ETHICAL CHALLENGES IN RESUSCITATION

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Short Running Head: Ethics and Resuscitation**;** Word Count of Manuscript: 3996. **Conflict of Interest Statements:** Gavin Perkins has received research funding from the National Institute for Health Research to conduct studies in cardiac arrest; he holds volunteer roles within the Resuscitation Council (UK), European Resuscitation Council and International Liaison Committee on Resuscitation. Leo Bossaert holds volunteer roles within the European Resuscitation Council. Robert Greif holds a volunteer role within the European Resuscitation Council and International Liaison Committee on Resuscitation.
No other author has a conflict of interest to disclose.

IMPORTANT ACKNOWLEDGMENT ON AUTHOR CONTRIBUTIONS

The contributions of the second, third, fourth, and fifth author should be considered as equally important and equivalent to a contribution from a second author. The contributions of the sixth, seventh, eighth, ninth, tenth, and eleventh author should be considered as equally important and equivalent to a contribution from a third author.

The authors are grateful to Prof. Antonio G. Spagnolo, Director of the Institute of Bioethics and Medical Humanities Università Cattolica del Sacro Cuore, Rome, Italy, for offering useful advice during manuscript preparation.
The authors acknowledge the support of the European Resuscitation Council for the conduct of teleconferences.

Key Words: Resuscitation; Personal Autonomy; Beneficence; Social Justice.

ABSTRACT

Purpose: A rapidly evolving resuscitation science provides more effective treatments to an aging population with multiple comorbidites. Concurrently, emergency care has become patient-centered. This review aims to describe challenges associated with the application of key principles of bioethics in resuscitation and post-resuscitation care; propose actions to address these challenges; and highlight the need for evidence-based ethics and consensus on ethical principles' interpretation.

Methods: Following agreement on the article's outline, subgroups of 2-3 authors provided narrative reviews of ethical issues concerning autonomy and honesty, beneficence/nonmaleficence and dignity, justice, specific practices/circumstances such as family presence during resuscitation, and emergency research. Proposals for addressing ethical challenges were also offered.

Results: Respect for patient autonomy can be realized through honest provision of information, shared decision-making, and advance directives/care planning. Essential prerequisites comprise public and specific healthcare professionals' education, appropriate regulatory provisions, and allocation of adequate resources. Regarding beneficence/nonmaleficence, resuscitation should benefit patients, while avoiding harm from futile interventions; pertinent practice should be based on neurological prognostication and patient/family-reported outcomes. Regarding dignity, aggressive life-sustaining treatments against patients' preferences should be avoided. Contrary to the principle of justice, resuscitation quality may be affected by race/income status, age, ethnicity, comorbidity, and location (urban versus rural or country-specific/region-specific). Current evidence supports family presence during resuscitation. Regarding emergency research, autonomy should be respected without

hindering scientific progress; furthermore, transparency of research conduct should be promoted and funding increased.

Conclusions: Major ethical challenges in resuscitation science need to be addressed through complex/resource-demanding interventions. Such actions require support by ongoing/future research.

INTRODUCTION

Ongoing changes in medicine, and the societal context in which it is practised, create a range of ethical challenges for clinicians. Rapid progress in resuscitation science and intensive care provides increased opportunities to treat patients [1,2], while an aging population and increased prevalence of people with multiple comorbidities raises questions about how much benefit these treatments can bring. Concurrently, there has been a move from paternalistic to patient-centered care with a more informed population and an increasing focus on individual rights and values. Key ethical documents and guidelines have both reflected and contributed to this change [2-6] and there is a substantial literature on the application of key ethical principles in resuscitation medicine [1,3-15; see also the electronic supplementary material (ESM)].

Evidence-based standards of emergency care and related ethical considerations should evolve simultaneously to ensure high-quality care [1,5]. However, the interpretation of ethical principles in the context of resuscitation/end of life decision-making may vary among different countries and cultures for various reasons [1,5,16,17].

The objectives of the current narrative review are to 1) describe current and emerging challenges associated with the application of ethical principles in resuscitation and subsequent critical care; a brief, pertinent summary is presented in Table 1; 2) propose possible ways, actions, and initiatives to address these challenges; and 3) highlight the need for research evidence-based ethics and international consensus [17] on the perception of ethical principles in relation to resuscitation.

We have defined the relevant ethical principles as follows:

- Autonomy: respect for the right of self-determination [1,7]
- Honesty: accurate and transparent communication to the patient/family of the best research evidence, and clinical judgment including uncertainties.
- Beneficence: selection of beneficial interventions for the patient after assessment of the risk-to-benefit ratio [1,3]
- Non-maleficence: avoiding harm or inflicting the least possible harm in the course of achieving a beneficial outcome [1].
- Dignity: comprises "*being human,*" "*having control,*" "*relationship and belonging*", *and* "*maintaining the individual self*" [1,18]; regarding resuscitation and postresuscitation care, dignity means avoiding disproportional interventions and an "end-of-life" contradicting patient's preferences.
- Justice: means fair and equal distribution of benefits, risks, and costs; pertains to the equality of rights to healthcare, and the legal obligation of healthcare providers to adhere to appropriate care and allocation of burdens and benefits [1].

REPECTING PATIENT PREFERENCES

Means to safeguard the autonomy of incapacitated cardiac arrest patients include advance directives, advance care planning (ACP), and consulting their trusted/loved ones to establish previously expressed wishes. Advance directives and ACP frequently concern an individual's preferences regarding cardiopulmonary resuscitation (CPR) and other life-sustaining treatments (LSTs) [19].

Advance directives

Advance directives address cases of patients with loss of decisional capacity and include living wills (instruction directives) and appointment of a "health care proxy" with durable power of attorney to make healthcare decisions (proxy directive) [1,10,19,20]. Instruction directives may comprise summary/general or detailed/specific descriptions of the patient's values, goals, and preferences regarding healthcare issues and interventions [1,11,19,20]. Specific preferences may include do-not-attempt CPR (DNACPR).

