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Ethical Considerations in Consenting Critically Ill Patients for Bedside Clinical Care and Research

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Abstract

Care of critically ill patients, as in any other field, demands the exercise of ethical principles related to respect of patient's autonomy, beneficence, nonmaleficence, and distributive justice. Professional duty and the common law require doctors to obtain consent before giving treatment or for requesting participation in clinical research. A procedure or research study must be adequately explained, and the patient must have the capacity to consent. If a patient does not have decision-making capacity, treatment must be given using alternative forms of consent or using principles of implied consent in emergency or life-threatening situations. In the case of clinical research, informed consent must always be sought. Exemptions to this rule are morally justified in circumstances related to research in life-threatening conditions or life-saving interventions in which the investigator departs from sound principles of equipoise. This usually implies the imposition of safeguards such as consultation with the community in which the study were to take place, oversight in patient screening and recruitment process by institutional review boards, special study designs, retrospective and prospective consent processes, and independent safety monitoring.

Keywords

decisional capacity, informed consent, surrogate

Introduction

Care of critically ill patients demands the exercise of ethical principles related to respect of patient's autonomy, beneficence, nonmaleficence, and distributive justice. Treatments in the intensive care unit (ICU) require an appropriate consent process; but in certain circumstances, like in the setting of life-threatening conditions, the process of obtaining informed consent for clinical care may be waived. Similarly, the issue of competency to decide participation in research in critically ill populations is based on the same ethical principles used in clinical practice, which stem from well-known codes of research ethics.[1-4] Several circumstances may enable investigators to waive the consent process for research in vulnerable populations,[5,6] as it may still be possible to conduct research in these patients and in those who lack decision-making capacity in a way that is morally justifiable.[7] This usually implies the imposition of conditions such as consultation with the community in which the study were to take place, oversight in patient screening and recruitment process by institutional review boards (IRBs), special study designs, retrospective and prospective consent processes, and independent safety monitoring.[6-8]

Although the boundaries of clinical practice and research in the ICU may sometimes be hazy, the definitions of these two practices are well established. In 1979, the Belmont Report delineated the differences between clinical practice and research, which may coexist in the ICU.[1] Clinical practice is specifically aimed at improving the physiology and the well-being of the individual, with the expectation of success and healing; research is defined as a scientific approach to test a hypothesis to generate general scientific conclusions, under the assumption of equipoise, and which may not immediately benefit the participating individual but the society as a whole.[2]

Research in critically ill populations presents unique ethical hurdles. Critically ill patients have complex physiological problems, have higher morbidity and mortality, and may also lack decisional capacity based on the inability to appropriately evaluate concepts of risk and benefit, which place them in a vulnerable position for unethical clinical and research

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practices. Although the consent process was conceived as a safeguard to appropriately deliver ethically acceptable clinical care and allows for participation in research, and despite the issuing of the Nuremberg Code in 1947[3,4] in response to illegal and unethical experiments in human subjects, the consent process was inconsistently achieved in the United States in the years after World War II.[9] More recently, several authors[10,11] have questioned the appropriateness of the consent process and the validation of this process by IRBs, which tend to concentrate more on the formalities or documentation of the consent process rather than on the process itself.[12]

The process of informed consent is a dynamic process that requires the application of basic principles of autonomy and self-determination, competence, and voluntariness.[13] In this sense, critically ill patients require special considerations for treatment and research including the use of additional safeguards that would allow them to receive treatments when needed and to allow them to participate in research whenever possible. In this article, we will review the ethical principles that should be considered in clinical practice and research in critically ill populations. We will review the issues related to consent and disclosure and the approach to competence or decisional capacity and voluntariness. We will also apply casuistry or case-based reasoning to further delineate the important interaction between ethics and jurisprudence and we will review recommendations and alternatives to enhance the process of obtaining consent for both clinical practice and research in the ICU.

