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REVIEW

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Ethics and research in critical care

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Abstract *Background:* The past few years have witnessed several controversies regarding the ethics of conducting research involving critically ill patients, and such research is ethically challenging. *Discussion:* Research ethics is a changing field, one that is influenced by empirical data, contemporary events, and new ideas regarding aspects of clinical trial design and protection of human subjects. We describe recent thoughts regarding several aspects of research ethics in the critical care context. *Conclusion:* The ability of the research community to conduct research ethically and to maintain public trust would benefit from heightened awareness to the principles and requirements that govern such research.

Keywords Research ethics · Proxy consent · Intensive care · Vulnerable populations · Informed consent · Emergency research

Introduction

Research involving critically ill patients presents special ethical challenges, largely due to such patients having deadly diseases, being vulnerable, and having cognitive impairments that preclude obtaining their valid, informed consent. Several publications have outlined the basic ethical principles of autonomy, beneficence, nonmaleficence, and justice [1] that govern the conduct of clinical research. These principles have also been further specified into ethical requirements that provide a systematic and coherent framework for determining whether research is ethical [2] (Fig. 1). We address several of these requirements that we believe need further clarification, especially when applied in the critical care context. Also, the recent introduction of the European Directive [3] warrants further examination and its applicability to critical care research.

Social value

To be ethical, clinical trials must be designed to answer valuable scientific questions. Indeed, the immense morbidity and mortality as well as the financial costs associated with critical illnesses warrant high quality clinical research. Such research is especially important in view of the tendency to introduce procedures into critical care practice without rigorous evaluation, thus exposing patients to the risks of untested interventions. However, the extent of the social value of the research must justify exposing human subjects to the potential harms of research as well as the use of finite resources to conduct the research.

Recent methodological issues (equipoise and control group selection)

Issues involved with the proper design of critical care research seem at first glance to exist exclusively within the sphere of science. However, studies that lack the method-

