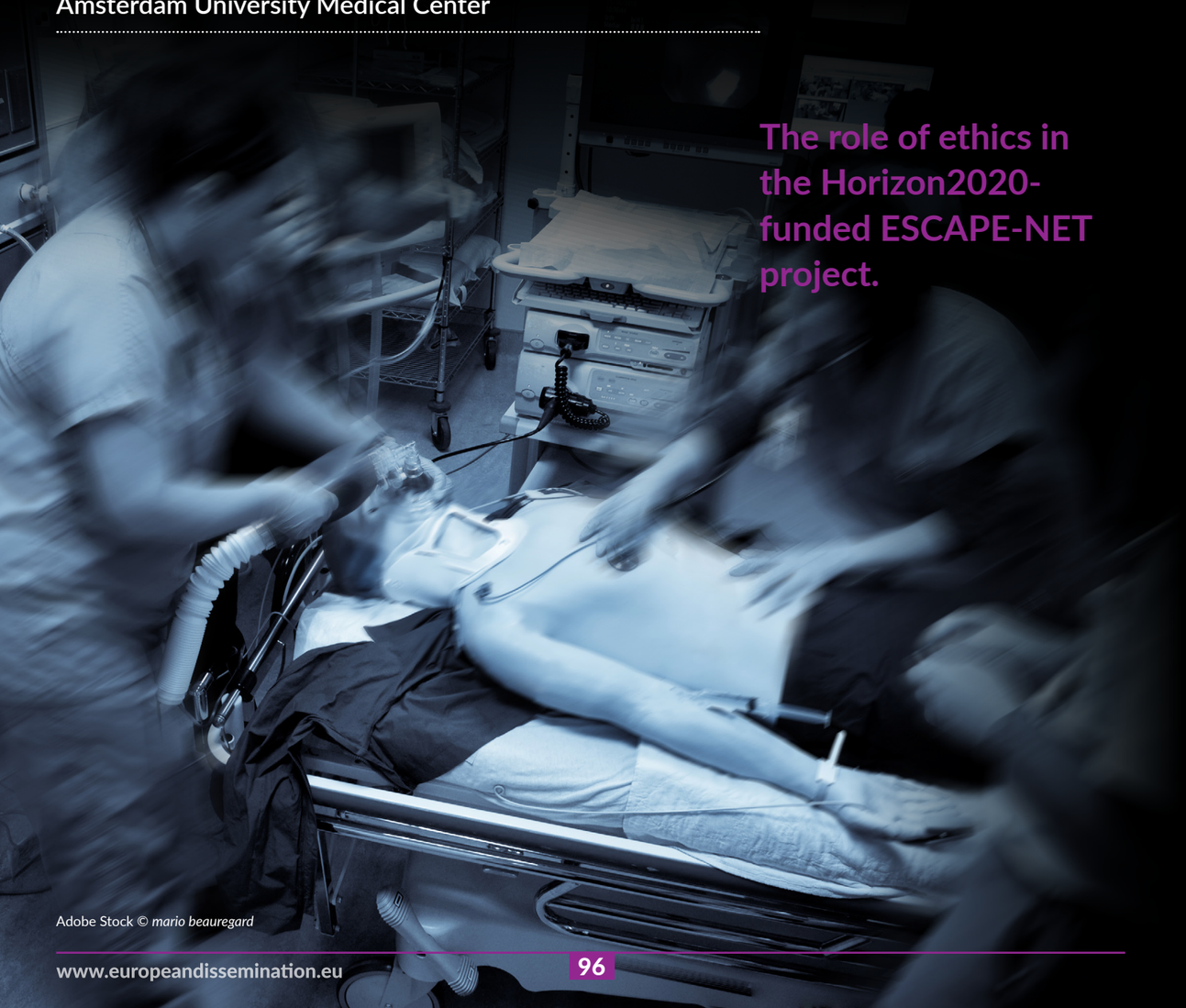

The role of ethics in the Horizon2020-funded ESCAPE-NET project.

