American Thoracic Society Documents

The Ethical Conduct of Clinical Research Involving Critically Ill Patients in the United States and Canada

Principles and Recommendations

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Outline

INTRODUCTION

Clinical research involving critically ill patients is necessary to reduce the extreme morbidity and mortality encountered in the intensive care unit (ICU). Yet such research is ethically challenging because critically ill patients usually are unable to consent for research participation, because conflicts of interest occur among investigators, and because discovering new knowledge while simultaneously protecting research participants from risk may be difficult to achieve. To explore these and other challenges and to elucidate ways of meeting them, the American Thoracic Society (ATS) sponsored a conference on the ethical conduct of clinical research involving critically ill patients on November 21 and 22, 2003 in Washington, DC.

The conference was initiated in response to a request for proposals from the Association of American Medical Colleges (AAMC), which hoped professional societies would educate their members about the ethical challenges of clinical research. After the AAMC decided to support the conference, further funding was obtained from the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH), and the ATS. At the conference, experts in clinical investigation, patient advocacy, ethics, and research oversight explored various aspects of clinical research with a general audience and a writing committee. The writing committee in turn authored this document.

The purpose of the document is to present a series of principles that govern the ethical conduct of clinical research involving critically ill patients and to make specific recommendations based on these principles. Prominent among the recommendations is the use of ethical checklists as tools to assist in clinical trial design, implementation, and monitoring by investigators and independent reviewers of research. Although these recommendations and the principles that underlie them may be relevant to clinical research conducted outside the ICU, we emphasize critical care research. Furthermore, although the recommendations and principles may be applicable to clinical critical care research in all countries, we focus on the United States and Canada in the document because these nations were represented among the conference presenters and on the writing committee, and because research is conducted and overseen similarly in both countries.

A. RATIONALE FOR CLINICAL RESEARCH IN THE INTENSIVE CARE UNIT

Principle

1. Clinical research involving critically ill patients is necessary. Critical illness caries a high mortality. For example, in 1999, 700,000 deaths, representing 20% of all deaths in the United States, occurred in an ICU (1). While the mortality from critical illness is high, the morbidity associated with it is also considerable, if harder to quantify. It includes serious complications of acute and chronic diseases, pain and suffering for patients and families, and incomplete recovery of quality of life among survivors. The morbidity and mortality of critical illness underscores the need for effective clinical research. Without such research, we are unlikely to improve our understanding of how to restore health, minimize discomfort, reduce organ dysfunction, increase survival, and improve quality of care in the ICU. Equally important is the need for research on accurate predictors of outcome and the consequences of basic and advanced life support, to inform patients, surrogates, and clinicians about whether, when, how, and why critical care services should be initiated, withheld, or withdrawn.

Great though the burden of critical illness is today, it is certain to increase. In 2001, 5.7 million adults were admitted to critical care units in the United States. The direct medical cost of their care, exclusive of physician payments, was $70 billion, which represents approximately 1% of the U.S. Gross Domestic Product (2). Demand for critical care services is expected to escalate even further as 78 million "baby boomers" age in the United States. In support of this expectation, Medicare enrollment is projected to grow over 50% in the next 30 years (3). Meeting the forecasted high demand for critical care will require more trained clinicians, modified practice patterns, and other health care reforms (4).

The huge human and financial costs of critical illness create a pressing need for high quality clinical research involving various complementary methods. Observational studies have played a crucial role in our understanding of the prevalence, incidence, risk factors, and prognosis of critical illness, and they also have provided major clinical advances (5). Randomized clinical trials have successfully tested numerous preventive and therapeutic interventions, teaching us which interventions are ineffective, do more good than harm, and vice versa. Extraordinary advances

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TABLE 1. ETHICAL PRINCIPLES FOR CLINICAL RESEARCH

Principle	Explanation
1. Respect for persons	Respect for research participants' autonomy and right of self-determination
2. Beneficence (and nonmaleficence)	The obligation to provide benefit to participants and to avoid harming them
3. Justice	The equitable distribution of risk and benefit across all possible research participants regardless of background and social standing

Adapted from Reference 8.

in fundamental biological sciences such as genetics are beginning to provide important insights into critical illness, and hold promise for the future. Fortunately, funding for both basic science and clinical research in critical care medicine has increased recently. This funding is essential in improving the outcome of the critically ill.

Recommendations:

1a. Clinical research on critically ill patients should be a health care priority.

1b. Federal, state, foundation, and private sources should commit to funding more clinical research on critical illness.

Principle

2. Clinical research involving critically ill patients poses special ethical challenges. Clinical research in the ICU is fraught with ethical difficulties. Critically ill patients are captive and thus vulnerable, and they are dependent on the ICU team for all aspects of their care. This vulnerability raises concerns about the patients' ability to give informed, autonomous consent to participate in clinical research, even if they can understand and judge the pros and cons of participation. At the same time, most critically ill patients lack decisional capacity due to their underlying diseases or the drugs they are receiving (6, 7). As a result, their family members or other surrogates usually are asked to provide informed consent for research participation in the United States and Canada. Surrogates may believe that the care their loved ones receive will be better if they give consent, and they may have difficulty refusing to participate in clinical research.