Doctrine of Informed Consent

Informed consent is defined as ''an autonomous authorization of individuals of a medical intervention or of involvement in research.''[14] The concept of informed consent stems from a principle of personal autonomy, which allows for moral self-determination and is based on five important elements: (1) decision-making capacity, (2) disclosure, (3) understanding, (4) voluntary choice, and (5) formal authorization to be treated or included in research.[14] The principle of autonomy implies that rational individuals with decisional capacity, or competency in legal terms, are uniquely qualified to decide what is best for themselves. It also means that people should be allowed to do whatever they want, even if doing so involves considerable risk or would be deemed foolish by others, provided that their decision does not infringe in the autonomy of another. Ethically, the principle of informed consent is also supported by concepts of beneficence related to professional duty to promote well-being, nonmaleficence related to the duty of not inflicting harm and justice by providing fair and equitable access to health care and research.

English and American common laws also support the principle of informed consent. To this end, jurisprudence has also held that physicians and health care providers in general have a duty to the patient to treat and to avoid harm, and failure to fulfill these duties may be considered as a breach of law, known as tort, which may result in punishment under civil or penal law. Legal obligation of physicians to obtain their patient's consent before any indicated procedure has been upheld by several landmark court rulings (*Schloednorff v. Society of New York Hospitals*, *Salgo v. Leland Stanford Jr. University Board of Trustees*, *Cobbs v. Grant*, *Bouvia v. Superior Court*, among others).[15-18]

In *Schloendorff v. Society of New York Hospitals*, the New York Court of Appeals ruled that ''every being of adult years and sound mind has the right to determine what shall be done with his own body; and a surgeon that performs an operation without the patient's consent commits an assault, for which he is liable for damages, except in cases of emergency where the patient is unconscious and where it is necessary to operate before consent can be obtained.''[15] In *Salgo v. Leland Stanford Jr. University Board of Trustees*, the California Court of Appeal extended the provisions of *Schloendorff v. Society of New York Hospitals* to include other interventions ruling that ''is the duty of the physician to disclose to the patient all the facts which mutually affect his rights and interests.''[16] The courts have generally upheld that physicians who do not meet their duty might be subject to liability not only under the principles of battery (contact without permission) but also under the principles of negligence (injury without permission, in violation of professional standards of care). In 1972, *Cobbs v. Grant* established the legal standard of informed consent. In this landmark case, the Supreme Court of California clarified that the principle of battery ''should be reserved for those circumstances where a doctor performs an operation to which the patient has not consented'' and that other actions may constitute negligence if physicians apply interventions without ''reasonable disclosure of the available choices with respect to the proposed therapy and the dangers inherently and potentially involved in each.''[17] The last case, *Bouvia v. Superior Court*, established the principle of refusal of any medical therapy including those that may be potentially life-saving.[18]

Decision Making and Competency

These are terms that may be used interchangeably. Technically, medical professionals can determine decision-making capacity but lack the legal authority to determine competence; however, their assessment of decision-making capacity serves not only as a guide for many legal determinations but also as the functional equivalent of such determinations in the absence of legal proceedings.[14] Competency is defined as the ability to perform certain tasks and the ability to make a decision. No clear definition exists, but it is understood that a competent individual must be able to perform well in the following capacities: (1) understand the information, (2) understand the current situation and its consequences, (3) rationally consider information in light of one individual's values, and (4) make an informed decision.[13] It is the physician's finding of incapacity that causes alternative forms of consent to be sought and a patient's legal rights to be temporarily suspended without the involvement of the court (see below ''Alternative Methods of Obtaining Consent''). The assessment of the individual's

decision-making capacity in the setting of clinical research has been studied before.[19-21] The results of these studies showed that patient's understanding of the information provided or their clinical situation may have been suboptimal.[19-21] Similarly, the studies showed that some patient s did not recognize or understood that they were giving consent for a research project or that they could even withdraw from it if they wished.[20,21]