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The international ESCAPE-NET consortium has created a large harmonised database of patients who suffered a sudden cardiac arrest (SCA). This condition accounts for half of all cardiac deaths in Europe, and survival rates have remained low. Understanding of SCA risk factors and the effect of prevention and treatment approaches require large amounts of data, which was the rationale for ESCAPE-NET.

However, data collection and protection in the SCA setting are particularly complex as patients are at least temporarily incapacitated and unable to provide prospective informed consent for research with their personal data—and patients who do not survive the SCA (>80 per cent) will never have this option. Thus, it was important for the ESCAPE-NET project to cover the wide spectrum of ethical issues surrounding the use and exchange of data of individuals with SCA. This was done in the work package on ethics, coordinated by the Department of Ethics, Law and Humanities at the Amsterdam UMC. Ethical questions were studied in three phases.

In the first phase, we performed literature studies involving searches in PubMed, CINAHL, and Philosopher's Index on the one hand, and a narrative analysis of the various national guidelines and regulations concerning data use on the other hand: one literature study was about ethics of SCA data research and the other about the use of deceased patients' data for research.

In the second phase, we interviewed 29 experts (SCA researchers, ethicists and jurists) in the participating ESCAPE-NET countries. We also conducted an interview study with SCA survivors and their next-of-kin (N=19) as well as several in-depth philosophical-ethical analyses of specific topics (e.g. post-mortem privacy).

In the third phase, we discussed our research and policy recommendations in a one-day invitational conference in September 2020, convening jurists, ethicists and researchers (N=18) from the countries participating in the ESCAPE-NET project.

What follows is a description of key findings from these studies. We do not discuss the results that specifically relate to data research with deceased SCA data subjects, which is a large topic. Instead, we focus on informed consent and data sharing for SCA data research and the data-driven personalisation of SCA treatment and prevention. The latter also relates to a study that builds on ESCAPE-NET and in which our group is involved: the Horizon2020-funded PROFID project. We report some preliminary results from that project as well.

Informed consent for SCA data research

In ESCAPE-NET, we studied the potential benefits and harms of SCA data research, or in other words, the ethical, legal and social implications (ELSI). In our literature review, we described potential harms like privacy breaches and suggested ways to deal with these risks (Bak *et al.*, 2018). Our interviews showed that for SCA data research, experts and patients find that the benefits generally outweigh the harms (Bak *et al.*, 2021; Bak *et al.*, 2023b). However, data security measures and ethics oversight should always be in place and be combined with **informed consent** procedures. The problem with SCA data research is that prospective informed consent is impossible, given the sudden and unexpected onset of the condition. However, consent for data use can be gained retrospectively.

We found that this is done ideally three months after the SCA event because patients need time to recover from the shock of the SCA event and to regain full mental competence (if they do).

