

**Ethical Issues of Recruitment and Enrollment of Critically Ill & Injured Patients for Research**

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Recruitment and retention of human subjects in research is a constant concern because the lack of a representative sample limits the generalizability of research findings. A large number of volunteer participants are needed to meet the expected demand of clinical research in all specialty areas of nursing. Critically ill and injured patients create special ethical challenges for nurse scientists and excellence in providing care to this population is dependent on the ability to systematically build the scientific foundation of critical care nursing. In order to do so, nurse scientists must be able to enroll and consent critically ill patients into their research studies. There are major challenges that can arise during the enrollment and consent process that are especially problematic in critically ill patients. In this column we describe several of these challenges and provide strategies for overcoming these challenges.

### Challenges

By its very nature, the onset of critical illness and injury often happens without warning and is life-threatening or life-altering. Because of the acuteness of an event leading to critical illness or injury, patients and critical care providers are often unknown to one another. Thus, at a time of intense physiologic instability and emotional turmoil, patients are faced with not only meeting new providers, but are expected to trust these providers in addressing their immediate care needs. Simultaneously providers must conduct rapid physiological assessments and make life determining decisions to stabilize the critically ill or injured patient in a complex, fast paced emergent environment. Family members may or may not be readily available to provide relevant medical information and in the case of injury, family members may have also experienced an injury in the same event. As definitive clinical goals are made, clinical decisions may be made to withdraw life sustaining treatment or not to resuscitate patients, which may be at odds with the goals of the clinical trial in which patients are enrolled.<sup>1</sup>

A challenge to conducting research with critically ill patients is acquiring informed consent since studies often require enrollment of critical care patients early in their care trajectory. Nurse researchers are faced with approaching patients and/or families for possible enrollment in a research study, when prior relationships between the patient and clinical team have not been developed and disturbances in family functioning and psychological distress may exist.<sup>2</sup> Indeed, in a recent study of attitudes of relatives of patients in intensive care and emergency departments, only 17% strongly agreed to research participation if they were critically ill and the provision of surrogate consent was only acceptable to 26% of respondents.<sup>3</sup> The first priority, however, must be on the stabilization and definitive treatment of the patient, which will always take precedence. Providing beneficent care and avoiding harm are ethical principles that providers are professionally committed to uphold.

A central tenet of consent is that the potential research subject is fully informed and freely consenting. Several problems common in critical care threatens the ability of the researcher in meeting this central tenet of consent. First, decision making capacity may be inadequate, requiring that patients' families or next of kin to serve as the surrogate decision maker for clinical decisions as well as research decisions. Loss of decision making capacity may be permanent as seen in severe brain injury, temporary as seen in recovery from general anesthesia, or fluctuating as seen with clinical instability due to hypoxemia or hypotension. Even when decision making is intact, the emotional burden of facing a life-threatening or life-altering illness or injury calls into question whether any patient or family can sufficiently process information to make an informed decision.

Fully informed research subjects are those who have had the opportunity to ask any and all questions and to have those questions answered to their satisfaction. Even in patients with

decision-making capacity, there are other hindrances in critical care that intrude on the important conversation between potential subjects and the research team. For example, there are patients who cannot verbally speak due to intubation or the presence of a tracheotomy. Thus, it is important to develop communication techniques appropriate to the situation.

Patients or their families are asked to carefully consider the benefits and risks of enrolling into a research study. In order to provide informed consent they need to understand the information provided, appreciate its significance to themselves, make decisions, and express a clear choice.<sup>4</sup> Their assessment does not occur in a vacuum, but rather in the midst of a life-threatening illness or injury and during a time when they are in the midst of multiple and competing demands. Repeated assessments, interventions, treatment decisions, and multiple diagnostic tests can consume the mental, emotional, and physical energy of patients and families and may push to the background decisions about entry into a research study.

Clinical care differs substantially from the focus of research. In clinical care, healthcare providers work with patients and families and focus on making optimal treatment decisions beneficial to the patients care. Research, however, is meant to generate new knowledge and “although many patients receive therapeutic benefits from participating in clinical trials,” the risk-benefit profile is not focused on direct benefit to an individual patient.<sup>5</sup> In clinical trials, the principle of clinical equipoise should be present. This means that a genuine medical consensus exists about the uncertainty of the therapeutic merits of the interventions being proposed.<sup>6</sup> Potential research subjects are informed of this. Nonetheless, research subjects often misconceive the value of participation - a problem known as therapeutic misconception –the belief of the patients that they will receive personalized medical care or therapeutic benefit from the study.<sup>7,8</sup> Critically ill patients are at exceptional risk for

therapeutic misconception and investigators' professional integrity requires them to assess each intervention with a patient-subject in order to discern whether it is aimed at patient care or at research.”<sup>5</sup>

Scientific advancements require the enrollment of patients who meet specific study entry criteria and high rates of refusal to participate threaten the validity of the study's findings. In research-intensive settings, it is common to have multiple studies being conducted at any given time. This means that critically ill patients may actually meet criteria for more than one study. In this event, there are several problems that need to be considered, including bombarding the patient with sequential visits by different study teams who want to explain their studies and secure consent and inadvertently introducing confounders into the study.

