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CLINICAL COMMENTARY

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Will ethical requirements bring critical care research to a halt?

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Introduction

If current trends continue, within several years it could become nearly impossible to conduct research in critical care medicine. These trends have evolved in parallel in both North America and Europe. In North America, the catalyst for controversy has been the ARDSNet trials [1, 2]. In Europe, the focus has been on European Directive 2001/20/EC [3]. Although these developments differ in their details, they essentially reflect the public's mistrust of clinicians and investigators involved in clinical research. This is a sad paradox, because critical care medicine consumes a large proportion of societal resources—more than 1% of the gross domestic product in the United States [4]—such that development of improved and more cost-effective interventions is in everyone's best interests.

Are RCTs the problem?

This crisis has rightly received much attention in the pages of "Intensive Care Medicine," with commentary that is passionate and at times even angry [5]. In this and other recent issues of this journal D. Dreyfuss has contributed to this dialogue with his claim that the problem is not just with the requirements of informed consent, but rather with our unreasonable insistence upon RCTs as the only way to acquire knowledge [6, 7]. This criticism has a long history, going back at least to 1974 when Charles Fried concluded that "the claims for the RCT have been greatly, indeed preposterously overstated. The truth of the matter is that the RCT is one of many ways of generating information, of validating hypotheses. The proponents of the RCT; however, have elevated what is in theory a frequent (though by no means universal) advantage of degree into a gulf as sharp as that between the kosher and the non-kosher ... We should not proceed on the fallacious assumption that where there is no randomization, there is no truth" [8]. Yet we continue to see evidence of a blind reverence for the superiority of RCTs. For example, despite persuasive evidence from an observational database and two convincing clinical trials demonstrating the efficacy of ECMO for treatment of pulmonary hypertension in newborns [9, 10, 11] investigators insisted upon performing a conventional RCT before this treatment was accepted in the UK. This study was terminated early by the DSMB with a $p<0.0005$, following 54 of 92 deaths in the control arm with only 30 of 93 deaths in the ECMO arm [12]. Some authors have questioned whether this study was truly necessary to confirm the superiority of ECMO, or whether it merely satisfied the appetite of the medical community for "proof" from an RCT [13].

In addition to these ethical issues, insistence upon the use of RCTs has raised practical concerns as well. The ARDSNet ARMA trial, which cost an estimated $15 million US (T. Thompson, pers. commun.) established that a tidal volume of 6 ml/kg is superior to 12 ml/kg [1]. While not disputing the importance of this knowledge, can society afford to use this same approach to investigate the myriad other questions that can be asked about optimal ventilator strategies for ARDS, involving all the variables of FIO_2, PEEP, fluid administration, and so forth? More fundamentally, as citizens of our societies, should we as intensivists even advocate for funding these

studies, given the other research priorities that exist in critical care and medicine more generally, or given the other needs of our communities, such as education and welfare? If other methodologies are possible, should they not be considered? [14, 15].

For these ethical and practical reasons, I agree with Dreyfuss' plea that intensivists give greater consideration to alternatives to the RCT. I believe Dreyfuss is wrong, however, when he states that the advantage of non-randomized designs is that they involve "the removal of the need for specific consent for research in favor of consent for medical care under most, if not all, conditions" [7]. He suggests, for example, comparing the outcomes of a treatment used during one period with another treatment used at a later period. In making these suggestions, I believe Dreyfuss is confusing two different types of objections to RCTs. The first objection relates to the act of randomization per se. Here the concern is that some patients might be assigned to a therapy that is known to be inferior. This should not be an issue at the beginning of a trial, when all arms of the study are thought to have an equal likelihood of success, but can emerge later, when evidence builds in favor of one of the arms. This ethical issue persists even when, as is commonly the case, the investigators agree not to look at the data until the end of the study, since even with this agreement the data are still available and, if known, could certainly impact the willingness of a subject to enroll in the study. This objection is captured by the question, "Who would want to be the last person enrolled in the inferior arm of a randomized trial that shows a difference between treatments?" Dreyfuss is correct in his claim that nonrandomized research designs avoid this ethical tension. The more fundamental problem, however, relates to research and the requirement for protocolized care.

Research and the problem of protocolized care

In a more general sense, what differentiates clinical research from clinical care is that trial participants must forego their right to individualized care [8, 16]. In other words, physicians have a duty, grounded in the fiduciary nature of the patient–physician relationship, to make individualized decisions for their patients. Any research that requires physicians to treat patients according to a particular approach forces physicians to violate that duty. This is a problem for any research that is not strictly observational. The RCTs are often singled out for ethical scrutiny because the process of randomization highlights the fact that the patient's care is not being determined by individual judgment, but it is a mistake to assume that this is a problem unique to RCTs—it is a problem for any research that requires subjects to be treated in a standardized manner.

