Good science at heart

Lessons on ethics from big data research in sudden cardiac arrest

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4 | Regulating registries and biobanks for research in sudden cardiac arrest: European experts' views

> The terminological Tower of Babel overshadowing survival rates prompted the Utstein consensus conference on a small island off the Norwegian coast, [where] an international task force recommended a template approach for data reporting.
> (Stefan Timmermans, *Sudden Death and the Myth of CPR*. 1999; p. 71)

Summary[i]

Observational studies using large-scale databases and biobanks help improve prevention and treatment of sudden cardiac arrest (SCA) but the lack of guidance on data protection issues in this setting may harm patients' rights and the research enterprise itself. This qualitative study explored the ethical implications of observational SCA research, as well as solutions. European experts in SCA research, medical ethics and health law reflected on this topic through semi-structured interviews (N=29) and a virtual roundtable conference (N=15). The ESCAPE-NET project served as a discussion case. Findings were coded and thematically analysed. The first key theme related to the potential benefits and harms (at individual and group level) of observational data-based SCA studies and included the following sub-themes: scientific validity, privacy breaches, disclosure of genetic findings, stigma and discrimination, resource allocation and medicalisation. The second key theme involved governance through 'privacy by design', 'privacy by policy' and associated regulation and oversight. Sub-themes were: de-identification of data, informed consent (broad and deferred), ethics review, and harmonisation. Researchers and scientific societies should be aware that ethico-legal issues may arise during observational studies in SCA and other emergencies, and should mitigate these in collaboration with colleagues from other relevant disciplines and patient representatives. Combining technical data protection safeguards with appropriate informed consent policies and proportional ethics oversight will serve to protect research participants' privacy, without discouraging researchers to carry out important research. We recommend the establishment of 'codes of conduct' to ensure responsible conduct of this type of research.

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4.1 Introduction

Sudden cardiac arrest (SCA) is lethal within minutes if left untreated through cardiopulmonary resuscitation and is characterised by low survival rates.[1,2] Increasing amounts of patient data and tissue combined with improved processing capabilities carry the potential for breakthroughs in SCA prevention and treatment.[3-5] Such observational studies provide advantages over randomized controlled trials in terms of both real-world applicability and ethicality, given their non-interventional nature.[6] The ESCAPE-NET (European Sudden Cardiac Arrest network towards Prevention, Education, New Effective Treatment) consortium combines large SCA datasets and (when available) biobanks from multiple countries. This collaboration is necessary because large datasets are needed to unravel the multiplicity of causal factors, while SCA data collection is difficult.[7]

The use of these sensitive data and biospecimens gives rise to privacy concerns.[8,9] The medical emergency makes it impossible to obtain prior informed consent from research participants ('data subjects'), while acquiring consent after the SCA event is often problematic because some people become mentally incapacitated and a majority does not survive. Guidance is needed on the right balance between expected benefits and potential harms of observational studies with this vulnerable population.[10,11] In Europe, the General Data Protection Regulation (GDPR) provides basic data protection rules and principles, but specific regulations for research (e.g. safeguards) are left to Member States.[12-14] Moreover, the GDPR does not apply to deceased data subjects, nor does it contain a provision for proxy consent of incapacitated subjects.[15] In those situations, guidance follows from national law and, if available, ethical guidelines. With regard to tissue samples, there is a similar lack of uniform European regulation. There is the Tissues and Cells Directive 2004/23/EC but its scope is more in clinical uses of tissue, so biobanking research is mostly regulated through international 'soft law' instruments and national legal frameworks.[16-18]

With this study we aimed to identify and explore the main ethical implications of (internationally organized) observational research in the context of SCA, as well as strategies to deal with these issues responsibly and lawfully. Figure 1 graphically depicts this aim and the structure of our findings. We focus on data in registries and, where relevant, we discuss issues associated with biobanking. To this end, we conducted interviews with experts from several European countries, and hosted a virtual roundtable conference, using the ESCAPE-NET project as an example. We believe that our findings will have significance for other emergency settings, such as those relating to trauma, stroke, or COVID-19 research, and for the broader field of observational health research.