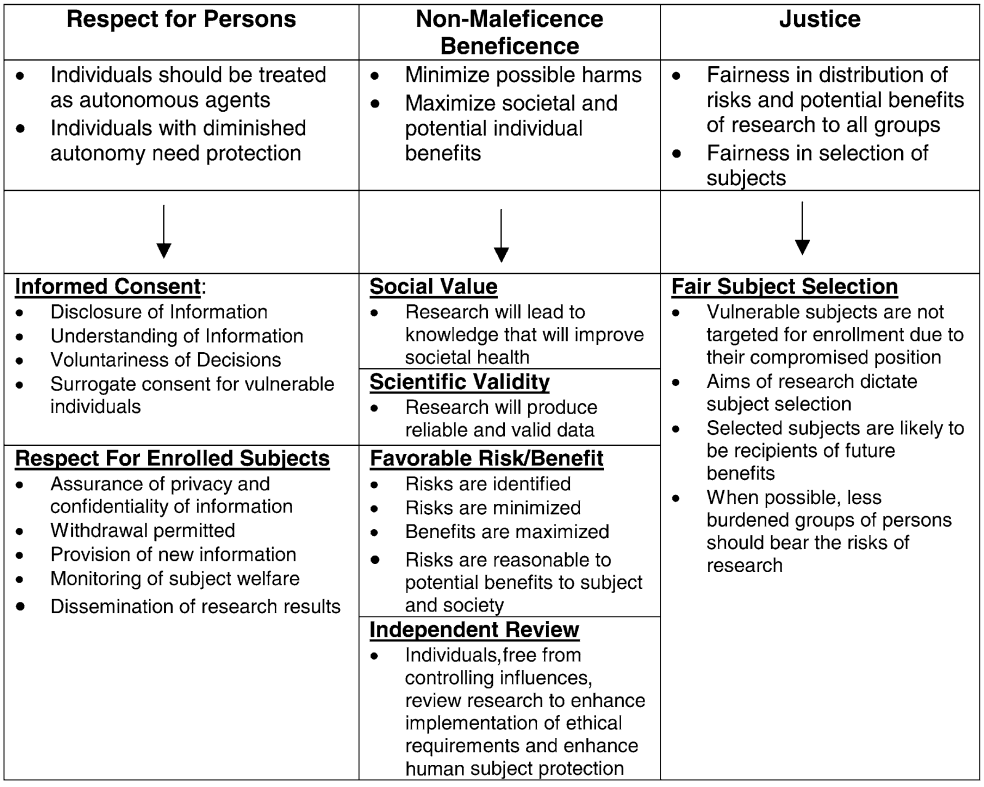

Fig. 1 Principles and derived requirements for ethical research

ological rigor to answer the motivating hypothesis waste valuable resources and do not justify exposing human subjects to the risks of research. On the other hand, while responsible research must strive for rigor, special scrutiny is in order when the most comprehensive trial design pushes the boundaries of what is ethically permissible [4]. For example, study design can be unethical if it leads to questionable and unfair subject selection practices, or if it results in unnecessary risks to subjects.

An important ethical construct in clinical trials, especially for critical care research, is that of clinical equipoise [5]. This notion refers to a state of uncertainty in the community of expert physicians concerning the relative merits (benefits and harms) of comparator interventions. The presence of clinical equipoise serves two important goals [4]. The first is to ensure that the welfare and integrity of research subjects are not knowingly sacrificed for the interests of future patients. This is achieved when neither of the interventions in the study groups dominates the other in terms of perceived safety and efficacy, and hence it is ethically permissible to allow a subject's care to be determined by random selection. The other goal is to ensure that the research will yield reliable, generalizable information that will disturb clinical equipoise. The randomized controlled trial (RCT) is a formal method of resolving epistemic uncertainty, although well conducted observational cohort and case-control studies can also provide valuable information to disturb equipoise and might lead to better human subject protections [6, 7].

Critical to enhancing the ability of an RCT to disturb equipoise is the appropriate selection of a control group. This issue has received recent attention because of its importance in ensuring a clinically meaningful result [8, 9, 10, 11]. Control group selection also has implications for monitoring subject safety during a trial which are especially relevant for critical care trials that involve rapidly fatal diseases, a topic that we discuss below. The type of control group selected depends largely on the purpose of the clinical trial, i.e., either pragmatic or explanatory. Pragmatic studies measure the degree of beneficial effect of an intervention (effectiveness) in routine clinical practice. Explanatory trials measure the benefit that an intervention produces under ideal conditions (efficacy), often using carefully defined subjects.

Pragmatic studies seek to maximize external validity to ensure that the results can be generalized. Therefore trialists select a control intervention that is identical or similar to commonly accepted therapy. For continuous parameters (e.g., tidal volume and hemoglobin) usual care practices in the critical care setting often consist of a range of accepted treatments that are titrated based on the clinical characteristics of patients. In such cases control groups would reflect unrestricted "usual care" practices, whereby care is individualized for each patient. Usual care control groups have been used in several important critical care

studies [12, 13, 14, 15, 16], including those involving mechanical ventilation [17, 18, 19], and has proven to be extremely informative in such studies [20].

Explanatory studies seek to maximize internal validity and thereby impose constraints on study and nonstudy interventions in both the experimental and control groups to reduce sources of variation (noise and bias), thereby maximizing the ability to detect, if present, differences in outcome (the signal). Accordingly, subjects in the control group are managed by protocols that specify and restrict the parameters of usual care practices. However, to change clinical practice (i.e., disturb equipoise), such protocolized control groups should be representative of usual care practices. Surveys and observational studies of clinicians' practice patterns would help ensure that the design of a protocolized control group reflects usual care. An international trial evaluating two target ranges for glycemic control in intensive care unit patients has taken such an approach [21].