In my opinion, therefore, Dreyfuss is wrong when he claims that for these non-randomized approaches patients and families could simply be asked to consent to care, and not specifically to research. The mistrust of the public towards clinical research, I believe, stems precisely from their fear that by agreeing to participate in research they will not receive care based solely on the best clinical judgment of their physicians, but rather according to a predetermined protocol—even when this protocolized care may not be the best for them given their clinical situation.

Some authors might object by pointing to studies that have demonstrated the superiority of protocol-driven care over individualized care [17]. Recent evidence has cast doubt upon whether this so-called trial effect actually exists [18], but even if it does, this is not the issue. When physicians follow clinical practice guidelines, they do so with the conviction that this is in the best interest of their particular patient, and they are free to deviate from the guidelines whenever they believe this not to be true. In other words, care delivered in accordance with clinical practice guidelines still qualifies as individualized care, and does not violate the covenant of the patient–physician relationship. Conversely, when physicians follow protocols for patients on research studies, the purpose of following the protocol is not to provide the best care for the patient as an individual, but rather to create and preserve a situation where the outcome of the individual patient can be scientifically compared with the outcomes of other patients who are treated differently in a systematic manner. As the ethicist Jay Katz put it: "A dilemma confronts physician–investigators ... As physicians they are dedicated to caring for their patients ... As investigators they are dedicated to caring for their research ... These two commitments conflict whenever an individual physician/investigator comes face to face with an individual patient/subject" [19].

Possible solutions to the clinician–investigator conflict

The conflict between the roles of clinician and investigator is therefore the core ethical issue faced by physicians doing research in critical care, and it has been a question of sustained debate for several decades. One extreme view would hold that the obligations of physicians are fundamentally at odds with those of investigators, and that research of any sort must therefore truly be limited to "guinea pigs." A less extreme, but still rigorous, approach is to insist that physicians deviate from individualized care only when they can honestly claim that they have no basis for preferring one arm of a protocol over another [8]. This requirement, termed "personal equipoise," is theoretically sound but completely impractical. The difficulties are obvious. Physicians almost always have preferences or beliefs about what care is best. Under the personal equipoise standard, physicians are

obligated to share these preferences with patients and to act on them, whether these preferences are based on personal experience and hunches or on solid scientific evidence. While personal equipoise provides a theoretical solution to the physician/investigator dilemma, in reality it would preclude the possibility of conducting research in the ICU.

The late Canadian ethicist Benjamin Freedman is credited with the best known attempt at solving this dilemma. In his landmark 1987 paper, he noted the problems with personal equipoise, and put forward the alternative concept of clinical equipoise [20]. In his words, a state of clinical equipoise exists when "There is no consensus within the expert clinical community about the comparative merits of the alternatives to be tested." He believed that clinical equipoise resolves the tension between the roles of the physician and investigator, allowing the intensivist to say to a prospective research subject: "While I personally believe that treatment A may turn out to be superior to treatment B, there is genuine uncertainty within the medical community about which is better, and other clinicians that I respect don't share my belief. I can therefore offer you the opportunity to participate in this study without violating my obligation to treat you as an individual."

Freedman provided physicians with an ethical foundation that supported the conduct of research in the clinical setting, by stating that there need not be any fundamental conflict between the roles of physician and investigator. Recently, however, Miller and Brody have strongly challenged this view [21, 22]. They begin by recalling the words of the Belmont Report, a foundational document regarding the ethics of clinical research: "The ethics of clinical trials must start with the realization that medical research and medical treatment are two distinct forms of activity, governed by different ethical principles." In their view, Freedman misleads us when he suggests that clinical care and research can be "collapsed" together under the concept of clinical equipoise. Miller and Brody insist that we need to move in the opposite direction, and stress the fundamental distinctions between clinical care and research.

While their critique has provided a healthy opportunity for reflection on the ethical principles of clinical research, it is not clear that this formulation is well suited to the needs of either patients or physicians. Imagine a physician saying to a patient, "This morning I was your doctor and you were my patient, but this afternoon I am going to be giving you an experimental medication, and then I am no longer your doctor, but an investigator, and you are my subject. During this time you need to know that I will place the pursuit of scientific knowledge above your interests, and will no longer be providing you with individualized care." While this conversation is hard to imagine in any clinical setting, it would seem almost inconceivable in critical care.