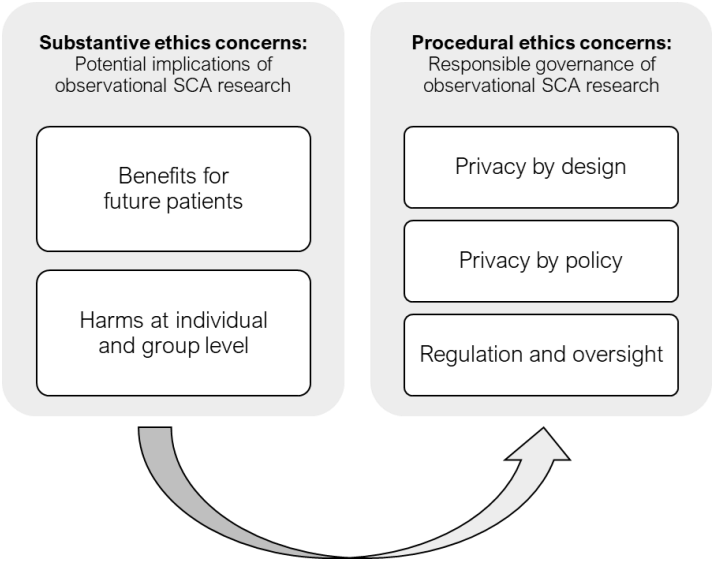

Figure 4-1. Ethical aspects of SCA research registries and biobanks

4.2 Methods

4.2.1 Study design

A qualitative design fits the exploratory nature of our study.[19] Data sources were semi-structured interviews with experts who served as "crystallization points" for knowledge on data protection in this setting,[20] and a roundtable conference where findings and open questions were discussed (via Zoom, due to the Covid-19 pandemic). The ESCAPE-NET project was used as discussion case (Box 1). ESCAPE-NET combines SCA study cohorts from multiple European countries. These studies collect prehospital data from emergency medical services (EMS) according to uniform ('Utstein Style')[21] reporting guidelines, as well as hospital treatment and outcome information through patient records or interviews, and some groups collect data from pharmacists and general practitioners. In Scandinavian countries, most data are gathered through linkage to national registers with detailed information on medical treatment, cause of death, prescription medication, genealogy and socio-economic status.[22] A number of participating centres operate genetic biobanks of SCA patients and control whose DNA is extracted mostly from residual biosamples taken for clinical purposes, e.g. blood samples during hospitalisation, or endotracheal tubes placed by EMS.

Box 4.1 Aims of the ESCAPE-NET project

(a) To combine Europe's largest deep-phenotyped SCA cohorts for full exploitation.

(b) To improve and maximize data sharing and stimulate hypothesis-driven research by using new technologies in building and maintaining this large-scale database.

(c) To develop a financial strategy to keep the database alive after the project.

(d) To reach out to other SCA investigators for collaboration and data sharing.

(e) To identify genetic, epigenetic, acquired, and environmental risk factors, and interactions, for SCA occurrence in a combined large-scale European study population.

(f) To design and validate a personalized risk score for SCA occurrence.

(g) To relate differences in first-response SCA treatment strategies to survival across different European countries.

(h) To evaluate effects of novel technologies for SCA treatment by utilizing smartphone applications (for rapid deployment of lay rescuers) and novel technological solutions (e.g., based on ventricular fibrillation waveform analysis).

(i) To design a personalized risk score for survival after SCA.

4.2.2 Participants

We conducted interviews (N=29) with researchers working with SCA registries and biobanks (n=16) as well as with ethical and legal experts (n=13) across six EU countries (The Netherlands, Italy, France, Denmark, Sweden, Czech Republic) representing different geographical regions of the European Union. Respondents from the field of SCA research were medical doctors or epidemiologists involved in ESCAPE-NET. Respondents with expertise in ethics and law were key opinion leaders in their field who did not participate in the ESCAPE-NET consortium. Some were members of a Research Ethics Committee (REC). Prior to the interview, respondents received information about the ESCAPE-NET project and a brief description of relevant ethical considerations. For each discipline (medicine, ethics, law) at least one expert per participating country was interviewed. In the roundtable conference, 15 experts from the different fields participated; these experts had been previously interviewed (n=10) or were newly invited (n=5). The latter group included researchers from additional European countries (Germany, Norway). The roundtable format was chosen to give all participants the possibility of equal input.[23]

4.2.3 Data collection and analysis

Interviews were conducted face-to-face or through video conference, between May 2018 and June 2020. Interviews lasted 60-120 minutes and were conducted using topic guides based on a previous literature study.[11] They were pilot-tested with experts from the research team. Interviews were audio recorded and transcribed following consent. The local REC stated that approval for this study was not required under Dutch law. Respondents were given the opportunity to receive the full transcript and a written summary to enable corrections. Interviews were conducted until data saturation was reached, and thematically analysed using MAXQDA 2018 software. Coding was done by two researchers (MARB and JCHV). Changes in coding structure were tracked to conclude that data saturation was achieved. The invitational roundtable conference was held in September 2020, and was transcribed and coded in the same manner. A document with conclusions was shared with conference participants to allow for corrections and the final report will be made publicly accessible on the website of the ESCAPE-NET project (https://escape-net.eu).