Disclosure

In the United States, the legal doctrine of informed consent incorporates a third element, the disclosure of information, which cannot be properly exercised without voluntary choice and competence. In clinical practice and research, excessive emphasis on the disclosure requirement may undermine the implementation of informed consent.[14] A frequently expressed issue in the consenting process is that too much disclosure may produce anxiety in the patient and undue influence to agree for a particular therapy or to participate in research.[13] This may be particularly true in critically ill patients whose decisions made under duress may be clouded with misinformation. Nevertheless, the Declaration of Helsinki,[2] the most widely recognized code of ethics related to human research, explains that participants must receive information concerning the objectives, methods, benefits, and potential harms of the proposed study. The main issues with the enforcement of disclosure in research is that though IRBs monitor the inclusion of relevant information pertaining the study, there is no oversight of what investigators tell prospective research participants.[22] Finally, other type of variables, such as financial relationships between industry, practitioners, and clinical investigators, and incentives to enroll participants to maintain them in the study,[23] may present an opportunity for a conflict of interest, so local IRBs may need to scrutinize and oversee these interactions to guarantee ethical practices and to evaluate if such information is pertinent to the patient's decision to participate in the study.

Understanding

This refers to the ability to comprehend propositions related to the intervention or treatment being sought, or participation in research in the setting of one's condition (objectives, risks, benefits, alternatives, and potential outcomes[24]). Appropriate understanding depends on several factors including level of intelligence, language skills, attention, orientation, recall, and memory. When health care professionals approach their patients to obtain consent for procedures or participation in research, it is important to determine the level of education to appropriately convey the necessary information. Similarly, disclosure of information related to the proposed intervention in the form of statistics may be helpful. Patients with appropriate understanding can discuss the differences between proposed interventions.

Voluntariness

The universal right of respect for a patient's autonomy is rooted in the rulings from the proceedings of the Nuremberg trials of 1947 (Nuremberg Code).[3,4] These are the basis of modern statements of human rights[1,2] and serve as guidance to the basic requirements of voluntary informed consent and the individual's right to refuse treatment or participate in research. The informed consent process should be guided by the freedom to act voluntarily, without coercive forces or due influence. There are several issues during the delivery of care or when consent for research may impede voluntariness in critically ill patients. First, the natural setting of critical illness that leads to inability to evaluate the concepts of risk–benefit ratios, confused states and delirium, among others, which may impede the appropriate consent process for care and research. Second, the frightening setting of the ICU may impose coercive forces in these participants based on the need for emergency treatments or terminal illnesses when patients may feel they have little choice but to get treated or to participate in the proposed research. Third, the enthusiasm of the practitioner or investigator could lead to undue influences by manipulation of the information or incomplete disclosure.[19]

Assessing Decision-Making Capacity in the Critically Ill

How can we assess for decision-making capacity in critically ill patients and particularly during emergency situations? To determine whether a patient lacks capacity or not, a physician must establish that the participant is able to (1) understand the information relevant to the decision, (2) retain that information, (3) use or weigh that information as part of the process to make the decision, (4) include information about the reasonably and foreseeable consequences of deciding one way or another or failure to make the decision, and (5) communicate their decision (whether by talking, using sign language, or any other means).[14,25]

However, the determination of all of these points may be difficult in critically ill patients as even in the absence of cognitive impairment. Evidence shows that acute illness can impair the understanding of disease and especially the concepts of proportionality and risk-to-benefit ratios.[22] Additional obstacles inherent to obtain consent in critically ill patients are the emergent nature of the disease, the presence of fluctuating or fixed neurologic deficits such as confusion, aphasia, and anterograde memory loss, among others.[25,26]

Based on these, it has been suggested that the development and standardization of a procedure for capacity assessment specifically for use in patients with critical illness should be implemented akin to tools used in patients with dementia[27-29] and that the disclosure should include concise points such as an explanation of the diagnosis, proposed treatment by focusing on the risks and potential benefits of treatment and its alternatives, and outcome statistics.[26]

Alternative Methods to Obtain Consent for Clinical Care

When a critically ill patient is deemed not to have capacity, the physician must seek an alternate pathway to define a course of

action. The options in these cases are to determine whether the patient has drafted an advance directive such as a living will or a durable power of attorney (DPA; for health care); or in the absence of an advance directive, the physician must seek the substituted judgment of a proxy or surrogate authorized by the state law. In life-threatening situations, the physician must choose whether to forgo emergency therapy or to invoke the emergency situation as justification for treatment without consent using a ''best interest'' standard.