Patients and their surrogates participate in clinical research for many different reasons: hope for a cure, extension of life, preservation of function, reduction of pain and suffering, the fulfillment gained from feeling engaged in a battle against their illness, and the altruistic sense of contributing to the quest for knowledge that may help others in the future. For any of these reasons to be honored, the research must satisfy the ethical requirements discussed in this document. This is necessary because patients and surrogates place themselves in trust with investigators, and this trust must be respected if society is to support clinical research.

Critical illness usually evolves rapidly, and the consent process often must occur within a short time after the onset of illness. These factors place stress on patients, surrogates, investigators, and oversight bodies alike. Study procedures may involve risk to research participants, and although this risk may be proportional to the participants' underlying illness, it nevertheless must be appreciated in its own right. The adverse effects of study procedures can be difficult to separate from complications of the underlying illness, and therefore require special scrutiny during a study. Broad variations in critical care practice often complicate the design of control arms in randomized trials. These and other issues must be addressed to optimally protect study participants, promote innovative research, and optimize the scientific contributions of clinical studies.

Recommendations:

2a. The ethical challenges inherent in clinical research involving critically ill patients must be acknowledged and confronted by all persons involved in the process: patients and surrogates, clinicians, investigators, and those parties involved in research oversight.

2b. The ethical integrity of the research must be ensured at all steps of the process, including the research question posed, the study design, the consent process, the research oversight, data management and analysis, and interpretation and dissemination of the results.

B. ETHICAL ASPECTS OF CLINICAL CRITICAL CARE RESEARCH

Principle

3. Clinical research involving critically ill patients is governed by ethical principles and requirements. As outlined in the Belmont Report (8), the ethical principles governing critical care research include (*1*) respect for persons, (*2*) beneficence, and (*3*) justice (Table 1). The principle of respect for persons includes the obligation to treat research participants as autonomous agents, for example by obtaining their informed consent before such participation and, if they have diminished autonomy, obtaining consent from surrogates who can speak for them and represent their interests. The principle of beneficence and its corollary, nonmaleficence, require that investigators act to maximize the possible benefits that participants may gain through research and act to minimize the possible risks to them. The principle of justice mandates that research participants be enrolled in such a way that all populations have equal access to the potential benefits and risks of the research.

Emanuel and colleagues (9) have enumerated seven ethical requirements for clinical research based on these ethical principles. They include (*1*) social value, (*2*) scientific validity, (*3*) fair participant selection, (*4*) a favorable risk-benefit ratio, (*5*) independent review, (*6*) informed consent, and (*7*) respect for enrolled participants (Table 2). These seven requirements provide a framework for evaluating the ethics of clinical studies. Emanuel and colleagues (9) list them in chronological order from the design of the research to its implementation. Essential to several of the research requirements is the concept that ethics and science are intertwined such that studies that are poorly designed and conducted are unethical because they do not yield results that achieve social value by advancing knowledge or improving health. This concept is fundamental to both the Nuremberg Code (10) and the Declaration of Helsinki (11).

The concept of equipoise is essential to the requirement of scientific validity, and is particularly relevant to research that compares interventions. Clinical equipoise exists when the medical community is uncertain about the merits and demerits of interventions to be compared with each other or against a placebo control (12). If the medical community strongly believes that one intervention is superior to the other, equipoise does not exist; the study in question may not be scientifically valid or ethically sound, and it may have no social value because it would not contribute to knowledge or health. From the perspective of research participants, equipoise is present if rational,

TABLE 2. ETHICAL REQUIREMENTS FOR CLINICAL RESEARCH

Requirement	Example
1. Social value	The research must improve health or advance knowledge
2. Scientific validity	The research must be scientifically rigorous and provide reliable results
3. Fair participant selection	The research must expose the vulnerable and the privileged to the same risks and benefits
4. Favorable risk-benefit ratio	The research must minimize risk and maximize benefit to participants whenever possible
5. Independent review	The research must be reviewed, approved, amended, or terminated by unaffiliated observers
6. Informed consent	The research participants or their surrogates must be informed about the research, must understand it, and must agree to it voluntarily and without coercion
7. Respect for enrolled participants	The research participants' privacy must be respected, their withdrawal permitted, and their safety monitored

Adapted from Reference 9.

informed persons would express no consistent preference for one intervention over another (13). If research participants do not believe that equipoise exists, they are unlikely to participate in clinical trials.