4.3 Results I: Ethical implications of observational SCA studies

Respondents mentioned potential benefits and harms related to SCA registries and biobanks (see Table 1 for illustrative quotations). Hereafter, these are discussed and linked to four core moral principles in biomedical ethics: *autonomy*; *beneficence*; *non-maleficence*; and *justice*.[24] Of note is that ethical and legal experts stated that most of the issues are exacerbated by the emergency setting of SCA but are relevant for other observational studies with data or tissue. Findings from the interviews and round table discussion are combined and presented together (supplemented with literature).

4.3.1 Benefits for future patients

All interviewed experts acknowledged that observational SCA studies offer great potential for societal health benefits, which is an important precondition for research that carries potential risks.[25] This societal value requirement reflects the duty of *beneficence* (i.e., relieving, lessening or preventing harm, and providing benefits that are weighed against risks and costs) and is enshrined in ethical guidelines like the Helsinki Declaration and the Nuremberg Code. Examples of ESCAPE-NET research with societal value are the discovery that the widely prescribed drug nifedipine, used to treat high blood pressure and chest pain, is associated with increased SCA risk,[26] or the evaluation of European first response systems for out-of-hospital cardiac arrest.[27]

Table 4-1. Potential benefits and harms of SCA data research: illustrative quotations

Benefits *(beneficence)*	
General	"We are very much in a protection-paradigm, but what can be forgotten is that patients really like to participate and have their data used for good science." (23 – Ethico-legal expert)
Scientific validity	"We do not have the manpower to manage it for the whole country. We collect a huge variety of data, but only for a small area, which gives rise to questions about representativeness." (9 – SCA researcher)
	"In the UK they have do-not-resuscitate [DNR] orders, but not in Italy. The denominator changes if you remove all patients with DNR from the dataset." (8 – SCA researcher)
	"You would create an enormous selection bias, because deceased patients are the most ill patients of your cohort." (18 – Ethico-legal expert)
Individual harms *(autonomy, non-maleficence)*	
Privacy breaches	"It would be a breach of trust if personal data were available for a third party without the patient's knowledge." (5 – SCA researcher)
	"Before coming into the clinic, we'll tell them, do all your insurance before you meet me. Because once you're in my system and I have to write, 'I have seen an ECG with this and this', then the insurance company will get that information. But that is only when it goes from research to the clinical setting." (4 – SCA researcher)
	"If I would share data with commercial parties, it is to hire staff and continue doing this research. Trying to explain takes up a lot of time, and not everyone will agree. Would you have to exclude that person then? Or did they just misunderstand?" (13 – SCA researcher)
	"It might be possible to wrong some patients by using their data, without actually harming them." (19 – Ethico-legal expert)
Disclosure of genetic findings	"It happened a few times that we looked at single genes and found stuff that could potentially save the lives of relatives. That's been difficult, not to inform them." (4 – SCA researcher).
	"Each case is specific and cannot be answered with a single question. When information can save a life, it's different than when it's not life-threatening. The most important thing is to be clear about people's expectations" (25 – Ethico-legal expert).

	"Having this knowledge might increase stress which is in itself a risk factor. There should be exceptions only when a preventative measure can target that one mutation. But then it should be a screening program run by public health agencies." (28 – Ethico-legal expert)
Group level harms *(justice)*	
Stigma and discrimination	"If your study finds that a minority group have a higher risk, then that group can be labelled as having these problems, while it might not apply to everyone." (6 – SCA researcher)
Broader societal impact	"The money you spend for one patient you don't spend on another. I think the researchers, most are clinicians too, should consider medical as well as social factors. (…) We always want to cure people and prevent sudden death. We think about having a good life, but we never think about having a good death. And sometimes I think that sudden death is a good death." (11 – SCA researcher)

Scientific validity

For studies to be valuable, it is an ethical prerequisite that they are designed in a scientifically valid manner. The GDPR has 'accuracy' as one of its core principles (5,1,d). Interviewed SCA researchers made use of research data management plans and/or standard operating procedures, and audit and quality control were regularly performed for a number of studies. Still, respondents noted that several issues may impact scientific validity of SCA research: low quality of data and inconsistencies in reporting, especially for linkage from various sources in the chain of care[28-31]; difficulties in international comparisons due to variations in health system characteristics and definitions[32,33]; and limited generalisability because of true differences across different regions and populations or due to selection biases when severely ill or deceased patients are excluded, which changes study outcomes.[34-37] Inclusion of deceased patients is necessary to improve evidence-based care and, moreover, not including the data might be against the person's wishes.[38] Lastly, beneficial SCA research requires adherence to general research integrity standards, so research institutions, funders and journal editors should limit perverse incentives that may lead to questionable research practices.[39]

4.3.2 Individual harms

SCA data research can bring about risks to patients, which are relevant in the context of researchers' duties of *nonmaleficence* (i.e., avoiding the causation of harm) and respect for *autonomy* (i.e., supporting patients' self-governance).