Advance Directive or Living Will

Probably, it is the best tool to direct care in the event of incapacity but usually not very helpful in situations related to terminal conditions, futile care, and multiorgan dysfunction. Shortcomings of these documents are (1) that the physician may not find instructions that clearly guide certain treatment decisions and (2) the ethical argument that once cannot predict a person's own reaction when faced with disability.[30] Studies have demonstrated a tendency among the nondisabled to view disability as equivalent to death,[31,32] and historically, investigators frequently dump death with the severe disability group.[33] In this sense, advance directives or living wills, even if legally valid, are suboptimal to find treatment directions in critical illness, particularly when goals of self-determination and perceptions that guide one's chosen moral course may change.[30]

Substituted Judgment Standard

Obtaining informed consent by an authorized surrogate decision maker is an alternative to direct informed consent. Appointees by advance directive, or living will, or DPA (for health care decisions), or a family member identified by state law are expected to make the same decisions as the patient would if the patient's capacity were intact. This idea of substituted judgment is widely accepted as a valid means of respecting patient preferences.[34] The basis of this standard is framed by landmark court rulings such as the one *in the matter of Quinlan,* 70 NJ 10, 1976. In this case, the Supreme Court of New Jersey established the concept of *substituted judgment standard.* The court determined that a guardian ad litem (appointed by court order) was not necessary to represent a patient independently in a particular case and allows family members to make decisions on their behalf. The ruling is rooted on an individual's legal right to privacy and the notion that a family member could make the assertion based on the family's best judgment (*substituted judgment standard*). The decision included legal immunity for the physicians and the suggestion to involve ethics committees in such cases.[35] Shortcomings of the substituted judgment standard are related to the poor accuracy of the proxy's ability to predict the patient's will, which some studies have found to be no better than random chance,[34,36] the inherent difficulty of making therapeutic decisions for other persons which may make proxies reluctant to participate in a consent process and make them more likely to defer to the physician's expertise without even considering the full disclosure of risks and benefits associated with the intervention.[32,37]

Best Interest Standard

A legal exception to the consent process may be invoked in certain clinical settings and particularly in emergency situations, in which case the consent of a reasonable person to appropriate treatment is implied,[14] so the *best interest standard* may be applied in these circumstances. The best interest standard is a widely used ethical, legal, and social basis for policy and decision-making involving incompetent persons to determine a wide range of issues relating to their well-being.[38] The basis of this standard is framed by landmark court decisions such as the one in the matter of Conroy (In re Conroy, 486 A.2d 1209 NJ 1985). In this case, the Supreme Court of New Jersey permitted the use of the *best interest standard* to allow the guidance of therapy for an incapacitated patient whose guardian did not know the explicit wishes for a particular situation. This principle is also applicable in those cases when the burden of a therapy outweighs the benefits and the pain of interventions that would make them inhumane.[35] One of the shortcomings of using the *best interest standard* is the possibility of the physician being judged as paternalistic[39] based on the inherent role of physicians to prevent evil or harm by promoting good and welfare for others (beneficence).[14]

Ethical dilemmas cannot be addressed successfully unless the probability of outcomes is entertained. In this case, the physician should make every effort to acquire the highest level of certainty regarding the diagnosis and prognosis with the patient's wishes in mind. The effort will require knowledge of the literature and a multidisciplinary team approach to attain a balanced view of the impact of therapeutic decisions and the expected disability to the patient. In addressing issues related to advance directives and withholding and withdrawing life supportive therapy, clinical prognostic questions that require specific answers include the following:

1. What is the probability of death during the next month and next year (and what are the confidence intervals around that probability)?
2. What are the likely causes of death during the first and subsequent months?
3. If the patient survives, what level of disability and handicap will she/he suffer?
4. What impact will the intervention have on survival and/or disability?[40]

Advanced directives, the substituted judgment standard, best interest standard, and a clear and convincing evidence principle (see below) may be applied in these circumstances.