When an explanatory study investigates a practice that involves a continuous parameter, trialists might design a control group that incorporates a solitary intervention option that differs significantly in value from that in the experimental group. The impetus for a large separation between the interventions is to ensure a strong signal between the two study arms. Such trials involving contrasting strategies hold important clinical value because they might clarify physiological mechanisms. However, these trials may be limited in their ability to change usual care practices if both study arms lack adequate representation of usual care practices [9].

Trialists need to consider other issues when designing trials involving contrasting strategies. First, a significant number of physicians in the community may not be in equipoise between each study arm and usual care practices. This can occur if the interventions studied in each trial arm lack an important aspect of usual care practices, or if physicians believe that therapy should be continually titrated on the basis of the physiological characteristics of their patients (e.g., tidal volume). As the extent to which physicians are willing to enroll their patients in such studies becomes less, the greater becomes the likelihood that such trials will not disturb equipoise.

Another concern with trials that incorporate contrasting strategies is that patients with specific characteristics may receive inferior treatments after randomization to either of the study arms. This would occur if randomization causes large changes in care that lead to significant adverse effects, for example, large changes in tidal volume or changes in targeted hemoglobin. Inclusion of such patients in the alleged control group would question any positive results attributed to the experimental intervention, as such results may be due to greater than expected mortality in the control group [11]. Concerns with such comparator bias, whereby an experimental therapy is compared against an alleged inferior control strategy, have been raised in several critical care trials [22, 23, 24, 25, 26, 27]. Pretrial surveys and observations of physicians' practice patterns would help determine whether significant changes in individualized care are caused by study enrollment.

Analysis of risks and benefits

Clinical research involves the assessment of drugs, devices, and procedures about which there is limited knowledge, and hence there is relative uncertainty about the degree of risks and benefits. Such uncertainty regarding risks is more pronounced in research involving the critically ill due to their being more susceptible to the toxic effects of experimental interventions.

Assessment of the potential risks involves three steps [2]. First, all of the risks and discomforts of the trial must be identified. Risks include not only the physical risks but also psychological, economic, and social risks. Important social risks include those emanating from breaches of confidentiality that might lead to stigma and discrimination (e.g., health and employment insurance). Second, once risks are identified, they need to be minimized by using procedures that are consistent with sound research design and which do not unnecessarily expose subjects to risk. Examples of efforts to minimize risk include (a) changes in study design, (b) excluding subjects who are at substantially higher risk of being harmed (c) substituting invasive procedures with less risky procedures, and (d) enhanced safety monitoring during the trial (see below). Finally, an assessment must be made that the risks are reasonable to the potential benefits to the subjects, if any, and to society. In weighing risks against benefits some have found it useful to use a component analysis framework that distinguishes between procedures with potential for direct benefits and those that merely answer a scientific question, and hence have no potential for direct benefit to subjects [28, 29].

Within a framework of a component analysis a study should be acceptable only if the risks of each component (i.e., procedures) of the research are justified separately. Components designed solely to gather data to answer a research question are justified by whether their risks are reasonable in relation to their potential to generate scientific knowledge—a so-called risk/knowledge calculus. In contrast, procedures that also offer the prospect of direct benefits must meet an additional standard of equipoise, that is, there is genuine uncertainty about whether the balance of risks and potential benefits of the study procedures are inferior or superior to those associated with accepted practice. A major advantage of a component analysis approach (as opposed to assessing the protocol as a whole) is that procedures designed solely to answer the research questions cannot be justified based on the inclusion of procedures that offer the prospect of direct benefit.

Justifying risks by the separate components of the study should not imply that there is no upper limit to the determination of acceptable risk to any of the study procedures [30]. The evidence used to evaluate the separate risks and potential benefits (to subjects and to society) of each component is fraught with uncertainty, and therefore to minimize risks there should be more caution attached to the evidence underlying the degree of risks as opposed to that for potential benefits. Indeed, the intensive care literature reports many deadly trials [31, 32]. Also, without such an absolute risk threshold the degree of permissible risk could be linked to the severity of the subject's condition, and hence trials involving high-risk procedures with the prospects of direct benefits would mistakenly be judged to be ethically sound.