Privacy breaches

Observational SCA studies collect a variety of personal data on inherited and acquired SCA risk factors such as gender, ethnicity, genetic predisposition, medication use, comorbidities, lifestyle, environmental factors and socioeconomic status.[7,40,41] The GDPR stipulates that health data may not be processed unless there is a specific legal ground, and that processing should be subject to certain safeguards. For genetic data, some countries have stricter regulations due to the identifiable and hereditary nature of DNA. Multiple respondents shared notions of this 'genetic exceptionalism'[42] but others thought that viewing DNA as extra sensitive may block genetic epidemiology and would be inconsistent because identifying individual patients is also possible with clinical and demographic data. Even non-health information can be used to make inferences about health.[43]

All researchers and some ethico-legal experts believed that the current data protection regime renders the possibility that a third party will illegitimately re-identify patients mostly theoretical because of the disproportionate effort needed. If a data breach would occur, privacy concerns for SCA patients were regarded as less worrisome than for more sensitive conditions (examples mentioned were circumcision registries and studies of acute psychosis or sexually transmitted disease). For SCA victims who do not survive, most of the harm was thought to have disappeared; although experts acknowledged a risk of posthumous reputational harm and the fact that some types of data (e.g. genetic) may bring privacy concerns for relatives.[44] While researchers mostly focused on consequences of privacy breaches, ethico-legal experts recognised that confidentiality is important regardless of potential harm but rather out of respect for participants' autonomy and to safeguard public trust in science.[45]

Disadvantages resulting from findings being shared with insurance companies were not experienced in the research setting of ESCAPE-NET. None of the research groups shared identifiable data with commercial third parties; some shared pseudonymised data with defibrillator manufacturers or data mining companies. Respondents noted that an increasing amount of valuable research is conducted by public-private partnerships[46],[ii] but SCA researchers were worried that participants would not understand this. Still, a number of experts thought that patient data, even when de-identified, should not be shared with commercial parties without explicit consent from the data subject – out of respect for patients' privacy and to protect the social license for research. Referring to health data research scandals, Expert 17 noted that *"juridical legitimation is not always sufficient"* for creating public trust.

[ii] This is partly because collaboration with private partners may create more financially sustainable research. However, details on the topic of public-private partnerships are outside the scope of this article.

Disclosure of genetic findings

SCA biobanking research presents particular ethical questions. Firstly, some studies draw participants' blood for research purposes: this was seen as minimally invasive (which is in line with SCA survivors' views)[47] but experts preferred the use of residual blood leftover from care. Secondly, studies collecting DNA need to have a policy for the return of individual genetic findings. While most SCA studies have focused on single nucleotide polymorphisms (SNPs), i.e. common genetic variants without direct health implications, the issue becomes more pressing with whole genome sequencing where disease-causing gene mutations may be detected. Different policies were present across ESCAPE-NET. In two cases, patients could only participate if they agreed to be informed of actionable findings, following institutional policy. Some experts found this problematic because they recognised patients' autonomy in the form of the *right not to know* without being excluded from participation.[48] On the other hand, one researcher experienced moral distress from not being allowed by his institution to contact relatives of deceased patients with relevant findings.

Whether researchers have a moral duty to contact deceased patients' relatives with clinically actionable genetic findings from research on SCA – where the patient has had no opportunity to register preferences or inform next-of-kin – is a complex ethical issue for which the legal options differ per jurisdiction.[49-51] In the Netherlands, for instance, doctor-patient confidentiality remains in place after death, but there are exceptions in certain situations, such as relatives who have a major health risk.[52] Experts recommended that researchers create an incidental findings policy together with ethico-legal experts, and that a genetic findings committee should be installed for large biobanking projects. Especially for low penetrance variants (variants that cause a phenotype in only few carriers) it is important that disclosure is done cautiously, preferably by genetic counsellors, so that people are not unnecessarily alarmed. Clear guidelines should be drafted beforehand that describe what counts as a serious and valid finding. One expert emphasized that the fading boundary between research and screening purposes might require upholding the Wilson and Junger screening criteria.[53] This notion is shared in the literature by Cho,[54] who states that "blurring the lines between clinical and research obligations should not be taken lightly. It is important to cross this line only with compelling reason, accurate information, and clear informed consent".