The Principle of "Clear and Convincing Evidence"

In some states, the principle of "*clear and convincing evidence*" may be used in lieu of the *substituted judgment*

standard. This is one of the legal principles used in the US legal system (the other two being beyond the reasonable doubt and preponderance of evidence). This principle can be used by physicians in certain states (Missouri, New York, and Florida) to withdraw life support or any other intervention when there is *"clear and convincing evidence"* of previous patient's statements and in the absence of a "declaration" such as a living will, advance directive, or DPA. The decision is based on *Cruzan v. Director, Missouri Department of Health*, 497 US 261 case when the court endorsed the right of a competent person to refuse medical therapy even if this results in the patient's death and is based on the liberty interest set forth by the Fourth Amendment. The case of Terry Schiavo (*Schindler v. Schiavo*, 866 So2d 140 Fla Dist Ct App, 2004) was ruled following the same principle and endorsed Cruzan's historic court decision.[35]

In 2010, the New York State Legislature enacted the Family Health Care Decisions Act (FHCDA). The enacted law covers treatment decisions, including decisions to forgo life-sustaining therapies, in those adult patients who lack decision-making capacity and have not signed an advance directive. For adults who lack decision-making capacity and have no one available to vouch for them, the FHCDA authorizes physicians to approve medical treatments, creating a much-needed alternative to a court-appointed guardian for decisions to provide treatment for this patient population. The FHCDA overcomes long-standing case law in New York State that severely limited the authority of family members and others close to the patient to withdraw or withhold life-sustaining measures in the absence of a health care-proxy or living wills.[41]

Applying Ethical Principles for Clinical Research in the ICU

Most of the landmark legal cases reviewed before and related court rulings dealt with establishing or providing the framework for the patient's rights to be upheld and for surrogates to provide or refuse consent primarily in the setting of clinical situations. The development of clinical research in all medical fields, including critical care, provided an opportunity to apply the same ethical principles considered for clinical situations; however, most of the jurisdictions did not enact laws to describe how the informed consent process should be obtained for research purposes. Most important, jurisdictions did not have special statues that allow surrogates to consent for research in patients who lack decision-making capacity.

To this end, the Nuremberg Code[3,4] of 1947 provides the ethical framework of how to conduct human research. This document describes the necessary conditions for clinical research after the provisions of its solid statement that "the voluntary consent of the human subject is absolutely essential." In 1964, the World Medical Association described in greater detail the ethical principles for medical research that involved humans in their landmark proclamation "The Declaration of Helsinki."[2,4] The American Medical Association code of ethics was also revised to include the concepts of informed consent for both clinical and research procedures.[42]

Some erudites of medical ethics defend the view that no research is permissible in the absence of the patient's voluntary informed consent by stressing that scientific progress is morally optional, while respect for humans and principle of autonomy is not. Others support experimentation in humans in the absence of consent process as long as certain conditions designed to protect patients are entertained.[7] Despite this controversy, research in minors and other vulnerable populations has continued to grow even after the promulgation of the Nuremberg Code.[7] These practices have been justified by the use of alternate ways of what many believe would be the moral equivalent of the patient's consent including parental consent and assent,[43] the notion that significant benefits of the research endeavor would be foregone if the consent requirement were strictly interpreted, and the use of conditions to the research such as the use of IRBs, special study designs, retrospective and prospective consent processes, and independent monitoring.[6-8]