As Emanuel and colleagues (9) point out, benefit to society from clinical research is assumed if the research has social value and scientific validity. Nevertheless, research may not necessarily benefit those who participate in it from a therapeutic standpoint even if it benefits future patients. The term "risk-benefit ratio" generally applies to the risks and benefits that accrue to study participants themselves, not to patients in the future. Special consideration therefore must be given to clinical research, such as phase 1 safety studies, that offers no apparent benefit to participants beyond satisfying their altruism but may have social value because it provides information that may benefit future patients (14). Such studies may be ethical only if their potential social value is great and the risks to participants are minimized.

Recommendation:

3. Critical care practitioners, in their role as clinicians or investigators, must have a sound working knowledge of the ethical principles that govern clinical research, and the research in which they participate must meet ethical requirements (Tables 1 and 2).

Principle

4. Critical care research and practice differ in that the investigator's primary interest is to gain valid and generalizable knowledge from research, whereas the clinician's primary interest is to benefit individual patients. As stated in the Belmont Report (8), clinical research is conducted primarily "to test a hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to knowledge." Practice, on the other hand, "refers to interventions that are designed solely to enhance the well-being of an individual patient or client that have a reasonable chance of success." Intentions, however, may overlap. Critical care practitioners who serve as investigators of studies wherein their patients are asked to participate may want to benefit the patients directly through participation in the research, and may also want to benefit future patients through the knowledge gained from it. Nevertheless, although the intentions of practitioners as investigators may overlap with those of practitioners as clinicians, practitioners who serve as investigators must remind themselves that gaining knowledge is their primary intent with regard to their research activities. As a result, they may have a conflict of interest in asking their patients or the patients' surrogates to participate in studies in which the practitioners are involved.

Because critically ill patients and their surrogates seek opportunities for life-saving interventions and are dependent on their clinicians, they may attribute therapeutic intent to investigational procedures. This attribution is called the therapeutic misconception (15). It may complicate the informed consent process by allowing patients and their surrogates to overestimate the potential clinical benefit they may gain by study participation. Investigators must minimize therapeutic misconceptions to preserve the autonomy of prospective research participants (16, 17). Furthermore, ICU clinicians who wish to enroll their own patients in studies must avoid unduly influencing the patients' or surrogates' decision to participate because of their therapeutic relationship with them. Thus, they should use a third party to provide informed consent whenever possible. All persons obtaining consent should declare their involvement in studies in which they are involved.

Recommendations:

4a. Practitioners who serve as investigators and clinicians must recognize the differences between clinical research and clinical practice, and distinguish these differences for potential study participants and their surrogates.

4b. Practitioners sometimes serve as investigators and clinicians for the same patients. If they do so, other persons (e.g., co-investigators, research coordinators, or persons not involved in the study) should explain the research to potential study participants and obtain their consent.

Principle

5. Critical care clinicians should support sound clinical research, but they are also obligated to ensure the safety of their patients from excessive or unnecessary risk. Considerable medical progress has been achieved through clinical research to the benefit of critically ill patients. Clinicians have an obligation to support the research enterprise that benefits their patients, and to recommend that patients consider participating in it if the research meets ethical and scientific requirements. Even though equipoise about an intervention in a trial may exist in the medical community, or exist from the perspective of patients or their surrogates, individual practitioners may strongly believe that one of the interventions being compared is superior. If this belief is well founded, clinicians who adhere to it may remove themselves and their patients from research participation, because their primary responsibility as clinicians is to benefit their patients. On the other hand, clinicians who do not have a good reason to prefer one intervention over another should consider allowing their patients to participate in research, to help create knowledge relevant to critical care medicine.

To ensure the safety of their patients, clinicians should carefully review and endorse studies before patients or their surrogates are approached by investigators to participate in them. If their patients do participate, clinicians should monitor for adverse effects, discuss their concerns with the investigators and institutional review boards (IRBs) or research ethics boards

(REBs) as appropriate, and urge withdrawal from the study if they believe that their patients are being harmed.

Recommendation:

5. Critical care clinicians must be satisfied about the ethical and scientific validity of the studies in which their patients participate.

C. ETHICAL ASPECTS OF RESEARCH DESIGN

Principle

6. Ethical considerations are intrinsic to sound research design. There is no ideal clinical study. Choices have to be made about study design, which should be based on sound ethical principles in addition to sound scientific principles. With regard to clinical trials, Emanuel and coworkers operationalized these principles as the seven key ethical requirements shown in Table 2 (9). Many of these principles hold equally for other important clinical research methods, including observational studies. In Table 3, we present a framework showing the relevancy of several elements of study design to the seven key ethical requirements. The table might be used by an investigator or independent reviewer to understand how the ethical requirements pertain to certain aspects of study design in a given investigation. The requirements are shown in **bold** for easy reference in the discussion that follows.