4.3.3 Group-level harms

To fulfil the aforementioned duties as well as the criterion of *justice* (i.e., fairly distributing benefits, risks and costs), findings from SCA data research should not only be

valid but also translated to practice in a responsible manner since "many of the privacy harms of big health data arise not merely in the collection of data, but in their eventual use".[43]

Stigma and discrimination

Privacy harms may occur at group-level, affecting not only the individuals who contributed the study data but also the broader community.[55] One of the aims of ESCAPE-NET is to develop a risk prediction model to enable personalised prevention of SCA. Respondents noted that the use of such risks scores requires ethical reflection on how to communicate and use the information, especially given the small effect sizes expected in the general population. Another issue put forward was the fact that creating (genetic) risk scores for certain groups of patients can cause stigmatisation of these groups, such as ethnic minorities, if findings feed into social stereotypes (e.g. related to health behaviour).[56] Stigma is harmful in itself, but can also lead to discrimination.[57]

Broader societal implications

Another societal issue briefly touched on by some experts, is the allocation of resources between different patient populations. Two researchers wondered whether SCA constitutes a 'good' death for elderly people (who constitute the majority of SCA victims), and whether it might be more ethical to spend resources on other conditions. This theme is reflected in discussions about the medicalisation of death and dignity in dying.[58] Whether researchers have a responsibility for those broader societal impacts, indirectly related to their work, was considered by the experts as a topic for further debate.

4.4 Results II: Responsible governance of observational SCA research

Governance of observational research can be divided into three components[59]: 'privacy by design' consisting of privacy-enhancing technical and organizational measures built into the study design, such as anonymization; 'privacy by policy' that refers to the study's data protection policies, such as on informed consent; and the overarching influence of (inter-)national regulations and oversight bodies. In Table 2 illustrative quotes are presented relating to the discussion hereafter.

4.4.1 Privacy by design

Most interviewed researchers were aware of the GDPR requirement to conduct a Data Protection Impact Assessment (DPIA) for large-scale health data processing. Such a DPIA can give direction on what measures researchers ought to employ in order to comply with legal principles such as confidentiality and data minimisation

(i.e., collection of data limited to what is necessary for the research). Examples of measures operated by researchers were data access logging, data separation, pseudonymization, and encryption (i.e., encoding of information that can only be recoded by the persons for whom it is intended)[60]. These were already in use before the introduction of the GDPR, although some experts recognized a stimulus from the GDPR (which contains a requirement for data protection by design [Article 25; Recital 78; Article 89 for research purposes]). The most common privacy by design measure was to render data less identifiable, which we discuss below.

De-identification of data

Aggregating data into groups of multiple individuals or removing identifying information decreases the likelihood that specific individuals can be identified. The GDPR does not apply to completely anonymous data. To determine whether a natural person is identifiable, "account should be taken of all the means reasonably likely to be used" in terms of cost, time, and available technology (Recital 26). Another safeguard, mentioned in Article 89, is the pseudonymization of data, which is required provided that the research purpose can still be fulfilled. Instead of irreversibly anonymizing data, pseudonymization ascribes a code which is separately stored but can be linked back to the data subject.[61] This code may be kept by the treating physician or a Trusted Third Party (TTP) so that the data remain anonymous at least for the researcher.[62]

Within ESCAPE-NET study cohorts, some researchers were authorised to have a nominal database with personal data, while others worked with pseudonymized data. Some respondents voiced concerns on the quality of pseudonymized data: one researcher had worked with old genetic samples where outdated codes in the lab and the database had to be re-matched manually. Still, experts preferred pseudonymization over anonymization as it allows addition of new data to a subject's profile and enables an audit trail to source documents. Full anonymization would also make it impossible to provide data subjects with transparency and access to their data, which several ethico-legal experts found problematic. What is more, complete and irreversible anonymization is practically impossible because of the ability to cross-link with other datasets, arguably even more so when genetic data is collected, and especially in emergency research with many data sources along the 'chain of care'.[63, 64]

4.4.2 Privacy by policy

For data that cannot be anonymized, policy measures may be needed around data sharing, access, and informed consent. Within ESCAPE-NET different research policies are used, depending on national legislation and contextual ethical factors, such as the level of data sensitivity (e.g. consent was asked in all genetic studies). Interviewed researchers experienced that most SCA survivors consent because they want

to give back to society; as of May 2018 in all studied ESCAPE-NET cohorts ≥90 % of patients consented to the use of their data. As informed consent is the most pertinent issue for SCA research, hereafter we discuss experts' views on this topic: whether consent is needed at all for observational studies; and if so, what form this consent should take in the setting of SCA research.