In the United States, federal agencies that regulate research in humans are part of the Department of Health and Human Services through its division: the United States Public Health Service. The federal branches in charge of regulation of human research in the United States are the Food and Drug Administration (FDA), the National Institutes of Health (NIH), and the Office of Human Research Protections (OHRP). The FDA oversees the research of experimental drugs, devices, interventions, and biologics. The OHRP develops regulations for the protection of humants and oversees compliance with them. Clinical research conducted at all institutions that are federally funded is governed by the Department of Health and Human Services Code of Federal Regulations (CFR) for the Protection of Human Subjects.[44] The CRF is a set of regulations that have evolved over time and it required that IRBs be established to be a safeguard for the ethical conduct and protection of humans who participate in clinical research. In 1974, the United States Congress passed the National Research Act, which gave birth to the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. In 1979, the National Commission issued its landmark "Belmont Report."[1] Shortly after in 1981, the National Commission was dissolved and the responsibility to implement its recommendations was assigned to the Director of the Office of Protection from Research Risks that rewrote the CFR.[44] The CFR was revised in 1991 and adopted by 16 federal agencies including the NIH and became known as the "Common Rule."[44,45]

Consent for Research by the Patient's Legally Authorized Representative

According to the 1981 version of the CFR for the protection of Human Subjects, "no investigator may involve a human being as a subject in research covered by this policy unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative."[46] An authorized legal representative is defined as an individual or judicial body authorized under applicable law

to consent on behalf of a prospective subject to the subject's participation in the procedures(s) involved in the said research.

Many patients appoint family members, friends, and others to make pertinent decisions on their behalf during periods of incapacity (DPA for health care). Many advocate to extend this legal right to enable the DPA to make research participation decisions. A critical difference between delegating decisions to DPAs in the clinical setting and the research setting is that recognizing the authority to decide about someone else's care seems more justifiable when there is potential that the intervention will be in the patient's best interest.[7] In contrast, experimental procedures are not undertaken with the primary goal of the patient's best interest but rather are intended to improve general knowledge and advance science, so as explained by Jonathan Moreno, "allowing other persons to decide about making someone an experimental subject, even when the individual in question has authorized them to do so, is a qualitative departure from ordinary DPA arrangements. Such decisions may entail considerable risks with little likelihood of substantial benefit."[7]

The 1981 CFR also allows to waive consent procedures in certain circumstances: "An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that:

1. The research involves no more than minimal risk to the subjects.
2. The waiver or alteration will not adversely affect the rights and welfare of the subjects
3. The research could not practicably be carried out without the waiver or alteration.
4. Whenever appropriate, the subjects will be provided with additional pertinent information after participation."[46]

Although the political system of the United States enables agents to autonomously appoint DPAs for health care-related decisions, there seems to be a societal interest when such private agreements represent a potential harm to the patient itself, in the absence of potential benefits, particularly related to participation in high-risk research.[7] On the other hand, the possibility of potential greater benefit for the society as a whole may argue in favor of such agreements to go forward despite their potential risks, particularly in circumstances when the rejection of those individuals who have made themselves available to participate in research through DPA would significantly hinder studies of the condition that led to the patient's incapacity.[7] A balanced approach may be achieved by limiting the circumstances in which the DPA's authority would be valid. Studies that present no prospect of direct benefit to the patient, but entail a significant risk, could be ineligible for participation through DPA. However, studies that entail minimal risk could be regarded as consistent with the patient's best interest and therefore eligible, even if they do not advance those interests.[7] Minimal risk is defined in the 1981 CRF as "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."[46]

Consent for Research by the Patient's Legally Authorized Surrogate

Usually, individuals who lose decision-making capacity have not made an advanced directive or identified a designee in a DPA. The law allows for family members, friends, or surrogates to provide consent for treatment in the clinical setting but if they can grant permission for participation in research carries an uncertain legal basis.[7] Jurisdictions could potentially recognize "natural" surrogates (family members of close friends) as enablers to participate in clinical research; however, an objection to such legal arrangements is that, unlike a legally appointed representative by advanced directive or DPA, the surrogate's standing as a substitute decision maker may arise only from the law.[7] The moral basis for the surrogate's authority to decide participation in research may appear inadequate for the following reasons: the patient has not selected the surrogate a priori, surrogates are supposed to act on behalf of the patient's best interest or in accordance to the patient's "substituted judgment," and there is no guarantee that even the closest relative is aware of the patient's values toward research or that the surrogate would act on the basis those preferences even if they are known.[7] To this end, the medical best-interest standard could not apply to studies that offer no prospect of direct benefit to the patient.[7] Knowing the dubious legality of these arrangements, several studies and a large number of subjects have been enrolled on the basis of surrogate decisions, so restrictions in this pathway could minimize advances in research achieved by prior clinical trials and their investigators.