Healthy individuals drafting living wills may attempt to cover a broad spectrum of diseases, without having the required "medical knowledge and a grasp of the resulting conditions" [21]. This may result in ambiguity of the directive, challenging its applicability, and necessitating interpretation under specific clinical conditions [20]. Advance directives' legal status depends on cultural, religious, sociolinguistic, political, and medico-ethical factors [22], and varies widely among European countries from "*not mentioned in law*" to "*legally binding*" [6,20].

Living wills drafted during health may not reflect changing preferences due to aging, occurrence of serious illness, and/or cognitive decline [23-25]; such factors may also affect the physicians' preferences about their own healthcare [25]. However, >70% of elderly inpatients with previously stated resuscitation preferences may ultimately wish their family and physician decide for them [26]. Conversely, recent evidence suggests that advance directives may promote comfort care and prevent end-of-life overtreatment [27]; this is consistent with nonmaleficence and dignity.

ACP

Advance directives and ACP exhibit major differences. ACP focuses on shared decision-making between clinician and patient**.** It is a dynamic, iterative process of eliciting and recording informed preferences of patients about end-of-life care, and accordingly pre-specifying and prioritizing future treatment goals. This is achieved through communication among patients, trained healthcare professionals, family, and other loved ones [28]. ACP may help the patient cope with death, and alleviate ethical burden from and strengthen relationships with his/her loved ones [29].

Recent evidence on complex and resource-demanding interventions (see ESM) suggests that ACP promotes congruency of care with patients' wishes and associated patient and/or family satisfaction; reduces family stress, anxiety and depression; and may reduce the overall rates of ˚aggressive˚ LSTs [28], which accords with nonmaleficence and dignity. The effective linking of patients' wishes to realizable care plans requires multifaceted approaches {eg, the Physicians Orders for LSTs (POLST) forms / registry [30]} and a specific healthcare policy of enacting supportive regulations and making recorded patients' preferences and goals easily accessible to emergency caregivers [31].

Integration of DNACPR preferences with ACP - which includes patient preferences about outcomes and/or other treatments (besides resuscitation) - has been advocated to help address major issues currently associated with "isolated" DNACPR orders [8]. Such problems include lack of participation of patient/family in decision-making [8], inappropriate CPR [3,4,6,8] or CPR resulting in poor, patient-perceived quality of life [1], and withholding of other indicated treatments such as pain relief and fluid intake [8]. Withholding of indicated treatments is related to misinterpretation of DNACPR and is not ethically justified [32].

Consent for interventions and shared decision-making

Article 5 of the Biomedicine Convention states that "*An intervention in the health field may ONLY be carried out AFTER the person concerned has given free and informed consent to it*" [33]. Consent validity may depend on 1) an individual's ability to understand essential information about their illness and indicated treatment, appraise the gravity of their condition, compare risks and benefits, and express a rational choice [10]; 2) availability of adequate time to decide [14]; and 3) concurrent emotional stress [15]. In emergency situations such as cardiac arrest, and in the absence of any readily accessible, CPR-specific, recorded patient preferences and/or DNACPR orders, immediate necessity dictates a "treat first, discuss later" approach (Tables 1 and 2).

In challenging cases of ongoing, postresuscitation patient incapacity and absence of any associated, advance directives or ACP, decisions on LSTs should reflect the result of a collaborative process enabling shared-decision making of surrogates and clinicians after considering the available evidence [34] and the patient's values goals and preferences [10,35]. Other challenges may include accuracy of surrogates' estimates of patient preferences [36], potential subjectivity of physicians' predictions for post-discharge, health-related quality of life (QoL) [37], and possible disagreements/conflicts between surrogates of equivalent standing and/or between surrogates and clinicians [38]; in the absence of recorded, informed DNACPR preferences, physician-issued DNACPR orders based on poor prognosis may occasionally contradict surrogates' overoptimistic expectations from aggressive LSTs [1,6]. Conflicts -if not timely resolved (eg, with the aid of an Ethics Committee)- may

lead to indecisiveness regarding indicated treatment(s) and poor patient outcomes [38].

PRESENTING INFORMATION FOR DECISION MAKING

An essential prerequisite for autonomy is the informed and meaningful patient/family involvement in decision-making. In the context of honesty, the physician should:

a. Present all options and likely outcomes in a clear and comprehensible manner [7]. Failure to thoroughly discuss with surrogates comfort care alternatives to aggressive care may lead to therapeutic decisions that do not accord with patient preferences [39].
b. Discuss the relation between resuscitation intervention-associated burden and benefit, preferably by using individualized choice architecture; this includes a hierarchical presentation of treatment options starting from the most appropriate according to physician judgment [40].
c. Actively engage in religious/spiritual discussions as pertinent end-of-life concerns may substantially affect surrogates' decisions; a multicenter, prospective, cohort study suggested that intensive care professionals frequently fail to address such concerns [41].
d. Ensure that the patient/family is given sufficient time to consider options, weigh up risks and benefits, and consult with others [42].

Models for predicting survival from attempted CPR have been developed and internally validated using large, in-hospital registry data sets [34]. However, the communication of statistical estimates of risk for poor outcome to patients/families

may prove challenging, depending on their ability to comprehend the message, their beliefs about their individual risk relative to the general population, and the elicitation of emotional reaction(s) [43]. Furthermore, even if probabilistic outcomes could be accurately conveyed, the reality of a prolonged recovery period in a neurologically deficient state may be difficult to predict [44]. Uncertainties about the potential severity and duration of disability should be disclosed.

Physicians may feel torn between the desire to present a "full picture" – including that of limited resources - in order to meet stringent criteria for respecting patient autonomy, and the desire to protect patients from anxiety and burdensome decision-making while they are already unwell; occasionally, doctors may exercise a "therapeutic privilege" and withhold some information [45] about a resuscitation decision.

BENEFITING WITHOUT HARMING

Since medical interventions are potentially harmful, physicians should ensure that the balance favors benefit. The ethical challenge arises because of uncertainty about potential benefit and harm that might occur in an individual case. This is increased in situations where patients cannot communicate and their views on potential benefits and harms of interventions are unknown. In the context of CPR, these ethically difficult decisions occur when considering initiating CPR, terminating CPR and limiting LSTs following return of spontaneous circulation (ROSC).