The need for informed consent

The decision whether SCA survivors' consent for data use should be asked or may be waived entirely, "*must be made considering the tradeoffs associated with both*"[65]. Some respondents felt that informed consent should not be required for non-genetic minimal risk research, similar to Porsdam Mann et al.[66] who argue for a *duty of easy rescue* in this context.[iii] This would prevent participation bias and lower the burden on researchers. Most jurisdictions contain exemptions to the consent requirement, for instance if obtaining consent would be reasonably impracticable or impossible, provided that the research serves a public interest and that privacy by design safeguards are in place.[67] Experts said this must be determined for every study separately: there should be no general exemption for observational emergency research. Legal experts explained that even if a consent waiver is justified, an accessible opt-out possibility should remain (e.g. with the help of a public information campaign). This was not the case in all ESCAPE-NET countries. For instance, in Denmark, there is no way to opt out of the use of clinical or socio-economic data for research, as a result of the country's history of data-driven epidemiology.[22]

Some respondents thought 'opt-in' informed consent should be the default as *"it can give people a good feeling that they were able to give their data for science"* (11 – SCA Researcher) or *"in light of respect for patients' autonomy"* (8 – SCA researcher). Even if obtaining consent may not be legally required, doing so shows respect and promotes public trust.[68,69] To preserve trust, one ethicist noted that researchers should not reason solely from the law but from respect and reciprocity ('what would they want to happen if it was their data?'). Another commented that it may be most important to inform patients about what will *not* be done with the data, e.g. sharing for commercial purposes. Consent is not a panacea, however, as data can cause privacy concerns for people other than the person consenting, such as blood relatives, or non-participants who are subject to risk prediction models created on the basis of the research (the 'tyranny of the minority')[70]. Also, patients cannot always recount what they consented to[71,72]; so the value of informed consent lies in the promotion of autonomy and the fact that people can refuse when they do not trust the researchers.

[iii] Some ethicists think that there is a moral (societal) obligation to help others when this can be done at small cost to oneself; in this case, by donating data. This duty of easy rescue is then used to justify waiving of consent.

Table 4-2. Governance of SCA data research: illustrative quotations

Privacy by design	
General	"Pseudonymized data should be used, that is one safeguard. Another is that it should be stored according to an ISO27001/2 norm, that a data transfer takes place in an encrypted way and that the key is kept by a data manager." (21 – Ethico-legal expert)
De-identification	"Right now there is broad consensus that double-coded data is not anonymous. Somewhere in the chain, personal data will be processed." (17 – Ethico-legal expert)
	"With the chain of care it's impossible to collect anonymised data. Later on, while analysing, you can anonymise. But if you do genetic analyses and need to report to the patient or the patient's family, you need to be able to get back to the patient." (2 – SCA researcher)
	"But if you seriously hamper data quality, then pseudonymization is not in the interest of the patient." (1 – SCA researcher)
Privacy by policy	
Informed consent	"[If you do not ask consent] you should provide a lot of information about the scientific research, to create openness and transparency. For example, a website containing the studies that have been conducted with the data and with results, and information about the researchers and the affiliated research institutes." (20 – Ethico-legal expert)
	"Consent is about trust in doctors, which is more crucial than any kind of information about the research." (2 – SCA researcher)
	"The best thing would be if you had an online electronic system for the whole population where people could opt in or out of registry studies." (6 – SCA researcher)
	"As a researcher I prefer opt-out, also because people often do not understand what they sign for anyway. If you do ask consent, it should be after a few months. In the ICU, the person is in a dependency position and I don't think that is right." (13 – SCA researcher)
	"I usually say, "You can think about it and I'll come back later" or "I will call you later". Because sometimes it's so confusing what's going on, so I would contact them later when they were at a coronary care unit or at home. I look at the situation and the people and make a decision based on that." (12 – SCA researcher)