Is informed consent always necessary for research?

Miller and Brody [21, 22] also re-emphasize the central importance of informed consent to the conduct of clinical research. Indeed, the need to obtain informed consent before enrolling subjects in clinical research has been so uniformly accepted that there has been little examination of the priority it receives. This requirement does present a paradox, however. Consider, for example, if I decide to change my personal practice so that all of my patients are switched from conventional- to high-frequency ventilation when they reach a certain plateau pressure on conventional settings. While I will probably discuss this decision with the patient's family at the time I make the transition, I do not need any special permission or consent to make this change in clinical care. If, on the other hand, I want to go beyond my anecdotal experience and learn whether there is a scientific basis for switching patients from conventional to high-frequency ventilation at this threshold, I need to prepare a detailed protocol, obtain the approval of an ethics board, generate a detailed informed consent document, and obtain the specific consent of the family before I proceed. This paradox has been succinctly captured by the observation that "I need permission to give a new drug to half my patients but not to give it to all of them" [23].

This paradox provides an interesting insight into what I view as a serious flaw in the accepted ethics of clinical research. This flaw relates to seeing informed consent as an essential goal or ideal in itself. The reasons behind this focus are historically rooted in the Nuremberg trials and the codes that followed them, and are understandable in that context. Outside of that context, however, the priority of informed consent needs closer examination. An alternative but compatible view would place respect for patient autonomy as the highest and most important requirement of clinical research. Under this view, we would accept and acknowledge that obtaining the informed consent of the subject would, in most cases, be an essential way of demonstrating respect for the individual's autonomy. This alternative view would, however, open up the possibility of considering situations where respecting the autonomy of the individual would not necessarily involve obtaining the subject's informed consent.

This view is not as radical as it may first appear. There are a number of examples where RCTs are performed without the consent of the subjects. Consider an RCT where cities of a certain size are randomized with regard to whether they will receive an anti-smoking campaign over radio and television stations, with research to determine the effects of this campaign upon rates of teenage smoking. Certainly obtaining the informed consent of the teenagers who are the subjects of this randomized study would be neither possible nor ethically mandatory.

To take an example from the medical setting, imagine a situation where two different hand soaps are in use in a

hospital's ICU, and where the clinicians choose which to use by chance or personal preference. Suppose the hospital wants to save money by switching exclusively to one brand. One rational and scientific approach might be to stock one side of the ICU with one brand, and the other side with the alternative, and then track rates of nosocomial spread of infection. Patients would be "randomized" to one side of the ICU or the other by chance at the time of admission. In one view, this is a randomized controlled trial of a serious medical condition (nosocomial infection) and should therefore require the consent of the subjects. In another view, however, informed consent seems superfluous to the higher goal of respecting the autonomy of the patients. After all, in the absence of the study, the caregivers would still be using either one soap or the other. Furthermore, if consent was required, what should the investigators do for patients who refuse to consent for the study? Should they be required to introduce a third soap into the hospital for these patients, perhaps, to "prove" that they are not a part of the study? In other words, blind obedience to the accepted dogma that informed consent is required for all research can lead to some unnecessary and even silly practices. If, however, we recognize that respect for the autonomy of the patient is the more fundamental requirement, then we are free to ask when the informed consent of the patient is required to meet that requirement, and when it is unnecessary.

Some authors might argue that the hypothetical study described above is not "research" but rather "quality improvement," and therefore does not require the informed consent of the subjects. Although some authors have attempted to state the features that differentiate quality improvement from research, the distinction remains vague at best [24]. If the investigator intends only to produce local knowledge for a specific clinical setting, the work is usually described as quality improvement, whereas if the investigator intends to produce generalizable knowledge, it is categorized as research. Operationally, if the investigator intends to publish the results, then the work is generally considered to be research. From the patients' perspective, however, one might reasonably ask why considerations about whether the results are local or generalizable, or whether the work will be published, should be the determining factors about whether the investigator should approach the patients for informed consent. From the patients' perspective, should not the question hinge upon whether patients will feel that their autonomy has not been respected if the investigators fail to seek their informed consent? A somewhat cynical conclusion, but one I believe contains at least an element of truth, is that when ethics boards believe that the informed consent of the subjects is not necessary, the work is labeled as quality improvement, whereas when the informed consent of the subjects is considered ethically required, the work is labeled as research. If true, then "quality improvement" is often just a euphemistic expression for "research where we think the informed consent of the subjects is not ethically required."