There is a potential risk of harm during/after CPR. Data from 27 European countries suggest that among patients resuscitated from out-of-hospital cardiac arrest (OHCA), 75% (individual, country-reported range, 50-90%) do not achieve ROSC before hospital admission; and the overall, in-hospital/30-day mortality rate amounts

to 90% (country-reported range, 69-99%) [46]. Similar mortality data have been reported for the United States and Canada (year 2010, in-hospital mortality, 90%; region-specific range, 81-94%) [47] and Australia (year 2015, in-hospital/30-day mortality, 88%; region-specific range, 83-91%) [48]. In OHCA survivors to hospital discharge, hypoxic-ischemic brain injury (HIBI) frequently results in long-term cerebral disability, including persistent vegetative state [49]. Among Australian patients aged ≥65 years, the estimated proportion of moderate-to-severe neurological disability or death at 12 months postarrest amounted to 44% [50]. Predicting when CPR is unlikely to result in a neurologically meaningful survival and knowing in advance the patient values and preferences is crucial to prevent harmful resuscitation efforts. This is difficult to achieve, especially in OHCA which is more unpredictable, with little available information about the patient's clinical status or personal wishes. The default is therefore to start CPR immediately in all OHCAs, unless obvious signs of irreversible death are present or when there is a valid advance directive or a DNACPR order [Table 2; 3,4,6]. The ethical default is to preserve life and defer assessments of best interests until relevant information is available.

Conversely, for in-hospital cardiac arrest (IHCA), most events are witnessed and/or monitored and life support from healthcare personnel is immediately available. DNACPR may be in place in those in whom attempted CPR would probably be unsuccessful (Table 2; see ESM) In a recent survey, DNACPR orders were used in 22/32 European countries (69%) [5]. IHCA differs from OHCA in terms of patients' prearrest, acute/chronic comorbidities, prearrest therapeutic interventions, cardiac arrest-precipitating cause, and prognosis (Table 2). In the United States, the 2009 risk-adjusted, in-hospital mortality was 78%; among survivors, the proportions of clinically significant and severe disability were 28% and 10%, respectively [51]; risk-

adjusted, in-hospital mortality varies widely among hospitals, ie, from 68% to 100% [52].

If initial resuscitative efforts are unsuccessful the original assessment of pertinent benefits and harms should be reviewed. The European Resuscitation Council's (ERC's) ethical guidelines suggest that healthcare professionals should consider terminating resuscitation efforts in cases of asystole for >20 minutes despite ongoing advanced life support, in the absence of a reversible cause [3]. In general, survival with good neurological outcome is unlikely when OHCA duration exceeds 30 minutes [3]. However, this rule is not universal (see ESM) and it has been recently challenged by the advent of extracorporeal CPR [53]. Regarding IHCA, clinical decision aids have been proposed [34; see above and ESM]; however, a large-scale external validation of the associated clinical scoring system is still pending.

Assessment of HIBI severity can guide the ethically difficult decision of whether and when to avoid disproportionate care for these patients. In 2014, guidelines for neurological prognostication after cardiac arrest were co-issued by the ERC and the European Society of Intensive Care Medicine [54]. These guidelines are based on a multimodal approach combining clinical examination and relevant investigations to predict poor neurological outcome with the greatest possible accuracy in patients who are comatose with absent or extensor motor response to pain at ≥3 days after ROSC. However, the quality of evidence supporting these predictors is low or very low and when prognosis appears to be indeterminate, or indicators give contradictory results, prolonged LST may be indicated.

Another limitation of neurological prognostication indices is the inconsistency in definitions of what represents a poor neurological outcome [55]: the QoL reported by cardiac arrest survivors or their caregivers is generally lower than that described by

traditional outcome measures [56]. When assessing the appropriateness of resuscitative interventions, prognostication aids should be based on patient-reported and/or family-reported rather than clinician-reported outcomes. Cardiac arrest studies should include QoL measures and assess patient/family-reported outcomes [57,58].

OPTIMIZING END-OF-LIFE TREATMENT

Successful implementation of ACP with support by the next-of-kin and attending physicians should result in efficacious, end-of-life comfort-care.

In postresuscitation care, LST is often withdrawn based on shared decision-making [9,10], and/or when the likelihood of neurologically favourable survival is extremely low [34], and clinical evidence indicates "disproportionate use" [59]. The distinction between allowing a patient to die after LST withdrawal and deliberate termination of life remains unanswered. Many doctors believe that a ventilator-dependent patient is allowed to die after LST withdrawal due to the underlying patient’s condition or severe organ failure. Others regard LST withdrawal as the immediate cause of death as most patients die within the next 30 minutes [60]. Varying viewpoints on LST withdrawal may reflect cultural/religious influences [22]. Distressing symptoms should be anticipated and alleviated by sedatives and opioids; these agents do not seem to shorten the dying process [61]. Current European Guidelines are consistent with palliative sedo-analgesia to reduce patient awareness of pain and suffering, without hastening death [10].

EQUAL ACCESS TO BEST-QUALITY CARE

Cardiac arrest patients should be provided with the same, timely, and high-quality resuscitation and postresuscitation care. Contrasting this ideal, a ten-fold,

intercontinental variation in reported OHCA incidence and outcomes (eg, overall survival to hospital discharge from approximately 1% to 10%) has been previously documented [62].

As detailed above, OHCA outcomes vary greatly among European countries; this may be attributable to between-country differences in emergency care organization and quality, and availability and allocation of resources [5,46]. In North America, substantial, regional differences in OHCA in-hospital mortality may be partly explained by variable bystander CPR rates, and differences in the quality of postresuscitation care among hospitals [47,63; see ESM].

In Europe, emergency care quality seems to be affected by patient comorbidity and age, and location (eg, urban or rural) and type (eg, teaching, tertiary care) of admitting and/or treating hospital [5; Table 3]. Urban versus rural location (eg, in Japan; see ESM) can impact the available workforce, quality and frequency of provider training, volume of emergency care resources, and response time (due to geographic dispersion, distance, and ambulance availability). In the United States, the combination of low income and black race seems to negatively impact bystander CPR rates [64]; these findings cannot be generalized to other racial or ethnic groups, given the scarcity of relevant studies. Collectively, these challenges represent inequalities in access, treatment, and outcome.