An alternative would be to recognize in regulation the role of surrogates in research and allow for participation in those studies in which procedures may be potentially beneficial or offer minimal risk,[7] but even with this approach, surrogates may not provide adequate assessment of the patient's values in regard to research.[36,47,48] Strikingly, even competent patients and surrogates are unable to fully understand the main objectives of clinical trials, and most of these patients and families consent to research on the basis of patient–physician relationships, trust, and hope for some benefits even when researchers have indicated the unlikely event of beneficial outcomes.[49,50] So if the discussions during the process of informed consent among critically ill patients, surrogates, and others are clouded with misunderstanding or misinformation, it is possible that the informed consent process for participation in research in these patients may not be entirely valid.

Deferred and Waiver of Consent for Research in Emergency Situations

The 1981 CRF provides some flexibility to enroll subjects without decision-making capacity and without DPAs or surrogates, but the definition of "minimal risk" may exclude some

individuals from emergency research, such as cardiopulmonary resuscitation and stroke interventions, among others, which may be potentially harmful and not routine in "daily life." Based on this hurdle, some investigators used a procedure called deferred consent under which patients could be enrolled into clinical research without their informed consent and then informed to them or to their surrogates about the procedures later or when the patient regained decision-making capacity.[51] This procedure was heavily criticized on the basis that there was no legal definition of consent for procedures that have occurred previously.[8] As the practice of deferred consent declined in the 1990s, the members of the Coalition Conference of Acute Resuscitation and Critical Care Researchers argued that potential risks of not allowing the practice of deferred consent in vulnerable patients would be to equivalent to being denied the potential beneficial therapy in the absence of known effective treatment for their life-threatening condition.[5] The members of the Coalition also proposed that the term "minimal risk" would be changed by one of an "appropriate incremental risk," which is defined as "any potential risk associated with participating in the research protocol relative to the natural consequences of the medical condition, or any potential risk associated with receiving the experimental intervention relative to receiving the standard treatment for the medical condition."[5] On the basis of these arguments, the 1981 CRF was modified in 1996 to allow research to be conducted in emergency settings without patient, DPA, or surrogate consent as long as certain provisions are met:

1. The humans are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.
2. Obtaining informed consent is not feasible.
3. Participation in the research holds out the prospect of direct benefit to the subjects.
4. The clinical investigation could not practicably be carried out without the waiver.
5. The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempt to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact the legally-authorized representatives and make this information available to the IRB at the time of continuing review.
6. The IRB has reviewed and approved informed consent procedures and an informed consent document.
7. Additional protections of the rights and welfare of the patients will be provided, including, at least consultation with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn; public disclosure to the communities in which the clinical investigation will be conducted.[52]

Some international guidelines also recognize that research in emergency situations may be performed after a waiver of the individual's consent.[53,54] Nevertheless, few clinical research studies have been conducted under this waiver with some criticisms from the scientific community.[55] The Public Access Defibrillation (PAD) Trial for example, a clinical study designed to compare 2 modalities of care for out-of-hospital cardiac arrest, was conducted under the new regulations[56] and is an example of the cumbersome yet morally acceptable process to perform research in critically ill populations. Although the authors of the PAD Trial concluded that the process to obtain approval for their research protocol "required significant and persistent effort" was "feasible," the mean time from submission to protocol approval was 138 days with 51 requests and revisions; the community required 1030 meetings, which were attended by 8169 individuals; and there were 475 press releases and 231 radio, television, or print commentaries.[57]

Should We Require Consent for Research in Critically Ill Patients?