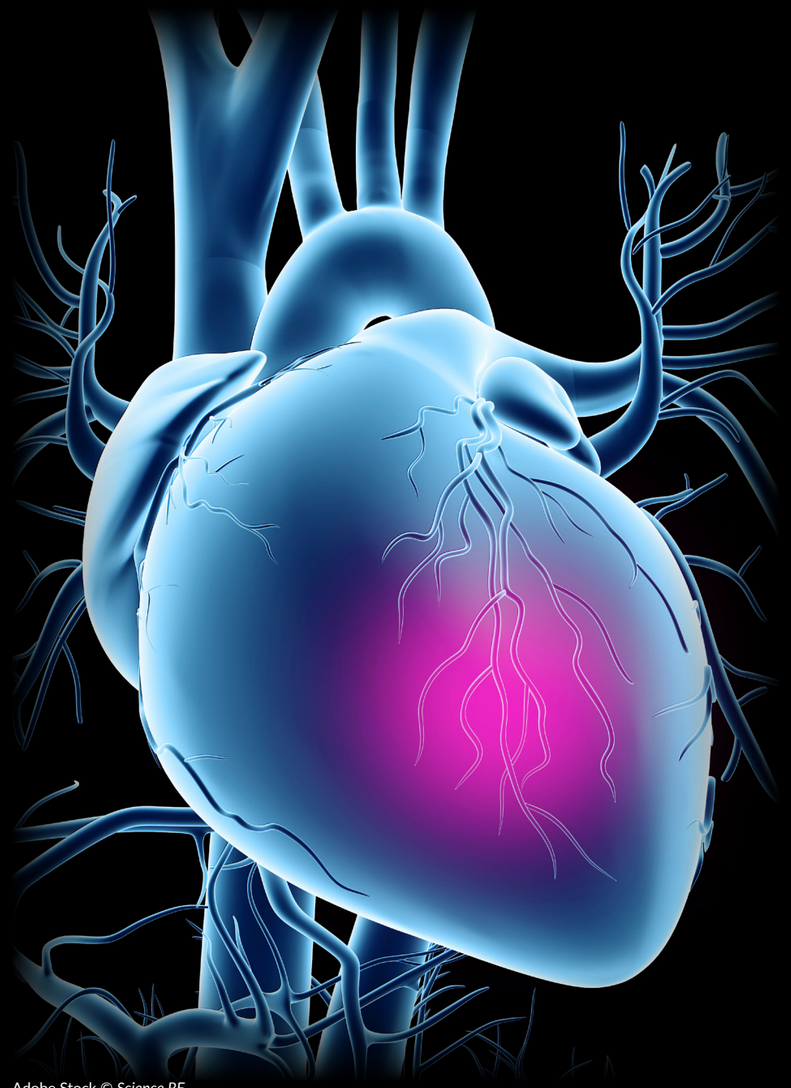
We also found that opt-in consent—rather than opt-out—would be recommended whenever possible because it shows respect and promotes public trust in research (Bak *et al.*, 2021). This informed consent can be broad, i.e. for SCA research in general, rather than specific for every study, so as not to overburden patients and researchers. One issue we encountered is that patients often do not remember having given consent for SCA data research. This is problematic particularly when they have changed their mind about the return of individual genetic findings (e.g. they initially expressed a preference for receiving such findings but would not want that anymore, years later). Thus, we think consent should not be a one-time affair but that regular reminders to participants or dynamic online consent procedures are needed.

Access and equity: who decides how data are used?

Health data should be used in a way that is fair, and that gives equal access to the benefits of those data. Automated external defibrillators (AEDs) are life-saving, publicly accessible devices for people who suffer from SCA. In ESCAPE-NET, the AED was used as a case to study ethical aspects related to the fair implementation of data-driven medicine for SCA patients.

Firstly, we published an article describing the case of 'AED data', such as the ECG that is recorded in by the AED after the person has been resuscitated. The problem is that these AED data are often only stored locally and do not become part of the medical record. In the Netherlands, AED data currently only become available to clinicians because they are collected and shared by researchers of the ARREST group. We advocated the creation of guidelines to ensure sustainable and nationwide availability of these sometimes life-saving data (Bak *et al.*, 2020). Such guidelines should also safeguard that data are handled in accordance with data protection legislation. So far, this has been challenging because AED data are not stored securely in a healthcare setting but instead are stored in publically accessible devices.

Secondly, we studied the case of computer models for decision-making on the geographical distribution of AEDs across cities or regions. We find that ethical considerations, such as equity, are built into these models. For instance, the question whether it is better to save more lives within a smaller area (such as a city centre), or to have a more



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equal distribution of AEDs even when the total number of lives saved is lower (which might happen when including the outskirts of a city). Computer scientists struggle with the moral dilemma whether to create an equal distribution of AEDs or optimise towards saving the most lives. We think that ethical codes of conduct are not helpful in dilemmatic cases like this one. Instead, we have argued that professional responsibility and 'procedural justice' require deliberation with a range of stakeholders to discuss dilemmas (Bak, 2020).

Challenges of personalised ICD implantation: PROFID

Ethical issues also arise in another SCA research project that builds on studies like ESCAPE-NET. The PROFID project, funded by the European Commission, aims to integrate the collected SCA data into a prediction model for more personalised implantation of an implanted cardioverter defibrillator (ICD). Artificial intelligence (AI) methods are used to create this model and personalise ICD implantation by AI-based ECG and MRI data analysis.