	"There may be purposes that I couldn't have known about while I was alive, that I would not have consented to when my data are used after death." (22 – Ethico-legal expert)
	"It might rip open some scars if you have a husband or wife who has died and you get a letter that they have been included in a study. I don't know if that can be informed consent in any way because it's a stressful situation." (5 – SCA researcher)
Regulation and oversight	
Ethics review	"Not only because of the difficulty of consent, but also because data could be reused, it is really important to have oversight from a specific committee." (27 – Ethico-legal expert)
	"Most researchers here are only asking ethics committees for approval because of different journals requesting that, not because it's required by law." (16 – SCA researcher)
Harmonisation	"I think it is a very good plea to strive to European harmonisation, but it's far away still. Even in our own country it is difficult to get all the hospitals on the same policies for review. The GDPR still leaves room to all kinds of national regulations. In the end we stay in our countries with our own cultures." (21 – Ethico-legal expert)
	"It would be very nice to have someone who facilitates the process of the approval. They should give more advice. It is not that it is not clear, but it depends on the local ethics committee. The most important thing would be harmonising all the decisions at a national level. There are now only 40 ethics committees in [our country], but this is still a big number." (10 – SCA researcher)
	"But I think it is also a waste to jeopardise this whole registry system in order to harmonise everything. It is too heterogeneous to harmonise." (2 – SCA researcher)
	"Adjusting the GDPR or national law is a formal and difficult process, while a code of conduct is a living document that is able to withstand the ticking of time. (…) It should be possible to apply a more general code of conduct to different situations, also the emergency situation. We don't need too many codes for too many different situations. That would get very complicated again." (21 – Ethico-legal expert)

Deferred consent

Many data need to be collected during or shortly after the SCA event, e.g. ambulance ECGs which could be overwritten. Consent for research with such data is necessarily *deferred* until the patient is conscious, either in the hospital or preferably at home after a few months. Participants stated that obtaining patients' contact details outside a treatment relation is not allowed in many jurisdictions but several experts saw no issue with this: others did and suggested making contact through the healthcare provider or TTP. All experts regarded deferring of consent as acceptable for data-driven SCA research, which is consistent with the literature and perspectives of SCA survivors.[73-75] However, there was also agreement that data should be placed on hold until consent is obtained and that the timing of consent should be based on the patient's recovery. Experts stated that consent given before the patient's mental capacities are sufficiently restored after the SCA event, is not legally and morally valid. To assess decision-competency on an individual basis, the Appelbaum criteria can be used.[76] Some respondents suggested that the appropriate timing should be approved in advance by an REC. In most countries, proxy consent from next-of-kin may be asked if the patient remains incapacitated; this is described in national health law.

Broad consent

After consent has been obtained, data may be used for the purposes described in the consent form ('purpose limitation'). Respondents agreed these purposes can be as broad as 'SCA research' and some thought they extend to all health-related research. *Broad consent* was also found acceptable by SCA survivors as they prefer to make the main choice themselves but wish to leave specifics to researchers.[75] Broad consent seems acceptable in the eyes of the drafters of the GDPR (Recital 33), but there is still an intensive policy and scholarly debate about its legitimacy.[77] Asking specific consent for each study might be burdensome and one expert advocated for *dynamic consent*, where an online communication system is used to inform patients of changes in data use, and where participants can easily choose to opt-in or opt-out of specific uses, and decide with whom data may be shared.[78] In this system, participants may also provide preferences regarding (re)contact and whether they want to be informed of findings, similar to *meta consent* where preferences for the type of consent are recorded.[79] Such approaches may enhance autonomy, trust and social engagement, but depend on funding for the required communication infrastructure.

Deceased patients

We also discussed with experts whether consent would be required for the inclusion of deceased patients' data, an important question in research on acute and life-threat-

ening illness. In most ESCAPE-NET studies there is no role for next-of-kin in deciding about (non-genetic) data uses, as there is no legal basis and it may be an emotional burden on them. Experts agreed it would be best to inform people during their lifetime about the post-mortem use of data. Regarding genetic studies, experts noted that there is an ethical responsibility, albeit not a full legal duty in most countries, to disclose clinically actionable genetic findings that indicate serious risk to relatives of the deceased.[51] A number of respondents said that if a study may potentially give rise to such findings, it is useful to notify relatives as soon as possible about the research taking place.

4.4.3 Regulation and oversight

Ethics review of observational studies

Given the limitations of consent and anonymization, what is needed is a "shift from personal data protection to data protection tout court".[80] Most experts believed that observational studies should be subject to multidisciplinary ethical oversight even when consent is asked or data are anonymized. This is currently not the situation in many European countries, but was found important because of the potential impact on individuals and society, and because it provides the opportunity to give advice about ethical and legal aspects to SCA researchers, who expressed a desire for more guidance. For instance, RECs or data protection authorities evaluating observational studies should determine whether consent is needed, but should also assess study methodology, just like for randomised controlled trials, in order to gauge whether the public interest is served. Experts thought assessment needs to be proportional to the kinds of data (and tissue) used and the proposed uses.