a. Scientific rationale, background, significance, and preliminary work. A sound physiologic rationale and a clear appraisal of the existing literature are fundamental to an ethical study design. For example, a thorough systematic review should minimize the risk of simply repeating a study with no potential for increased knowledge; such a review can help to appraise the importance of the question, and build on prior study strengths, which are ethical requirements for social and scientific **value**. By conducting observational studies before initiating trials, key information can be obtained about the prevalence and incidence of the disease in question, the frequency with which relevant outcomes occur, existing practice variation, and projections of future enrollment. By conducting surveys, data can be obtained about the opinion, attitudes and beliefs of clinicians, and their practice patterns. Each of these pieces of information is crucial for the ethical requirements of **scientific validity**, generating a **favorable risk-benefit ratio**, and providing **informed consent**, regardless of whether the research is therapeutic or nontherapeutic.

b. Selection criteria. In selecting participants, there is an ethical requirement to ensure that enrollment criteria fit with the scientific goals (**scientific validity**). For example, when designing an observational trial to understand the incidence of a disease or an interventional trial to determine a treatment's effectiveness in a routine care environment, the criteria should allow generalizability of findings to other settings. In contrast, when designing an observational study to explore a mechanism of action or an interventional trial to explore the efficacy of an intervention under ideal conditions, then selection of a physiologically homogenous and less generalizable group may be more appropriate. It must be borne in mind that this group may be the only one in which the study results are applicable when they are disseminated. It is also important to ensure that the selection criteria do not disproportionately include or exclude vulnerable or stigmatized populations (**fairness**). In addition, investigators should consider studying a population for whom the risk-benefit ratio will be most favorable (**favorable risk-benefit ratio**).

c. Sample size and power (minimally important difference). An underpowered study runs the risk of providing no **value** to society because of a high risk of type I and type II error. An underpowered study is of poor **scientific validity**, and is of questionable benefit. This point is particularly relevant in large, definitive clinical trials intended to inform practice. In such cases, the study should be adequately powered to find the minimal clinically important difference (18). Pilot studies also should be powered to achieve their specific objectives.

d. Outcome measures. The outcome measure must reflect the purpose of the study (**scientific validity**) and allow generation of important knowledge (**value**). In small, mechanistic studies, the outcome may be a physiologic parameter, providing biological insight for future studies. In large definitive trials, the outcome must be relevant to the patient or society.

e. Study arm allocation technique. The decision to randomize or not has several important ethical implications, including the **value** of the information gained from the study, the **validity** of the methods chosen, and the process of **informed consent.**

f. Selection of control arm(s). Control arm selection, the subject of vigorous debate recently (19–22), has several ethical considerations. To ensure **value** and **scientific validity**, the selection of the control arm should fit with the question addressed by the study. For example, in small mechanistic trials or efficacy trials, it may be preferable to rigorously protocolize what might otherwise be variable management, to isolate the effect of the intervention being evaluated.

In contrast, in large effectiveness trials, the control arm should fall within the range of "best current practice" in accord with the Declaration of Helsinki (11). Customary or usual care in such trials often is not protocolized, and these trials themselves can be extremely informative (23–25). Nevertheless, reaching consensus on the definition of the best current practice may be difficult, if not impossible. Difficulties include deciding whether

TABLE 3. RELEVANCE OF CLINICAL TRIAL DESIGN ELEMENTS TO ETHICAL REQUIREMENTS

Design Element	Social or Scientific Value	Scientific Validity	Fairness	Favorable Risk-Benefit	Independent Review	Informed Consent	Participant Respect
Scientific rationale, background, significance, and preliminary work	+ + +	+ + +	+ +	+ + +	+ +	+ + +	+
Selection criteria	+ +	+ + +	+ + +	+ + +	+ +	+	+
Power and sample size	+ + +	+ + +	+	+ + +	+ +	+	+
Outcome measures	+ + +	+ + +	+	+ +	+ +	+ + +	+ +
Study arm allocation technique	+ + +	+ + +	+ +	+ +	+ +	+ + +	+
Selection of control arm(s)	+ + +	+ + +	+ +	+ + +	+ +	+ + +	+
Nature and scope of intervention	+ + +	+ + +	+ +	+ + +	+ +	+ + +	+
Monitoring and stopping rules	+ +	+ + +	+	+ + +	+ +	+ +	+ + +

Definition of abbreviations: + = somewhat relevant; + + = relevant; + + + = highly relevant.

Although the seven ethical requirements should be considered in all phases of design, the above table presents a framework for understanding which requirements are particularly relevant for select design elements.

TABLE 4. AN ETHICAL CHECKLIST FOR CLINICAL RESEARCH DESIGN

1. Will the study results provide social or scientific value? (i.e., will the answer matter?)
2. Is the study design scientifically valid? (i.e., is the rationale adequately argued and are the methods scientifically sound?)
3. Is the intended participant selection fair and suitable for the research question?
4. Is there a favorable risk-benefit ratio? (i.e., minimal risk relative to benefits to research participants?)
5. Has the design undergone, or will it undergo, independent review before starting the study?
6. Are adequate procedures in place to ensure informed consent, and have they been reviewed?
7. Are adequate procedures in place to ensure respect for potential and enrolled participants?
8. Are data and safety monitoring in place?
9. Have conflicts of interest been identified and minimized?

such practice is "customary" or "standard," defined legally as the care most clinicians actually provide, or "reasonable," defined legally as the care most physicians ought to provide, based on the evidence and/or expert opinion. Another complicating factor is time. What constitutes customary care may change during the period of a clinical trial, either as a consequence of the trial itself (contamination bias) or as a consequence of changing background of scientific information (maturation bias). These problems could undermine the **scientific validity** and **value** of an effectiveness study, and unfavorably change the **risk-benefit ratio**.