Delineating risk levels to each study is useful to provide focus on riskier research. Since subjects enrolled in critical care research should be considered vulnerable, the risk levels below are fashioned after those recommended for other vulnerable groups, such as children [28, 33]:

- All procedures of the research do not involve greater than minimal risk.
- Procedures of the research involve greater than minimal risk but present the prospect of direct benefits to subjects.
- Procedures involve no more than a minor increment above minimal risk and no prospect of direct benefit to individual subjects but likely to yield generalizable knowledge about the subject's disorder or condition.
- Procedures involve more than a minor increment above minimal risk and no prospect of direct benefit to individual subjects but likely to yield generalizable knowledge about the subject's disorder or condition.

Such risk levels also provide thresholds for making certain decisions, such as the level of review by institutional review board (IRB; e.g., certain types of minimal risk research might not require full IRB review), the nature of additional safeguards for vulnerable subjects (see below), or when research should not be permissible, because it exceeds a certain threshold of allowable risk.

This risk framework uses a concept of minimal risk as an organizing principle. Under United States regulations [Protection of Human Subjects, 45 CFR 46.102 (i), 18 June 1991] research may be characterized as minimal risk if "The probability and magnitude of harms or discomforts 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." The concept of minimal risk has been indexed to the risks encountered in the daily lives of normal, healthy adults [34, 35] (http://ohrp.osophs.dhhs.gov/nhrpac/nhrpac.htm), which conveys a defensible normative judgment that the types of minimal risks considered socially acceptable (e.g., driving to work, crossing a street, or those encountered in routine physical or psychological evaluations) might also be acceptable in research.

Subject vulnerability

Vulnerability refers to the inability to protect oneself. Vulnerability can be due to intrinsic (i.e., lack of decision-making capacity) or situational factors (e.g., coercive settings or undue inducements) that threaten voluntary choice. Critically ill patients often lack decisional capacity, and the voluntariness of their choices can be questioned if their treating physicians occupies the dual role of clinician-investigator and obtain themselves their patients' informed consent to enroll in trials. The concern in such situations is the presence of coercion because patients may perceive that adverse consequences will occur if they refuse participation in clinical trials mentioned by their treating physicians. Accordingly, someone other than the treating physicians should obtain informed consent from patients [36, 37].

Research ethics guidelines recommend additional protection mechanisms for vulnerable groups [3, 30] (Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans, 1998; http://wwwnsercca/programs/ethics/english/), which could be linked to risk levels. For example, for research at all risk levels ethics guidelines and regulatory agencies [38] (Compliance Determination Letters, http://ohrp.osophs.dhhs.gov/detrm_letrs/jul2000.htm) recommend that investigators outline a specific plan to assess the capacity of all potential subjects when groups that might involve decisionally impaired persons are targeted for research. Capacity assessments can consist of asking potential subjects several questions to assess their understanding of the involved research. Alternatively, formal methods to assess capacity are available [39].

For subjects who regain decisional capacity during the clinical trial and were entered into the trial through proxy consent, investigators should also obtain their informed consent as a condition of their continued participation [40]. Such retrospective consent should be required even when the research procedures have been completed because subjects need to know that they have participated in a trial, and that further data may be collected. An emerging issue is whether subjects should be given the right to withdraw the data obtained from them when they were unconscious if they believe they would have refused participation at that time. This is a sound proposal, ethically speaking, but from a methodological point of view it is arguable since it could ruin the comparability of study groups.

For research involving procedures that pose more than minimal risk additional protections for vulnerable subjects could include the availability of independent persons to monitor the subject's involvement in the study, mainly to determine when it is appropriate to withdraw the subject

from the study [35] or the requirement of independent consent monitors who could witness the informed consent process and provide independent assurance that proxies deciding for incapacitated adults understand sufficiently the "goals and risks of the research" [41].