Several years ago my colleagues and I suggested that informed consent not be required for all RCTs, using the reasoning outlined above [25]. Although I still believe the arguments are compelling, even then I knew that our proposal had no chance of acceptance. The climate of distrust that has developed around the conduct of clinical research is so widespread and deep-seated that virtually all regulatory changes at the present time are in the direction of increasingly stringent requirements for informed consent. The one striking exception to this trend is the exemption that currently exists for "emergency research" in the United States [26]. I applaud this exemption for recognizing that in certain circumstances informed consent may not be necessary to make research ethical, but I would caution the critical care community that, properly understood, this exemption should apply primarily to research in the pre-hospital and emergency department settings. Few of the research interventions in critical care can be categorized as emergent, in the sense required by the American regulations. I worry that attempts to extend this exemption into critical care research may reflect more of an effort to circumvent the current requirements for informed consent than a legitimate application of the emergency exemption.

The value of "component analysis"

Given the climate that many researchers, including myself, regard as hostile to the conduct of research in the ICU, I find the recent work of Weijer [27] to be especially helpful. I therefore close with a few insights gleaned from his work. To begin, most research performed in critical care initially appears to be "high risk," in that ICU interventions often have powerful physiologic and pharmacologic effects, the side effects from these interventions can be frequent and severe, and many patients die or suffer major morbidities. On closer examination, however, it is clear that all of these concerns are true for critically ill patients even when no research is being performed. In other words, it is essential to separate the risks associated with being critically ill in the ICU from whatever additional risks are specifically associated with the research per se.

Weijer has capitalized upon this insight with a method that he describes as "component analysis" [27]. Essentially, the idea is that every component of a research protocol is performed with either therapeutic intent or non-therapeutic intent, and should be specifically categorized as such (Figs. 1, 2). These two groups of interventions are analyzed by different standards. The main requirement for the therapeutic procedures is clinical equipoise. The non-therapeutic procedures are those performed solely to answer the research question; these

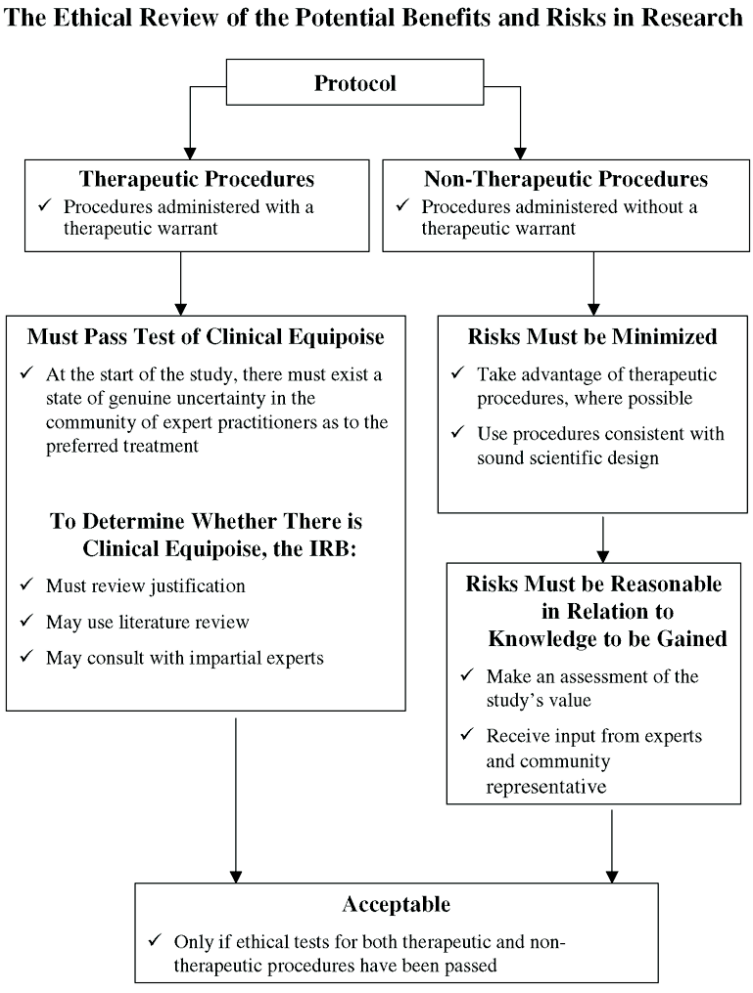

Fig. 1 Ethical review of the potential benefits and risks in research

would include, for example, non-therapeutic placement of catheters to measure pressures or facilitate blood draws, non-therapeutic imaging studies, or follow-up tests and procedures beyond those that are clinically indicated. These non-therapeutic procedures must meet several ethical standards. Firstly, their risks must be minimized by assuring that they be consistent with sound scientific design and that they take advantage of the therapeutic procedures whenever possible (e.g., using discarded blood for non-therapeutic tests if feasible, rather than requiring additional blood draws). Secondly, the risks must be reasonable in relation to the knowledge to be gained. Again, since these are non-therapeutic procedures, and they offer no possibility of benefit to the patient, any risks to the patient must be balanced against the expected benefit to society and future patients.