Consequently, subject to certain conditions, there is justification for protocolizing care in the control arm. In such instances, the investigator must, in good faith, attempt to ensure that the protocol is reflective of usual care, which ideally represents best current practice. Appropriate observational studies, surveys, and other preparatory studies and pilot trials will help to inform this design. Furthermore, although its intent is to mimic usual care, the decision to protocolize care in the control arm may result in denying participants some of the individualized care that would have been provided, for better or worse, if they had not consented to participate in the clinical trial. Therefore, careful explanation of these distinctions is mandatory in the **informed consent** process. These considerations apply both to experiments comparing a novel intervention to best current practice and to experiments comparing alternatives within the spectrum of customary and reasonable care.

g. Nature and scope of intervention. There are several obvious ethical requirements when selecting and tailoring the intervention under study. For example, the dose, timing, and route of delivery of a drug should all be selected to increase likelihood of success, which affects **value**, **validity**, and **risk-benefit ratio.** Understanding the nature and scope of the experimental intervention is essential for **informed consent**, and is required by federal regulations in the United States (the Common Rule [26]).

h. Monitoring and stopping rules. There are several ethical requirements for careful monitoring and stopping rules in all clinical trials. The primary purpose of the monitoring and stopping rules is to ensure protection of participants. This should be accomplished by an independent data safety and monitoring board (DSMB) or reasonable facsimile empowered by explicit statistical stopping rules and contemporary *ad hoc* review of adverse events (27, 28). Failure to have such a process threatens the **validity** and **value** of a clinical trial if it is terminated prematurely and may adversely influence the **risk-benefit ratio** and **respect for participants** if it is continued inappropriately. Although some studies have been stopped prematurely, others have been allowed to continue longer than they should, and patients have been harmed as a result (29, 30).

i. Ethical checklists. The scientific rigor and quality of clinical trials have been improved by the explicit identification and systematic incorporation of key scientific design elements, such as the required use of PHS Form 398, which specifies the application format and issues related to human subjects that must be addressed, for grant submissions to the NIH in the United States. A similar process for key ethical requirements may improve the ethical quality and rigor of clinical trials. To this end, we propose that Emanuel and colleagues' (9) seven ethical requirements (Table 2) be incorporated in the design, implementation, and monitoring of clinical trials through the use of ethical checklists, templates of which we have provided (Tables 4 and 5). The checklists might be used by investigators and IRBs or REBs before and after study protocol approval.

Recommendation:

6. Incorporate ethical checklists in clinical research design and implementation (Tables 4 and 5).

D. OBTAINING CONSENT FOR RESEARCH IN CRITICAL CARE

Principle

7. Critically ill patients rarely have the capacity to consent to participate in research, and therefore need special protection. As discussed earlier, most critically ill patients lack the capacity to provide voluntary and informed consent to participate in research, and family members or other surrogates usually are called upon to provide informed consent for tests and treatments for them in the United States and Canada. Some have questioned the legitimacy of obtaining consent from surrogates, citing data indicating that surrogates do not consistently make the same choices that patients would make for themselves (6). However, a recent study concerning research in the ICU suggests that

TABLE 5. AN ETHICAL CHECKLIST FOR CLINICAL RESEARCH IMPLEMENTATION AND MONITORING

1. Do new data or hypotheses undermine the social or scientific value of the ongoing study? (i.e., does it still matter?)
2. Do new results from this or other studies unfavorably alter the risk-benefit ratio? (i.e., are risks still minimized and reasonable in relation to benefits to participants?)
3. Is the participant selection process working as intended and designed? (i.e., is it fair?)
4. Are investigators carrying out the study as intended and designed? (i.e., is it valid scientifically?)
5. Are the data and safety monitoring procedures, including the detection and reporting of adverse events, working as intended and designed?

surrogates predict the choices of patients with a reasonably high degree of accuracy (31). Furthermore, regardless of the degree of agreement between patients and surrogates, most patients would prefer to have medical decisions made by a close friend or family member (32).

Surrogates who provide informed consent for research must recognize that they have agreed to be a "trusted proxy" for the patient. They have an obligation not only to determine whether enrollment of the patient into the study is compatible with the patient's wishes or in the patient's interests, but also to faithfully represent the participant's interests throughout the course of the research.