Access to specific hospital resources (eg, targeted temperature management, post-ROSC cardiac catheterization, extracorporeal CPR) are labor-intensive, expensive, and require specialized personnel with wide variation in availability. Even among high-resource countries with wide implementation of extracorporeal CPR, this resource is expectedly concentrated in urban tertiary hospitals with availability of advanced cardiovascular care (see ESM). Out-of-hospital use of extracorporeal CPR

is even less common and generally restricted to Emergency Medical Services systems staffed by physicians with mobile intensive care unit capability [65].

Focusing on improvement and consistent provider training, bystander CPR, availability and use of automated external defibrillators, and more standardized resuscitation practices would improve the justice of resuscitation. Modifying system-level factors likely require a central champion, dedicated funding, and organizations that are receptive and malleable to change. There is evidence that improvement in survival from cardiac arrest can improve over time with heightened focus on system factors, feedback, quality of CPR, tracking outcomes, and training [47].

Rationing in resuscitation presents challenges regarding the objectivity and ethical integrity of criteria applied for DNACPR/LST decisions [66]**.** Utilitarian allocation of limited resources can be based on futility and/or differences in prognosis/LST cost [66,67]. Futility has been defined as "*the use of considerable resources without a reasonable hope that the patient would recover to a state of relative independence or be interactive with their environment*" [66]. However, without quantification of "*considerable*", "*reasonable*", "*relative independence*", and "*interactive*", beneficial treatment can be arbitrarily/unethically denied to vulnerable population subgroups such as the elderly, the disabled, or those with chronic or hereditary or genetic diseases/anomalies [66].

Table 3 displays OHCA versus IHCA differences concerning justice.

SPECIFIC CLINICAL PRACTICES OR CIRCUMSTANCES

These include family presence during resuscitation, pediatric/neonatal resuscitation, slow code, provider safety, organ donation, and end-of-life treatments for "very

recent" (ie, ≤2 years) immigrants/refugees. Ethical challenges are summarized in Table 4 and detailed in the ESM.

ETHICAL ISSUES IN EMERGENCY RESEARCH

In cardiac arrest research, respect for autonomy is challenging, because the immediate necessity for resuscitation precludes obtaining pre-enrollment, informed consent [13,14]. For low-risk research [13], ethically/publicly acceptable, alternative consent models include deferred consent, and exception to informed consent (EFIC) with prior community consultation [13,68]. In deferred consent, the patient or his/her next-of-kin or legally authorized representative are informed about the study as soon as possible and informed consent for continued participation is requested; this consent model can be applied in emergency research involving incapacitated patients in the European Union [13]. If the patient dies before the next-of-kin can be reached, practices may vary based on weighing transparency and informing the relatives against the associated burden/harm. In EFIC, information is shared with the relevant communities and community members are provided with the opportunity to opt out by requesting "NO STUDY" [69]; this consent model can be used in emergency research in the United States [13; ESM]. Table 5 displays the characteristics of these consent models and associated ethical challenges, including the issue of consent validity [1,13-15]. Additional consent models such as integrated consent and prospective consent have been detailed elsewhere [1]. Once enrolled in a trial, withdrawal of consent may introduce bias, as those doing less well are more likely to withdraw [70]. Some authorities (eg, United States Food and Drug Administration) but not all (eg, European Union authorities) forbid participants from withdrawing data that have already been collected up to the time that they rescind their consent. Additional challenges are detailed in the ESM.

Commercial and noncommercial academic research

Efforts to address issues of flawed study design, selective reporting, "ghostwriting", and "guest" or "gift" authorship (see ESM) have included compulsory, pre-enrollment registration of trial protocols, posting of results to trial registries, and journal publication within 12 and 24 months of trial completion (respectively), and a call for disclosure of results from still-unreported trials [71]. Furthermore, journals oblige authors to detail the sponsor's role and their own contributions as regards study conception, design, and conduct, data analysis and interpretation, and manuscript preparation and approval for submission.

Another major issue concerns prioritization of research according to public health need. Despite recently confirmed steady improvements, cardiac arrest outcomes still remain dismal [46-48,50-52,72]. Considering the pertinent public health mortality burden, cardiac arrest resuscitation guidelines are based on 35 to 53 times lesser randomized clinical trials per 10000 deaths per year as compared with guidelines for myocardial infarction, heart failure, and stroke [72]. Research on high-cost, patent protected drugs or devices has received disproportionately higher industry and/or governmental funding relative to much-needed, non-commercial, academic resuscitation research on patent-unprotected, low-cost, widely used drugs of still-uncertain efficacy, such as epinephrine, or antiarrhythmics [72].

ADDRESSING MAJOR CHALLENGES – FUTURE DIRECTIONS

At global level, the respect for patient values, preferences, and goals varies according to country-specific, or region-specific balance between paternalism and patient-centricity. Cultural, religious, legal, and socioeconomic barriers would have to

be overcome to apply harmonized policies supporting resource-demanding approaches (eg, POLST [31,32]) so as to effectively safeguard patient autonomy.

Examples from regions such as Oregon, United States [31,32] suggest that provision of information to the public in an "unbiased manner", preferably through organized and "*free-of-charge*" education on the benefits and limitations of resuscitation as well as knowledge of illness prognosis at individual level, may help patients (and their families) articulate their wishes. Patients and their loved ones should also be clearly aware of their rights emanating from the key ethical principles, as well as of the extent of these rights. Such actions and initiatives could benefit the society in general and vulnerable groups (eg, persons with poor socioeconomic status, and new immigrants/refugees) in particular.

Currently active caregivers should receive ethical practice training followed by predefined, skill-level certification so as to integrate the respect for autonomy and the other ethical principles in their daily practice. This would likely promote convergence to a more uniform interpretation of key principles amongst physicians and nurses and facilitate the application of currently recommended, structured, shared decision-making procedures [9,10] in a preferably standardized manner. In addition, teaching of Medical Ethics at the pre-graduate level would equip the forthcoming generations of physicians and healthcare professionals with adequate theoretical knowledge (including *clear definitions*) of the key principles and of how they should be applied; this should be followed by ethical practice training and pertinent certification.