The need for harmonisation

Respondents experienced (inter-)national differences in REC requirements for observational studies, which complicated cooperation and affected study validity, as also reported in the literature.[81,82] In some countries, observational studies with existing, pseudonymised, data or tissue are exempt from ('full') ethics review, but there is no clear international guidance on the criteria for exemptions.[83] Creating a European ethics approval process would be difficult in practice but at a minimum, review procedures should be harmonised at a national level, as regional procedural differences unnecessarily impede progress in science.[84, 85] Experts also noted the differences in interpretation of privacy laws. In addition to the GDPR and its implementation laws in EU Member States, other legal regimes and national *lex specialis* may regulate data protection for health research. However, it is not always clear how these laws should be applied to the SCA setting, which may complicate the

conduct of research and the proper protection of patients' rights.[13, 69] Therefore, experts mentioned the idea of an ethical *code of conduct* specifically for observational research in emergency medicine, but in the conference they agreed that there should not be too many different codes. Instead, when general codes of conduct for observational studies are created or updated, these should contain a provision on research in the emergency setting, and SCA researchers may need to lobby for this.

4.5 Discussion

We have provided an overview of expert perspectives on ethical challenges and governance solutions for observational SCA research. The study finds expert consensus about the ethical imperative for conducting research with SCA registries and biobanks. Still, researchers should recognise that adhering to ethical and legal requirements is more than mere administrative necessity given the potential for individual and societal harms. We addressed the governance options relevant for SCA and other acute and critical illness research, but due to the variety of themes our descriptions are necessarily limited in detail. It was not our intention to study specific privacy-enhancing technologies and their effectiveness, or to conduct a comparative analysis of the current data protection and biobanking laws in the EU, but rather to identify and explore the ethical challenges related to SCA research, which are clearly not limited to specific data protection methods or jurisdictions.

We find that when privacy by design and privacy by policy measures are deployed correctly and in congruence, and combined with ethics oversight, observational SCA research poses minimal risk to the data subjects and others. Technical measures such as pseudonymization should always be in place, also for deceased patients, as long as this does not disproportionately limit the conduct of research. While some respondents thought that informed consent is only necessary when anonymization is impossible, this standpoint disregards the limitations of anonymization and the fact that control may still be important even if data are anonymized. Ignoring participants' expectations may also harm trust in the research enterprise. Experts agreed that exemptions from consent should be established by an REC on a case-by-case basis. If consent is asked, we found that a deferred and broad consent model is acceptable for observational SCA research, which is in line with patients' views and the recently updated European Resuscitation Council (ERC) guidelines.[86] Our study adds that consent from SCA survivors is most valuable when deferred until the patient has fully regained cognitive capacities. This may be some months after the SCA event.[75]

Further study is needed regarding innovative governance solutions to facilitate data sharing and improve data subjects' control.[87] For instance, digital consent tools would allow SCA survivors to easily register (broad) consent preferences, including

on when they can be approached for consent. Research aimed at improving communication about complex aspects of studies (e.g. involving commercial parties, genetic risk scores, or uses after death) would help avoid patients opting out due to lack of understanding. SCA research may also benefit from population-based democratic governance tools such as data cooperatives,[88] as these enable potential SCA victims to register privacy preferences in advance. Another valuable avenue would be to create government-appointed national SCA registries across Europe, which would help centralise ethical governance and remove some legal uncertainty, while allowing for larger and more representative cohort studies.[12, 29, 89] Specific research registries and biobanks will continue to be needed, however, for in-depth studies.

Our study highlights the interdisciplinary nature of this topic which calls for societal dialogue about data research in emergency medicine between medical, epidemiological, humanities, legal, policy, and ICT experts as well as lay people. Scientific societies such as the European Resuscitation Council, should position themselves and endorse an active, structured dealing with the topic. We advocate the development of an up-to-date code of conduct, or addition of a section about emergency medicine to an existing and more general code,[iv] in order to clarify to what rules observational SCA research has to oblige and so to stimulate collaboration on the EU-level. This might be a joint effort with societies in intensive care medicine that are facing the same issues.[85]

[iv] Such as the one being developed by BBMRI in the Code of Conduct for Health Research initiative (http://code-of-conduct-for-health-research.eu/) or the code of conduct for data sharing developed by the Global Alliance for Genomics and Health.[90]