While surrogate consent for research can be justified and supported from an ethical perspective, its status in the law is more ambiguous. Most states in the United States, for example, are silent on this issue, although California and Virginia recently created statutes that define which surrogates can consent for research participation and under what circumstances. These statutes do not delineate essential safeguards for vulnerable participants, but they are an important first step in codifying what sort of participation is allowed (33).

Recommendations:

7a. For patients unable to give informed consent, consent should be sought from a surrogate who is capable and willing to be a trusted proxy for the patient.

7b. Laws should be developed to recognize the legal authority of surrogate consent for research.

Principle

8. Informed consent is not a signature on a form, but a process that continues throughout the course of a clinical study. Investigators have an obligation to regularly reassess whether the continued participation of a participant in a study is desired by the participant, and whether it is in the participant's best interest. In particular, consent from the participant must be sought if and when the participant's condition improves to the point where he or she regains decisional capacity.

Recommendation:

8. Investigators should acknowledge the continual process of informed consent by revisiting the decision with the surrogate when possible, and obtaining delayed consent directly from the participant, if and when the participant regains decisional capacity.

Principle

9. Investigators show respect to study participants by involving them in the research process. The purpose of research is primarily to benefit future patients, and research participants make an inherently altruistic choice when they agree to participate in a research project, even if they also seek personal benefit. Involving them in the research process accords them the respect they deserve, as does allowing them to withdraw from the research and protecting their privacy through confidentiality (9). A secondary consequence is the potential increased willingness of others to participate in worthwhile and important research. One important way to involve participants in the research process is to share with them the results of studies to which they have contributed (34). For example, investigators might provide participants with key scientific publications or succinct summaries of study findings once they are published. Caution must be taken to ensure that the studies are not misinterpreted by participants.

Recommendation:

9. Investigators should consider disseminating the results of their work to their study participants to honor their participation.

Principle

10. Some interventions tested in ICU studies have the potential to benefit participants, whereas others have no immediate therapeutic potential. Both types of interventions also have the potential to cause harm. Investigators must communicate the risks and benefits of both types of interventions as part of the process of obtaining informed consent. Critically ill patients are, by definition, at high risk for death, and the interventions used to treat them may be associated with complications. Therefore, each intervention must be carefully weighed in terms of the risk-benefit ratio. Some have suggested that the risk categories used for research on children may also be useful in characterizing the risks and benefits of research on adults who lack decisional capacity (35, 36). For children, three acceptable categories have been defined: (*1*) interventions not involving greater than minimal risk (e.g., a physical examination); (*2*) interventions involving a minor increase over minimal risk, but likely to yield generalizable knowledge about the subject's disorder or condition (e.g., drawing blood); and (*3*) interventions involving greater than minimal risk, but presenting the prospect of direct benefit to the individual participants (e.g., a surgical procedure).

Similarly, when communicating the risks and benefits of a study, investigators should separate the interventions required by the study that have the potential for therapeutic benefit from those that do not, because although both types of interventions may place study participants at risk, they can only benefit from the former ones.

Most potentially therapeutic interventions in critical care research involve more than a minor increase over minimal risk. Using this approach, critical care interventions can be included in a research protocol only if there is a favorable balance between their potential for benefit and their attendant risks. Nontherapeutic interventions, on the other hand, could be included only if they fall into one of the first two categories above. Examples of nontherapeutic interventions that would fall into these categories might include blood sampling through existing catheters, additional tests performed on specimens obtained for therapeutic reasons, abstraction of data from the patient's medical record, and the like. Using this approach, even trials of high-risk therapies can be judged as ethically sound.

Recommendation:

10. The process of distinguishing between interventions that do and do not have the potential for therapeutic benefit, and then characterizing the risks and benefits of the interventions using the categories developed for pediatric research, may be a useful method for communicating about research to adult patients and surrogates.

Principle

11. Community education about critical illness is desirable, in part because of the time constraints under which consent for research participation must be obtained. That critical illness often evolves rapidly places significant time constraints on the process of obtaining informed consent. Surrogate consent for research participation would not be required so often if patients gave consent before they became critically ill. At the same time, interest in research among patients and surrogates might increase if they were more aware of critical illness, its consequences, and potential interventions, and the need for clinical research, as is the case with conditions such as cancer. For this and other reasons, community education about critical illness is essential. So is the consideration of techniques that begin the process of informed consent before patients become incapacitated.

One technique in use at some medical centers and in their respective ICUs is to familiarize patients and families on admission about the institution's commitment to research and the opportunities to participate in studies. A brochure or leaflet could convey this information. It might also include material describing the rights of patients and surrogates to refuse to participate in research if they are so inclined.

Recommendation:

11. Community and institutional education about critical illness should be promoted to facilitate informed consent, for example, through the distribution of informational brochures.