Ethical practices' terminology should be harmonized to improve communication among involved parties and prevent confusion. For instance, consensus should be reached about the most suitable of acronyms denoting withholding of resuscitative interventions such as DNACPR, or DNAR (do-not-attempt resuscitation), or DNR

(do-not resuscitate). In addition, potential conceptual differences between withholding and withdrawing of LST should ideally be clearly defined based on the broadest possible consensus. Some ethicists regard LST withdrawal as active causation of death; in contrast, LST withholding means "*passively allowing the patient to die*" [73]. However, consequentialists see no ethically relevant distinction, because the end-result of these practices is essentially the same [73]. Regarding palliative sedo-analgesia, current European guidelines are fairly explicit about indications and intensity of treatment (see above).

Addressing the issue of limited resources constitutes a major challenge in both developing and developed countries. Indeed, at global level, the equitable access to best possible emergency care [5] including expensive technological advancements such as extracorporeal CPR [65] seems like a theoretical ideal rather than a possible, near-future achievement. In sharp contrast, the widespread use of simple and beneficial interventions such as bystander CPR could be substantially augmented through organized, international education on resuscitation, preferably supported by the World Health Organization (WHO) and international Resuscitation Councils. WHO has already issued guidelines and launched initiatives to promote basic resuscitation of neonates in developing countries, thus improving accessibility to emergency care and potentially reducing subsequent morbidity/disability and/or mortality in this vulnerable population subgroup.

Regarding research, transparency could be promoted through data-sharing policies [74], and governmental funding of resuscitation research could be increased to become proportionate to cardiac arrest mortality burden [72]. Furthermore, the ethical credibility of partnerships between private and public sectors should be augmented by striking a balance between commercial interests and goals of investigators to promote

science [75]. Lastly, patients/families might actively contribute to the development of research objectives and ethical/clinical practice guidelines.

CONCLUSION

Major challenges regarding the ethics of the rapidly advancing resuscitation science need to be addressed through widespread, coordinated, and sometimes resource-demanding interventions. The physical, ethical and wider societal impacts of such actions need to be supported by ongoing and future research.

REFERENCES

1. Mentzelopoulos SD, Haywood K, Cariou A, Mantzanas M, Bossaert L (2016) Evolution of medical ethics in resuscitation and end of life. Trends Anaesth Crit Care 10: 7-14.
2. Parsa-Parsi RW (2017) The Revised Declaration of Geneva: A Modern-Day Physician's Pledge. JAMA 318:1971-1972. doi: 10.1001/jama.2017.16230
3. Bossaert LL, Perkins GD, Askitopoulou H, Raffay VI, Greif R, Haywood KL, Mentzelopoulos SD, Nolan JP, Van de Voorde P, Xanthos TT; ethics of resuscitation and end-of-life decisions section Collaborators (2015) European Resuscitation Council Guidelines for Resuscitation 2015: Section 11. The ethics of resuscitation and end-of-life decisions. Resuscitation 95:302-11. doi: 10.1016/j.resuscitation.2015.07.033
4. Australian Resuscitation Council; New Zealand Resuscitation Council (2015) Section 10: Guideline 10.5 - Legal and Ethical Issues Related to Resuscitation. Australian Resuscitation Council website. https://resus.org.au/guidelines/. Accessed February 1, 2018
5. Mentzelopoulos SD, Bossaert L, Raffay V, Askitopoulou H, Perkins GD, Greif R, Haywood K, Van de Voorde P, Xanthos T (2016). A survey of key opinion leaders on ethical resuscitation practices in 31 European Countries. Resuscitation 100:11-17. doi: 10.1016/j.resuscitation.2015.12.010
6. Mancini ME, Diekema DS, Hoadley TA, Kadlec KD, Leveille MH, McGowan JE, Munkwitz MM, Panchal AR, Sayre MR, Sinz EH (2015). Part 3: Ethical Issues: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 132(18 Suppl 2):S383-396. doi: 10.1161/CIR.0000000000000254

7. O'Neill O (1984) Paternalism and partial autonomy. J Med Ethics.10:173-178.
8. Fritz Z, Slowther AM, Perkins GD (2017) Resuscitation policy should focus on the patient, not the decision. BMJ 356:j813. doi: 10.1136/bmj.j813
9. Kon AA, Davidson JE, Morrison W, Danis M, White DB; American College of Critical Care Medicine; American Thoracic Society (2016) Shared Decision Making in ICUs: An American College of Critical Care Medicine and American Thoracic Society Policy Statement. Crit Care Med 44:188-201. doi: 10.1097/CCM.0000000000001396
10. Council of Europe (2014) Guide on the decision-making process regarding medical treatment in end-of-life situations. Bioethics.net website. http://www.bioethics.net/2014/05/council-of-europe-launches-guide-on-decision-making-process-regarding-medical-treatment-in-end-ofllife-situations/. Accessed January 29, 2018.
11. Nolan JP, Soar J, Cariou A, Cronberg T, Moulaert VR, Deakin CD, Bottiger BW, Friberg H, Sunde K, Sandroni C (2015) European Resuscitation Council and European Society of Intensive Care Medicine Guidelines for Post-resuscitation Care 2015: Section 5 of the European Resuscitation Council Guidelines for Resuscitation 2015. Resuscitation 95:202-222. doi: 10.1016/j.resuscitation.2015.07.018
12. Perkins GD, Jacobs IG, Nadkarni VM, Berg RA, Bhanji F, Biarent D, Bossaert LL, Brett SJ, Chamberlain D, de Caen AR, Deakin CD, Finn JC, Gräsner JT, Hazinski MF, Iwami T, Koster RW, Lim SH, Ma MH, McNally BF, Morley PT, Morrison LJ, Monsieurs KG, Montgomery W, Nichol G, Okada K, Ong ME, Travers AH, Nolan JP; Utstein Collaborators (2015) Cardiac Arrest and Cardiopulmonary Resuscitation Outcome Reports: Update

of the Utstein Resuscitation Registry Templates for Out-of-Hospital Cardiac Arrest: A Statement for Healthcare Professionals From a Task Force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian and New Zealand Council on Resuscitation, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa, Resuscitation Council of Asia); and the American Heart Association Emergency Cardiovascular Care Committee and the Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation. Resuscitation 96:328-340. doi: 10.1016/j.resuscitation.2014.11.002