Informed consent

Informed consent serves two major purposes. First, obtaining informed consent respects subjects' autonomy and ensures that they are not to be used merely as a means to another's ends (Immanuel Kant, "Groundwork for the Metaphysics of Morals"). Second, informed consent provides research subjects a mechanism to protect themselves; unlike the clinical setting, where the interests of patients and physicians converge, the investigator's interests in obtaining valid scientific data and with enrolling subjects can conflict with providing the best possible treatment for individual patients [42, 43]. Valid informed consent consists of three major elements: adequate disclosure of information, sufficient subject understanding of the information, and voluntariness of the decision [44].

Disclosure of information

Several research ethics guidelines list the basic elements of information required to be communicated to potential subjects and their surrogates [45] (Protection of Human Subjects, 45 CFR 46 116, 18 June 1991). Studies have demonstrated that some of these elements of informed consent are absent in many informed consent forms (ICFs), including those used in critical care clinical trials [46, 47]. A recent publication describes recommendations for writing ICFs for critical care studies [48].

Understanding of information

Studies have shown that many enrolled subjects have limited understanding of the research to which they provided consent [49, 50]. Many subjects have difficulty understanding the concept of randomization, the notion of a placebo design, and the risks in a study. Subject understanding is lower in severely ill patients than in healthier patients [51]. Investigators should make special efforts to ensure that potential subjects understand these elements of informed consent.

A particular concern regarding understanding is the presence of a "therapeutic misconception," whereby patients and families have a strong tendency to inaccurately attribute therapeutic intent to the research [52]. However, the intention of clinical trials is not to provide direct benefits to subjects. Several authors have written extensively on how research differs fundamentally from clinical care [1, 53]: while clinical care is focused exclusively on providing benefits to individual patients, the primary goal of research is to generate generalizable knowledge for future patients. This blurring of the distinction between research and medical practice has it roots in previous literature, in research ethics guidelines, and in the national legislation of many European countries [54]. Depending on the degree and nature of subjects' failure to understand this distinction, their consent might be called into question or become invalid [55]. Physician-investigators should explicitly refute such a "therapeutic misconception" and dispel any notion that clinical trials are designed to or will provide patients with direct benefits or that the research activity substitutes for clinical care. There is currently in France a lawsuit against investigators who did not make a distinction between treatment and research protocols when they asked parents for their consent to include their children in a trial.

Finally, the research community often assumes that subjects derive benefits solely from their participation in the research study, regardless of the study arm to which they are randomized. It is thought that such a benefit might be due to the additional monitoring and superior care associated with academic "centers of excellence." However, such an "inclusion benefit" has not been verified [56, 57].

Voluntariness

Valid, informed consent requires that patients' decisions to enroll in clinical trials are free from coercion and undue influence [1]. Coercion occurs when there is a perceived threat of harm if one does not enroll in the clinical trial, whereas undue influence occurs when offers to induce enrollment (e.g., financial payments, prospect of free medical care) are of such magnitude that they encourage careless decision making by the subjects [58]. Investigators and IRBs need to be sensitized to these issues affecting free choice.

Proxy decision maker

Although many critically ill patients have, or are at risk of having, decisional impairment, consensus statements on research ethics assert that ethically acceptable research may proceed with such vulnerable subjects with appropriate proxy consent [1, 36]. Both the United States federal regulations and the European Directive require proxies giving consent for subjects' participation in research to be legally authorized to provide such consent. Who shall be the legal representative for the patient is determined by the laws of the respective state in the United States or the those of individual European Union member nation. Such legal authorization may include

a person previously appointed through a legal process or a family member or close friend. Without such automatic legal authorization given to family members or friends many previously healthy persons who become temporarily incapacitated may not be able to participate in many types of critical care research because such persons had not previously appointed a legal representative, and such appointment of legal representatives usually involves a long process. Recently the European Directive clarified that decisionally impaired persons also include those individuals who may be only temporarily incapacitated [59].