E. OVERSIGHT OF RESEARCH INVOLVING CRITICALLY ILL PATIENTS

Principle

12. The oversight process in the United States and Canada provides multiple levels of protection for participants in clinical research. Oversight is organized vertically at local and national levels and longitudinally before, during and after research is conducted. From a vertical perspective, oversight of the ethical conduct of human research in the United States includes activities by the primary investigators; the agencies or groups that sponsor the research, such as the NHLBI of the NIH; the local IRB; and the Office of Human Research Protection (OHRP) in the Department of Health and Human Services (37, 38). In Canada, the primary investigators and local REBs provide research oversight without a national equivalent of the OHRP.

Oversight of research conduct and patient safety begins with the investigator, who has first-line responsibility for the conduct of the research team, as well as the design, implementation, analysis, and reporting of the research results (39). At the next vertical level, the sponsoring agency or group can heavily influence the ethical conduct of research by requiring that the study be approved initially by a protocol review committee (PRC) and then monitored over its duration by a DSMB, as is the practice in large clinical trials supported by the NHLBI in the United States. Next, the IRB or REB provides local oversight of research programs and is responsible for ensuring patient safety and ethical conduct of research.

At the national level in the United States, the OHRP has the responsibility and the authority to regulate IRB activities and make sure that institutions comply with the federal regulations on human subject research. It also is empowered to serve as a liaison with various commissions and agencies to examine ethical issues in medicine and to promote the development of methods to improve the quality of programs for protection of participants in research. There are also additional bodies with oversight responsibility for some types of research. For example, the Food and Drug Administration in the United States and the Therapeutic Products Directorate of Health in Canada also have regulatory authority over new drugs and devices.

From a longitudinal perspective, oversight occurs before, during, and after the conduct of the research. Before the research begins, investigators should obtain review from peers and subsequently from the IRB or REB. In addition, initial review of the research protocol may be conducted by an independent PRC, if one has been established. While a study is in progress, oversight may be provided by a DSMB, which reviews data and adverse events at predetermined intervals, and is empowered to recommend stopping a trial without the approval of the investigators when predetermined criteria are met. The IRB or REB is also responsible for ongoing review of adverse events and other concerns that may arise. The OHRP and IRB/REB retain authority to investigate concerns and complaints, even after the research has been completed. The OHRP has the authority to suspend all clinical research at entire institutions until such investigations are complete.

For the oversight process to succeed, IRBs and REBs must be independent, expertly informed, and free of conflict of interest (13). They must have appropriate expertise for evaluating studies in critically ill patients, because ethical evaluation cannot be completed without understanding the scientific rationale for study design. Critically ill patients are a vulnerable population and special precautions are required to ensure their protection. Expert consultants who understand the challenges of research in critically ill participants should be used as necessary in the peer review process. Appropriate and timely reports should be provided to the IRB or REB from the investigator about adverse events.

In contrast to IRBs and REBs, which oversee the entire study, DSMBs are responsible for monitoring data about risks and benefits longitudinally during its course (40). Like IRBs and REBs, DSMBs must be independent, and have members with appropriate scientific and statistical expertise. The DSMBs and IRBs/REBs have complementary but sometimes overlapping functions, which can create confusion. Unfortunately, international standards do not exist regarding the composition, charge, funding, or reporting responsibilities of DSMBs.

Recommendations:

12a. Oversight is necessary to ensure uniform application of ethical standards for the protection of study participants, and to maintain public trust in critical care research.

12b. Investigators must understand the structure of the oversight process and use it constructively to protect patients and improve the quality of critical care research.

12c. IRBs and REBs should encourage a consent process that effectively and efficiently educates patients and their surrogates about the risks and benefits of participation without inadvertently inhibiting understanding with long forms.

Principle

13. Although the current oversight process is focused on compliance with regulations, the ultimate goal of the process is to foster a culture of responsibility in critical care research. For all the protection that IRBs/REBs and DSMBs provide, the ethical and scientific integrity of investigators is fundamental to the research process. Documents such as this, with its ethical checklists, are designed to inform prospective investigators about many of the requirements for ethically sound research. A recent publication by the Institute of Medicine provides expanded requirements, including those that should be understood by research institutions in addition to individual investigators (13). The NIH now mandates that investigators have at least a basic understanding of these requirements before they can participate in studies funded by that agency. More advanced understanding is highly desirable.

Recommendation:

13. Investigators must understand and meet the ethical requirements of clinical research and not rely solely on external oversight.

Principle

14. The oversight process in the United States and Canada can and should be improved. Research oversight for clinical studies has increased in complexity and has become, at times, cumbersome and confusing for investigators and study participants alike.

To improve the oversight process, efforts are needed to reduce unnecessary complexity in documents presented to patients and their surrogates, and to enhance coordination between the vertical and longitudinal aspects of oversight. National and international standards should be developed for the composition and function of DSMBs and their interactions with IRBs or REBs. The use of single national DSMBs to monitor large clinical trials has simplified the prospective monitoring of adverse events in some critical care studies. National IRBs or REBs for some multicenter studies would potentially reduce redundancy, and allow local IRBs and REBs to evaluate protocols that had already been evaluated by national experts (41). Finally, the OHRP should work together with local IRBs or REBs to promote consistent interpretation of national regulations.