13. Mentzelopoulos SD, Mantzanas M, van Belle G, Nichol G (2015) Evolution of European Union legislation on emergency research. Resuscitation 91:84-91. doi: 10.1016/j.resuscitation.2015.03.006
14. Booth MG (2007) Informed consent in emergency research: a contradiction in terms. Sci Eng Ethics 13:351-359. doi: 10.1007/s11948-007-9028-3
15. Kompanje EJ, Maas AI, Menon DK, Kesecioglu J (2014) Medical research in emergency research in the European Union member states: tensions between theory and practice. Intensive Care Med 40:496–503. doi: 10.1007/s00134-014-3243-6
16. Gibbs AJO, Malyon AC, Fritz ZBM (2016) Themes and variations: An exploratory international investigation into resuscitation decision-making. Resuscitation 103:75-81. doi: 10.1016/j.resuscitation.2016.01.020
17. Sprung CL, Truog RD, Curtis JR, Joynt GM, Baras M, Michalsen A, Briegel J, Kesecioglu J, Efferen L, De Robertis E, Bulpa P, Metnitz P, Patil N, Hawryluck L, Manthous C, Moreno R, Leonard S, Hill NS, Wennberg E,

McDermid RC, Mikstacki A, Mularski RA, Hartog CS, Avidan A (2014) Seeking worldwide professional consensus on the principles of end-of-life care for the critically ill. The Consensus for Worldwide End-of-Life Practice for Patients in Intensive Care Units (WELPICUS) study. Am J Respir Crit Care Med 190:855-866. doi: 10.1164/rccm.201403-0593CC.

18. Enes S (2003) An exploration of dignity in palliative care. Palliat Med 17:263–269.
19. Martin DK, Emanuel LL and Singer PA (2000) Planning for the end of life. Lancet 2000; 356:1672–1676.
20. Andorno R, Biller-Andorno N, Brauer S (2009) Advance health care directives: towards a coordinated European policy? Eur J Health Law 16:207-227.
21. Fagerlin A, Schneider CE (2004) Enough: the failure of the living will. Hastings Cent Rep 34:30-42.
22. Sulmasy DP (2018) Italy's New Advance Directive Law: When in Rome….JAMA Intern Med doi: 10.1001/jamainternmed.2018.0462. [Epub ahead of print]
23. Mower WR, Baraff LJ (1993) Advance directives, effect of type of directive on physicians' therapeutic decisions. Archives of Internal Medicine 153: 375-81.
24. Ryan CJ (1996) Betting your life: an argument against certain advance directives. J Med Ethics 22:95-99.
25. Wittink MN, Morales KH, Meoni LA, Ford DE, Wang NY, Klag MJ, Gallo JJ (2008) Stability of preferences for end-of-life treatment after 3 years of

follow-up: the Johns Hopkins Precursors Study. Arch Intern Med 168:2125-2130. doi: 10.1001/archinte.168.19.2125

26. Puchalski CM, Zhong Z, Jacobs MM, Fox E, Lynn J, Harrold J, Galanos A, Phillips RS, Califf R, Teno JM (2000) Patients who want their family and physician to make resuscitation decisions for them: observations from SUPPORT and HELP. Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatment. Hospitalized Elderly Longitudinal Project. J Am Geriatr Soc 48(5 Suppl):S84-90.
27. Silveira MJ, Kim SY, Langa KM (2010) Advance directives and outcomes of surrogate decision making before death. N Engl J Med 362:1211-1218. doi: 10.1056/NEJMsa0907901
28. Brinkman-Stoppelenburg A, Rietjens JA, van der Heide A (2014) The effects of advance care planning on end-of-life care: a systematic review. Palliat Med 28:1000-1025. doi: 10.1177/0269216314526272
29. Vandervoort A, Houttekier D, Van den Block L, van der Steen JT, Vander Stichele R, Deliens L (2014) Advance care planning and physician orders in nursing home residents with dementia: a nationwide retrospective study among professional caregivers and relatives. J Pain Symptom Manage 47:245-256. doi: 10.1016/j.jpainsymman.2013.03.009
30. [No authors listed] (2017) Guidelines for Emergency Physicians on the Interpretation of Physician Orders for Life-Sustaining Therapy (POLST). Ann Emerg Med 70:122-125. doi: 10.1016/j.annemergmed.2017.04.046
31. Tolle SW, Teno JM (2017) Lessons from Oregon in Embracing Complexity in End-of-Life Care. N Engl J Med 376:1078-1082. doi: 10.1056/NEJMsb1612511

32. Fritz Z, Fuld J (2010) "Ethical issues surrounding do not attempt resuscitation orders: decisions, discussions and deleterious effects." J Med Ethics 36:593-597. doi: 10.1136/jme.2010.035725

33. Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine. Oviedo, 4.IV.1997. http://conventions.coe.int/Treaty/en/Treaties/Html/164.htm**.** Accessed January 29, 2018

34. Ebell MH, Jang W, Shen Y, Geocadin RG; Get With the Guidelines–Resuscitation Investigators (2013) Development and validation of the Good Outcome Following Attempted Resuscitation (GO-FAR) score to predict neurologically intact survival after in-hospital cardiopulmonary resuscitation. JAMA Intern Med 173:1872-1878. doi: 10.1001/jamainternmed.2013.10037

35. Kon AA, Davidson JE, Morrison W, Danis M, White DB; American College of Critical Care Medicine; American Thoracic Society (2016) Shared Decision Making in ICUs: An American College of Critical Care Medicine and American Thoracic Society Policy Statement. Crit Care Med 44:188-201. doi: 10.1097/CCM.0000000000001396

36. Scheunemann LP, Arnold RM, White DB (2012) The facilitated values history: helping surrogates make authentic decisions for incapacitated patients with advanced illness. Am J Respir Crit Care Med 186: 480-486. doi: 10.1164/rccm.201204-0710CP

37. Griffith DM, Salisbury LG, Lee RJ, Lone N, Merriweather JL, Walsh TS, RECOVER Investigators (2018) Determinants of Health-Related Quality of Life After ICU: Importance of Patient Demographics, Previous Comorbidity,

and Severity of Illness. Crit Care Med doi: 10.1097/CCM.0000000000002952. [Epub ahead of print].