One example of a 'popular' patient population is the acute spinal cord injury (SCI) patient who is managed in a specialized center. Because there are only approximately 11,000 new SCI cases annually and because this is an injury that results in permanent, major impairment and high costs to the individual and society, research to improve outcomes is a high priority. It is not unusual in such specialized centers that several investigators are interested in enrolling patients in multiple studies.

#### Recommendations for Enrollment & Consent in Critical Care

Building the scientific foundation for critical care practice provides the impetus to manage the challenges experienced when enrolling and consenting critically ill and injured patients into research studies. We provide four practical recommendations to enhance enrollment into critical care studies. These recommendations include: establish a structured plan to assess and track decision making capacity; develop a consent process that is

commensurate with the study risk; consider a multi-step enrollment and consent strategy; and develop an integrated approach to recruitment into studies.

Evaluating decision making is a first step in evaluating patients for the appropriateness of directly approaching the patient for enrollment and consent. Although there are several instruments available that are aimed at evaluating decision-making capacity, critical care nurses are more than adequately prepared to evaluate decision-making capacity. It is important to move past the classic assessment of arousability and orientation to determine patients' abilities to process information at a level to allow the weighing of benefits and risks. Certainly speaking with nurses and physicians providing care to patients is an important first step, however, this cannot be the sole source of evaluation of decision making capacity. One reason for assessing beyond the clinician's report is the presence of reports in the literature that clinicians may very well miss delirium or fluctuating cognitive deficits. It is important that a member of the study team directly interact with patients and engage them in conversations in order to ascertain their abilities to become fully informed.

When patients lack decision-making capacity to provide informed consent for research, the team needs to know the specific state laws regulating family members who may consent for research purposes. Statutes and regulations can be a complicated legal and ethical area. Therefore, it is wise to consult directly with the human subjects review board of the home institution as to whom can provide consent on the patient's behalf. Critically ill patients who are entered into a study by a surrogate consent process, should be continually reassessed and when decision-making returns, these patients should then be consented directly. This respects their autonomous rights as human subjects and that the research remains consonant with their values and goals.

Research studies conducted with critically ill and injured patients range in risk from minimal-to-no risk to high-risk studies. Institutional review boards provide guidance in evaluating risk and their guidance should be sought and followed. However, the investigator is expected to propose the most appropriate ways to secure consent for study entry in a way that is commensurate with study risk.

In certain emergent life-threatening situations, an exception from informed consent (21CFR50.24 rule<sup>9</sup>) is allowed. An emergency research consent waiver can be obtained if the subjects' situation is life threatening and the present treatments are deemed unproven/unsatisfactory. There must also be the prospect of direct benefit to subjects; no practical way to obtain informed consent and a defined "therapeutic window" of when treatments must be given with efforts made to contact a legal representative within the designated time period. As such, the research could not be conducted without the waiver. Additional requirements to protect human subjects in emergency research include community consultation and public discourse related to the research. Surveys have shown that as many as 84% of patients believe that in an emergent situations, research should be undertaken, but that consent should be obtained as soon as possible from relatives or the patient himself.<sup>10</sup>

Consent processes may also be a multi-step process that escalated over time. In a study by one of the authors (TSR) a three step process was used to obtain consent to enter into a NIH-funded research study after injury. Step one consisted of a verbal consent to obtain simple baseline data while patients were in the emergency department and also permission to release the patients name to the research team. Step one was completed by clinically-based enrollers who resided in the unit and could identify patients who met entry criteria. However, these enrollers were not adequately prepared or sufficiently knowledgeable about the study to obtain

a full consent. Step two of the process included the random selection of potential subjects from the entire pool of potential candidates who had been identified by the enrollers. If randomly selected, a member of the study team would visit the patient in the hospital to obtain a written informed consent. For patients who were no longer in the hospital, step two consisted of a telephone script that informed patients of study details and obtained a fully verbal consent. Step three consisted of an in-person meeting where a full written consent was obtained.

An analysis of reasons provided by individuals who refused entry into surgical randomized clinical trials was recently published. Reasons for refusal included a preference for a certain treatment, dislike of the idea of randomization, and a potential for increase burden.<sup>11</sup> These reasons are most likely compounded in critical care or when critically ill patients are approached for entry into multiple studies. To minimize burden on patients and to maximize likelihood of enrollment, a strategy is to develop an integrated approach to study recruitment and enrollment.

Researchers often need to obtain a sample that is representative of the population of interest. Therefore, recruitment and enrollment are central to good science. Several issues need to be considered, including the fact that patients in more than one study may be overwhelmed by multiple approaches as well as the possible introduction of factors that will confound study findings. When patients meet criteria for more than one study, a coordinated team approach needs to be established. This is beyond the role of the human subjects board. However, it is well within the purview of the critical care working group or leadership team. In principle, the plan should take into consideration what studies can be conducted simultaneously without confounding the study or harming patients and also a decision tree that is fair and equitable to all study teams. Finally, the plan should consider the timing of recruitment and enrollment and



determine if patients should be presented study information at one time or if a time lagged approach would work.

### Summary

The ethical issues of recruitment and enrollment of critically ill and injured patients into research studies is central to the conduct of nursing research in critical care settings. Nurse scientists can anticipate and plan for the challenges that arise during the recruitment and enrollment of these vulnerable patients into research studies.

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