Weijer [27] adds two other ethical requirements for patients who cannot participate in the informed consent process, which would include almost all of those who are critically ill. Firstly, there must be compelling reasons why the study must be done on these vulnerable patients. This requirement is easily met for most research in the ICU, where it would make no sense to be studying patients who are not critically ill. Secondly, whereas subjects who are capable of consenting can decide for themselves how much of a risk they are willing to take to advance medical knowledge, Weijer believes that for patients who are not able to consent for themselves the level of allowable risk for non-therapeutic procedures should be capped at "no more than a minor increase above minimal risk" (where minimal risk is understood as the risks associated with daily life).

Intensivists should become familiar with Weijer's approach to analyzing risk, because it leads to a remarkable and perhaps unexpected conclusion regarding research in the ICU. The vast majority of the interventions performed as part of critical care research are performed with therapeutic intent. The absolute magnitude of the risks associated with these procedures is irrelevant, as long as the overall risk–benefit assessment for the intervention is in clinical equipoise with the therapeutic alternatives. The non-therapeutic procedures associated with most research

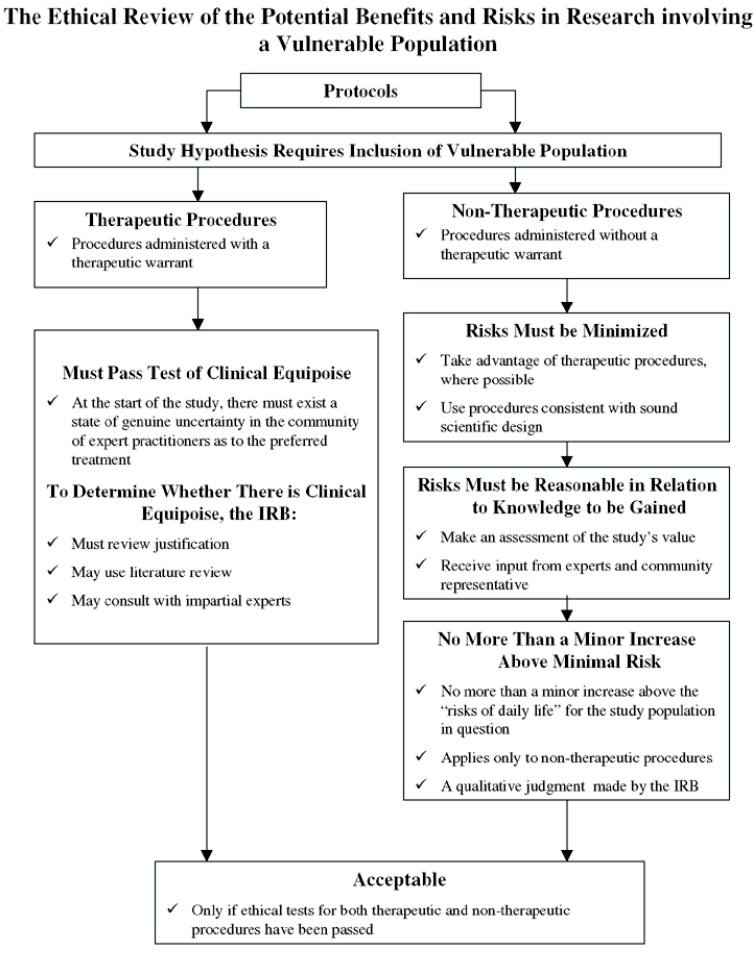

Fig. 2 Ethical review of the potential benefits and risks in research involving a vulnerable population

in the ICU—additional blood draws and the like—will usually fall within either the "minimal risk" or "a minor increase above minimal risk" categories. Using this approach, therefore, much of the research performed in critical care is clearly less ethically challenging than some of the research performed in outpatient settings! By promoting component analysis as the preferred approach to analyzing the risks involved in research, intensivists should be able to take important steps toward facilitating acceptance of research in the critical care environment by both ethical review boards and the public.

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