38. Venkat A, Becker J (2014) The effect of statutory limitations on the authority of substitute decision makers on the care of patients in the intensive care unit: case examples and review of state laws affecting withdrawing or withholding life-sustaining treatment. J Intensive Care Med 29:71-80. doi: 10.1177/0885066611433551
39. Schenker Y, Tiver GA, Hong SY, White DB (2012) Association between physicians' beliefs and the option of comfort care for critically ill patients. Intensive Care Med 38:1607-1615.
40. Anesi GL, Halpern SD (2016) Choice architecture in code status discussions with terminally ill patients and their families. Intensive Care Med. 42:1065-1067. doi: 10.1007/s00134-016-4294-7
41. Ernecoff NC, Curlin FA, Buddadhumaruk P, White DB (2015) Health Care Professionals' Responses to Religious or Spiritual Statements by Surrogate Decision Makers During Goals-of-Care Discussions. JAMA Intern Med Oct;175(10):1662-9. doi: 10.1001/jamainternmed.2015.4124
42. Stirrat GM, Gill R (2005) Autonomy in medical ethics after O'Neill. J Med Ethics 31:127-130.
43. Lipkus IM (2007) Numeric, verbal, and visual formats of conveying health risks: suggested best practices and future recommendations. Med Decis Making 27:696-713.
44. Periyakoil VS, Neri E, Fong A, Kraemer H (2014) "Do unto others: doctors' personal end-of-life resuscitation preferences and their attitudes toward advance directives." PLoS One 9:e98246. doi: 10.1371/journal.pone.0098246

45. Richard C, Lajeunesse Y, Lussier MT (2010) Therapeutic privilege: between the ethics of lying and the practice of truth. J Med Ethics 36:353-357. doi: 10.1136/jme.2009.033340

46. Gräsner JT, Lefering R, Koster RW, Masterson S, Böttiger BW Herlitz J, Wnent J, Tjelmeland IB, Ortiz FR, Maurer H, Baubin M, Mols P, Hadžibegovíc I, Ioannides M, Škulec R, Wissenberg M, Salo A, Hubert H, Nikolaou NI, Lóczi G, Svavarsdóttir H, Semeraro F, Wright PJ, Clarens C, Pijls R, Cebula G, Correia VG, Cimpoesu D, Raffay V, Trenkler S, Markota A, Strömsöe A, Burkart R, Perkins GD, Bossaert LL; EuReCa ONE Collaborators (2016) EuReCa ONE-27 Nations, ONE Europe, ONE Registry: A prospective one month analysis of out-of-hospital cardiac arrest outcomes in 27 countries in Europe. EuReCa ONE-27 Nations, ONE Europe, ONE Registry: A prospective one month analysis of out-of-hospital cardiac arrest outcomes in 27 countries in Europe. Resuscitation 105:188-195. doi: 10.1016/j.resuscitation.2016.06.004

47. Daya MR, Schmicker RH, Zive DM, Rea TD, Nichol G, Buick JE, Brooks S, Christenson J, MacPhee R, Craig A, Rittenberger JC, Davis DP, May S, Wigginton J, Wang H; Resuscitation Outcomes Consortium Investigators (2015) Out-of-hospital cardiac arrest survival improving over time: Results from the Resuscitation Outcomes Consortium (ROC). Resuscitation.91:108-15. doi: 10.1016/j.resuscitation.2015.02.003

48. Beck B, Bray J, Cameron P, Smith K, Walker T, Grantham H, Hein C, Thorrowgood M, Smith A, Inoue M, Smith T, Dicker B, Swain A, Bosley E, Pemberton K, McKay M, Johnston-Leek M, Perkins GD Nichol G, Finn J; Aus-ROC Steering Committee (2018) Regional variation in the characteristics,

incidence and outcomes of out-of-hospital cardiac arrest in Australia and New Zealand: Results from the Aus-ROC Epistry. Resuscitation 126:49-57. doi: 10.1016/j.resuscitation.2018.02.029

49. Pichler G, Fazekas F (2016) Cardiopulmonary arrest is the most frequent cause of the unresponsive wakefulness syndrome: A prospective population-based cohort study in Austria. Resuscitation 103:94-98. doi: 10.1016/j.resuscitation.2016.02.023.
50. Andrew E, Mercier E, Nehme Z, Bernard S, Smith K (2018) Long-term functional recovery and health-related quality of life of elderly out-of-hospital cardiac arrest survivors. Resuscitation 126:118-124. doi: 10.1016/j.resuscitation.2018.03.017
51. Girotra S, Nallamothu BK, Spertus JA, Li Y, Krumholz HM, Chan PS; American Heart Association Get with the Guidelines–Resuscitation Investigators (2012) Trends in survival after in-hospital cardiac arrest. N Engl J Med. 367:1912-20. doi: 10.1056/NEJMoa1109148
52. Merchant RM, Berg RA, Yang L, Becker LB, Groeneveld PW, Chan PS; American Heart Association's Get With the Guidelines-Resuscitation Investigators (2014) Hospital variation in survival after in-hospital cardiac arrest. J Am Heart Assoc 3:e000400. doi: 10.1161/JAHA.113.000400
53. Nolan JP, Sandroni C (2017) In this patient in refractory cardiac arrest should I continue CPR for longer than 30 min and, if so, how? Intensive Care Med 43:1501-1503. doi: 10.1007/s00134-017-4745-9.
54. Sandroni C, Cariou A, Cavallaro F, Cronberg T, Friberg H, Hoedemaekers C, Horn J, Nolan JP, Rossetti AO, Soar J (2014) Prognostication in comatose survivors of cardiac arrest: An advisory statement from the European

Resuscitation Council and the European Society of Intensive Care Medicine. Intensive Care Med 40:1816-1831. doi: 10.1007/s00134-014-3470-x