Recommendation:

14. Improvements such as the standardization of DSMBs and coordination among IRBs/REBs are needed in the current regulatory environment to enhance the effectiveness, coordination, and consistency of the oversight process.

F. CONFLICTS OF INTEREST

Principle

15. Financial and nonfinancial conflicts of interest are prevalent in clinical research; they may occur at any stage and involve any individual in the research process. Conflicts of interest occur when investigators, research team members, IRB/REB and DSMB members, institutions, reviewers, or editors have financial or other relationships with persons or organizations that influence their actions, whether or not these individuals believe that these relationships affect their scientific judgment (42). Relationships that are less likely to bias judgment are sometimes known as dual commitments, competing interests, or competing loyalties.

Conflicts of interest in research may be financial or nonfinancial; financial conflicts are easier to define and quantify, whereas nonfinancial conflicts are more subtle and pervasive. Examples of financial conflicts include receipt of gifts or funds related to support of research, consultancy, honoraria, stock ownership, options, expert testimony, grants, patents, royalties, and discretionary funds. Examples of nonfinancial conflicts include investigator zeal, academic competition, ghost authorship, and personal, professional, or political relationships.

Conflicts of interest may have a negligible or substantial effect on judgment, and they do not necessarily represent scientific misconduct. Nevertheless, conflicts of interest have the potential to influence the conduct of research at any stage in the process and therefore should be identified. For example, overstatement of benefit or understatement of risk in the consent process challenges the ethical integrity of a study. Nondisclosure of conflicts to the IRB or REB and undue leniency in peer or institutional protocol review may undermine the scientific integrity of a study, and thus, public and professional trust.

Institutions themselves may have conflicts of interest because much of their prestige and financial support stems from their involvement in research. Although recognizing such conflicts may be more difficult for institutions than for individuals, institutions are just as responsible as individuals for dealing with them. External review of institutional conflicts of interest, as advocated by the Institute of Medicine, may help to identify and manage them (13).

Recommendations:

15a. All persons engaged in clinical research should recognize and disclose conflicts of interest and comply with existing mechanisms to deal with them.

15b. IRBs/REBs and similar institutional bodies should develop guidelines to monitor, clarify, and manage personal and institutional conflicts of interest. Professional societies such as the ATS should also consider developing guidelines.

Principle

16. The ethical conduct of critical care research does not stop with study completion, but extends through the dissemination of study results. Investigators have a responsibility to avoid publication bias by making available research protocols (for example, in publicly accessible trial registries) and disseminating their study results, even if investigators, institutions, or sponsors are financially disadvantaged by these results (43, 44). Honoring critically ill research participants requires that investigators, sponsors, peer reviewers, and editors meet the obligation to publish well conducted critical care studies regardless of their findings. As one method to ensure the dissemination of research results, all clinical trials should be registered at their inception (45).

Even if studies are performed capably, their published results may be subject to misunderstanding and misinterpretation. Misunderstanding may be lessened if the results are reported in a standardized fashion, such as that proposed by the Consolidated Standards of Reporting Trials (CONSORT) statement (46). At the same time, investigators should avoid reporting their results in such a way that the results could be interpreted simplistically. For example, investigators should stress that conclusions drawn from experience in one group of patients should not be extrapolated to all other groups.

Many biomedical journals, including the *American Journal of Respiratory and Critical Care Medicine*, now require a disclosure of financial conflicts of interest by authors (47). This reflects the potential for financial relationships to lead to biased analyses, nontransparent reporting, or duplicate publication of research results. In addition, the International Committee of Medical Journal Editors now recommends a statement from corresponding authors confirming, "I had full access to all of the data in this study, and I take complete responsibility for the integrity of the data, and the accuracy of the data analysis" (48). Such safeguards may minimize overenthusiastic treatment recommendations in publications sponsored by for-profit organizations evident after adjustment for study quality and the size of treatment effects (49). Similarly, conflicts of interest may bias the interpretation of meta-analyses (50), and the recommendations in practice guidelines (51).

Recommendation:

16. While conflicts of interest in clinical research cannot be eliminated, investigators, peer reviewers, and journal editors must recognize them and take steps to minimize and disclose them whenever possible during the process of research dissemination.

CONCLUSIONS

The ATS Conference on the Ethical Conduct of Clinical Research Involving Critically Ill Patients highlighted the need to revisit principles for the conduct of ethically sound clinical research in the ICU. While ethical principles guiding research have long been established among ethicists, they are less often discussed openly among critical care investigators, and less well highlighted in specialty journals. We hope that the recommendations from this conference will serve as stimuli to improve both the ethical and scientific integrity of research conducted on vulnerable patients in the ICU.

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