Although the process of informed consent may be difficult in critically ill populations, it may not be impossible. Truog et al note that many clinical interventions in the ICU can be performed without informed consent, particularly those interventions that carry a "tacit" consent" or an implied consent in cases of emergencies but clinical research may definitely not.[58] When clinical procedures carry higher than minimal risk or are defined as high-risk procedures, the clinician must obtain informed consent from the patient or surrogate.[58] This is particularly important when procedures or treatments do not have an established safety track record or have not been designed for the indication for which they are being proposed (off-label use). Similarly, quality improvement studies may be performed without informed consent, but these may carry similar risks than those of clinical research, however, only clinical research may require informed consent.[44] To this end, Truog et al[58] argue that a double standard may be applied when one considers informed consent for clinical research only but not for quality improvement studies or certain procedures indicated on clinical grounds. Thus, the requirements for informed consent may be ethically waived if the following criteria are met: (1) all the interventions offered in the research study should be available outside of the trial without the specific consent of the patient or surrogate, (2) the treatments should not involve more than the minimal established risk, (3) the investigators should have clinical equipoise,[59] (4) no reasonable patient or surrogate should favor one treatment over the other one, and (5) the sponsor institution should verify that the prior 4 requisites and that the patient or surrogates be informed in this regard. Another view in support of waiving informed consent in clinical research is that in this

instance, consent may be considered tacit or implied as well,[44] as certain interventions may potentially be life-saving so patients or surrogates may not be allowed to refuse them because doing so would not be in their best interest.[60] This approach may be in conflict with the principles of autonomy and self-determination; however, if safeguards are implemented, it may still be a practical alternative to allow critically ill populations to be included in research that may have potential implications for future studies and improving patients outcomes.

Should we Exclude Critically Ill Patients Who Lack Decision-Making Capacity from Clinical Research?

In general, clinical research in populations that cannot consent has been done, especially under the safeguards of advanced directives, DPAs, surrogates, or some other monitoring entity. The exclusion of vulnerable populations including critically ill patients who are at risk of decisional incapacity or who lack decisional capacity will avoid philosophical and ethical problems inherent to clinical research by resonating with the statements of the Nuremberg Code but not go well with modern research practices or principles of justice and equality even in the decades after the code was promulgated.[7] More recent codes of ethics such as the Declaration of Helsinki[2] and guidelines in the United States [52] and other parts of the world have endorsed clinical research with those unable to consent under certain conditions and safeguards.[7] Recent scholarship indicates that the Nuremberg Code was implemented given the events of the time to condemn unethical practices in human research but was intended to refer to clinical research in normal populations and not in those who were ill.[7] As previously explained, the recently authorized exemption to informed consent in clinical research for emergency research[52] is a greater departure from the Nuremberg Code's requirements. A moral justification for this narrow exemption is the need for improvements in life-saving interventions and life-threatening conditions. To this end, a similar approach could be entertained on behalf of those who lack or are at risk of losing their decision-making capacity.[7]

The informed consent process is one of the steps, which makes research ethically acceptable.[61] Additional requirements of ethically acceptable clinical research include (1) value, related to improvements in health or knowledge; (2) scientific validity, meaning that research must be methodologically rigorous; (3) fair subject selection, the objectives of the research are based on balanced distribution of risks and benefits and appropriate selection of those needed for the research question; (4) favorable risk-to-benefit ratio, minimizing risks, and maximizing benefits; and (5) respect for the subjects. In addition, clinical equipoise is perhaps the most important requirement for ethical clinical research.[59]

Conclusion

The principle of autonomy, professional duty, and the common law require doctors to obtain consent before giving treatment or for requesting participation in clinical research. A procedure or study must be adequately explained, and the patient must have the capacity to consent. If a patient does not have decision-making capacity, treatment must be given using alternative forms of consent or using principles of implied consent in emergency or life-threatening situations. In the case of clinical research, informed consent must always be sought. Exemptions to this rule are morally justified in circumstances related to research in life-threatening conditions or life-saving interventions in which the investigator departs from sound principles of equipoise, as long as appropriate safeguards are implemented.

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