55. Sandroni C, Nolan JP (2015) Neuroprognostication after cardiac arrest in Europe: new timings and standards. Resuscitation 90:A4-A5. doi: 10.1016/j.resuscitation.2015.02.020
56. Smith K, Andrew E, Lijovic M, Nehme Z, Bernard S (2015) Quality of life and functional outcomes 12 months after out-of-hospital cardiac arrest. Circulation 131: 174-181. doi: 10.1161/CIRCULATIONAHA.114.011200.
57. Lilja G, Nielsen N, Bro-Jeppesen J, Dunford H, Friberg H, Hofgren C, Horn J, Insorsi A, Kjaergaard J, Nilsson F, Pelosi P, Winters T, Wise MP, Cronberg T (2018) Return to Work and Participation in Society After Out-of-Hospital Cardiac Arrest. Circ Cardiovasc Qual Outcomes 2018;11(1):e003566. doi: 10.1161/CIRCOUTCOMES.117.003566
58. Calvert M, Kyte D, Mercieca-Bebber R, Slade A, Chan AW, King MT; the SPIRIT-PRO Group, Hunn A, Bottomley A, Regnault A, Chan AW, Ells C, O'Connor D, Revicki D, Patrick D, Altman D, Basch E, Velikova G, Price G, Draper H, Blazeby J, Scott J, Coast J, Norquist J, Brown J, Haywood K, Johnson LL, Campbell L, Frank L, von Hildebrand M Brundage M, Palmer M, Kluetz P, Stephens R, Golub RM, Mitchell S, Groves T (2018) Guidelines for Inclusion of Patient-Reported Outcomes in Clinical Trial Protocols: The SPIRIT-PRO Extension. JAMA 319:483-494. doi: 10.1001/jama.2017.21903.
59. Kompanje EJO, Piers RD, Benoit DD (2013) Causes and consequences of disproportionate care in intensive care medicine. Curr Opin Crit Care 19:630-635. doi: 10.1097/MCC.0000000000000026

60. Epker JL, Bakker J. Kompanje EJO (2011) The use of opioids and sedatives and time of death after withdrawing mechanical ventilation and vasoactive drugs in a Dutch intensive care unit. Anesth Analg 112:628-634. doi: 10.1213/ANE.0b013e31820ad4d9

61. Bakker J, Jansen TC, Lima A, Kompanje EJ (2008) Why opioids and sedatives may prolong life rather than hasten death after ventilator withdrawal in critically ill patients. Am J Hosp Palliat Care 25:152-154. doi: 10.1177/1049909108315511

62. Berdowski J, Berg RA, Tijssen JG, Koster RW (2010) Global incidences of out-of-hospital cardiac arrest and survival rates: Systematic review of 67 prospective studies. Resuscitation. 81:1479-1487. doi: 10.1016/j.resuscitation.2010.08.006.

63. Nichol G, Thomas E, Callaway CW, Hedges J, Powell JL, Aufderheide TP, Rea T, Lowe R, Brown T, Dreyer J, Davis D, Idris A, Stiell I; Resuscitation Outcomes Consortium Investigators (2008) Regional variation in out-of-hospital cardiac arrest incidence and outcome. JAMA 300:1423-1431. doi: 10.1001/jama.300.12.1423

64. Sasson C, Magid DJ, Chan P, Root ED, McNally BF, Kellermann AL, Haukoos JS; CARES Surveillance Group (2012) Association of neighborhood characteristics with bystander-initiated CPR. N Engl J Med 367:1607–1615.

65. Lamhaut L, Hutin A, Puymirat E, Jouan J, Raphalen JH, Jouffroy R, Jaffry M, Dagron C, An K, Dumas F, Marijon E, Bougouin W, Tourtier JP, Baud F, Jouven X, Danchin N, Spaulding C, Carli P (2017) A Pre-Hospital Extracorporeal Cardio Pulmonary Resuscitation (ECPR) strategy for treatment

of refractory out hospital cardiac arrest: An observational study and propensity analysis. Resuscitation 117:109-117. doi: 10.1016/j.resuscitation.2017.04.014

66. Vogel L (2011) Can rationing possibly be rational? CMAJ: 183:1242-1243. doi: 10.1503/cmaj.109-3932
67. Arora C, Savulescu J, Maslen H, Selgelid M, Wilkinson D (2016) The Intensive Care Lifeboat: a survey of lay attitudes to rationing dilemmas in neonatal intensive care. BMC Med Ethics 17:69.
68. Callaway CW (2014). Studying community consultation in exception from informed consent trials. Crit Care Med 42:451-453. doi: 10.1097/CCM.0b013e3182a51f37
69. Nelson MJ, Deiorio NM, Schmidt TA, Zive DM, Griffiths D, Newgard CD (2013) Why persons choose to opt out of an exception from informed consent cardiac arrest trial. Resuscitation 84:825-30. doi: 10.1016/j.resuscitation.2013.01.030
70. Jansen TC, Bakker J, Kompanje EJ (2010) Inability to obtain deferred consent due to early death in emergency research: effect on validity of clinical trial results. Intensive Care Med 36:1962-1965. doi: 10.1007/s00134-010-1988-0. PMID: 20689926/
71. Moorthy VS, Karam G, Vannice KS, Kieny MP (2015) Rationale for WHO's new position calling for prompt reporting and public disclosure of interventional clinical trial results. PLoS Med 12:e1001819. doi: 10.1371/journal.pmed.1001819.
72. Ornato JP, Becker LB, Weisfeldt ML, Wright BA (2010) Cardiac arrest and resuscitation: an opportunity to align research prioritization and public health

need. Circulation. 122:1876-1879. doi: 10.1161/CIRCULATIONAHA.110.963991.

73. Melltorp G, Nilstun T (1997) The difference between withholding and withdrawing life-sustaining treatment. Intensive Care Med 23:1264-1267.
74. Kiley R, Peatfield T, Hansen J, Reddington F (2017) Data Sharing from Clinical Trials - A Research Funder's Perspective. N Engl J Med 377:1990-1992. doi: 10.1056/NEJMsb1708278.
75. Tierney WM, Meslin EM, Kroenke K (2016) Industry Support of Medical Research: Important Opportunity or Treacherous Pitfall? J Gen Intern Med 31:228-233. doi: 10.1007/s11606-015-3495-z.