We wrote a position paper about PROFID, arguing that there is a need for ethical-empirical studies about testing AI models in personalised cardiovascular care and the related clinical trials (Willems *et al*., 2021). Also, in the PROFID project, many ethics committees were involved, which raised organisational and ethical issues. Thus, there seems to be a need for a harmonisation procedure for data- and AI-based medical research, which could be comparable to the harmonisation of ethics approval for pharmaceutical clinical trials.

Beyond its potential for improving healthcare for individuals and society, AI poses ethical and social challenges in medicine. To integrate AI into medicine responsibly and successfully, it is important to understand healthcare professionals' perspectives and to address their concerns early on. Therefore, we reviewed empirical studies investigating the views of healthcare professionals on using AI in medicine. We searched various medical databases and extracted barriers and facilitators from the included articles [work in progress].

The results showed that many professionals expect high benefits from AI in their clinical activities, such as efficiency, support in clinical decision-making, and administrative support. Healthcare professionals generally have a positive attitude but lack technical knowledge of AI and experience in using AI-based applications—indeed, the majority of articles discussed hypothetical cases of AI use rather than actual uses. Perceived barriers were mostly related to ethical, legal and economic issues in implementing clinical AI.

Trust in health data research and medical AI

A crucial element in the adoption of data-driven medicine and medical AI is the (mis)trust of stakeholders and the general public. When interviewing SCA researchers, we found that they felt responsible for valid science and ethical data use and **trusted** the other project partners to handle data correctly. However, legal data protection difficulties and lengthy discussions about data-sharing agreements and other contracts can potentially crowd out the pre-existing trust that we encountered in the ESCAPE-NET consortium. Thus, we argue that the concept of trust should be more explicitly embedded in data governance and have provided recommendations on how to do so (Bak *et al*., 2023a). In addition, we recommend the creation of a 'code of conduct' for SCA data research, or a clause about emergency settings to an existing more general code (Bak *et al*., 2023b). This would help protect patients' rights in the complex setting of SCA whilst making data sharing between researchers easier.

In the PROFID project, we are studying trust and mistrust in medical AI. The ethical literature has almost no place for mistrust: many papers only discuss appropriate and inappropriate trust in AI. Therefore, we undertook an ethical and philosophical analysis of trust, mistrust and related concepts in the context of medical AI [work in progress]. In that paper, we define the characteristics of well-placed mistrust and critique a well-known test for the appropriateness of trust. Instead, we will propose to use the concept of the 'web of trust' and claim that looking at mistrust (and trust) as a relational phenomenon is more useful to help distinguish between appropriate and inappropriate mistrust in medical AI. Further attention for (mis)trust is necessary to preserve the social license for data-driven medical research.

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PROJECT SUMMARY

ESCAPE-NET aims to discover inherited, acquired and environmental causes of sudden cardiac arrest (SCA) and to improve resuscitation treatment for SCA. A shared database of >100,000 SCA patients has been created and >10,000 DNA samples collected, with procedures for data access by researchers outside the project consortium. ESCAPE-NET has generated 90 peer-reviewed scientific papers.

PROJECT PARTNERS

16 partners, 10 European countries:
6 universities: AMC University of Amsterdam, VU University Amsterdam, Copenhagen University, University Pavia, Université Paris Descartes, Karolinska Institute
4 research institutions: Istituto Auxologico Italiano, Istituto Mario Negri, Helmholtz Center Munich, Fundacio IMIM
2 professional societies: European Society of Cardiology, European Resuscitation Council
1 Emergency Medical Service: Hradec Kralove Region
3 SMEs: Catalyze, Panaxea, BC Platforms.

PROJECT LEAD PROFILE

Coordinator Hanno L. Tan is a cardiologist at Amsterdam University Medical Center AMC. He conducts various research projects on SCA, both in the general population and in specific subgroups such as patients with cardiogenetic diseases associated with SCA. He works towards elucidating the causes of SCA and developing novel treatments, including device-based therapies and molecular therapies such as gene therapy.

PROJECT CONTACTS

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