Decision-making standards

If possible, proxies should appeal to the "substituted judgment" standard whereby decisions for incapacitated patients are based upon a good faith judgment of what subjects would have chosen if capable of making a decision themselves. However, such a standard is frequently unrealistic because proxies often do not know patients' previous preferences [60, 61]. Accordingly, proxies should also consider what would be in the "best interests" of the patient. Finally, studies have shown high levels of anxiety and psychological distress in family members of critically ill patients which might impair their ability to give adequate informed consent for research participation for incapacitated patients [62, 63].

Research performed in the emergency setting

At times important research needs to be carried out involving the investigation of novel therapies in the emergency situation, such as cardiac arrest, stroke, severe arrhythmias, and life-threatening traumatic injury. In these situations patients themselves cannot give their own consent, and the narrow time window required for administering the intervention may not afford sufficient time to obtain consent from a legal representative.

Different countries and regions provide different regulations governing such research. For example, in 1996 the United States government specified several protection mechanisms under which research involving incapacitated subjects in the emergency situation can be allowed with an exception from the requirement for informed consent of a legally authorized representative [64]. Concerns have been raised that these regulations are unnecessarily complicated and burdensome, including the necessity to consult with the community in which the research will take place, on which little guidance has been offered [65, 66].

The recent European Directive regarding clinical research on drugs contains no provisions for exceptions or waiver of informed consent for research in the emergency setting. Such ambiguity has raised concerns among many intensivists because a literal interpretation of the Directive could prevent potentially beneficial research in the emergency setting and hence expose many patients to the hazards of unvalidated clinical practice [67]. Some member states, however, have issued national laws retaining previous provisions regarding the acceptability of waiver of consent in the case of emergency research, despite them being at odds with the directive [68].

Monitoring for subject safety

Safeguarding the welfare of subjects during the clinical trial is an essential ethical obligation of investigators, IRBs/research ethics committees, and data safety monitoring committees (DSMBs) [69]. Investigators need to be vigilant in observing and reporting adverse events to their research ethics committees and other pertinent regulatory agencies. Although interpretation of individual adverse events may be problematic for IRBs and research ethics committees, they do need to conduct effective continuing reviews.

DSMBs need to review individual reported adverse events as well as aggregate data on mortality or other outcome trends. By using preplanned statistical analyses DSMBs can determine at specified time points (i.e., interim analysis) when trials should be stopped early to avoid continued exposure of subjects to inferior interventional strategies, i.e., one study group shows results significantly different from the other. Early stopping of trials is especially important in critical care trials because such studies involve subjects with rapidly progressive diseases with high mortality rates, and it is not often possible to separate disease-related injury from treatment-related injury.

A concern arises when subjects are randomized to study groups involving protocolized care, neither of which is representative of usual care practices (as occurs with explanatory trials that seek large separation between studied variables). In such trials critically ill subjects may receive care that differs significantly from what they would have received outside of the trial. Despite the best intentions of investigators to minimize risks from highly protocolized interventions changes in care that depart from usual practices may result in unforeseen and adverse consequences to enrolled subjects. The absence of a representative usual care control group prevents the ability to monitor for excessive mortality rates in the study arms [9]. The impetus for this claim is the theoretical possibility that subjects randomized to either of the experimental arms could have mortality outcomes that are worse than that for comparable patients receiving usual care practices. Such a parabolic relationship between the independent variable (e.g., tidal volume or hemoglobin) and mortality outcome would go unde-

tected if a trial lacked a representative usual care control group.

Accordingly, redesigning such trials so that one of the study arms is more reflective of usual care practices or adding a third group that reflects usual care practices would permit a DSMB to stop the trial early in light of emerging data, indicating excessive mortality in either of the study arms. Other options, such as observing the mortality in "eligible, nonrandomized" patients, may also be useful [11].

Conclusions

The ethical conduct of research in the critical care setting is complex, evolving, and fraught with hazards to subjects who participate in such research. Heightened awareness to the principles and requirements that govern such research would enhance the ability of the research community to conduct such research ethically and maintain the public trust in the research endeavor.

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