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The Ethical Concerns of Seeking Consent from Critically Ill, Mechanically Ventilated Patients for Research – A Matter of Possessing Capacity or Surrogate Insight

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Abstract

Conducting clinical research on subjects admitted to intensive care units is challenging as they frequently lack the capacity to provide informed consent due to multiple factors including ICU acquired delirium, coma, the need for sedation, or underlying critical illness. However, the presence of one or more of these characteristics does not automatically designate a potential subject as lacking capacity to provide their own informed consent. We review the ethical issues involved in obtaining informed consent for medical research from mechanically ventilated, critically ill patients, in addition to the concerns that may arise when a legally authorized representative is asked to provide informed consent on behalf of these patients.

INTRODUCTION

The task of conducting clinical research involving critically ill subjects in intensive care units (ICUs) is especially challenging as oftentimes this vulnerable population may lack the capacity to provide informed consent. Although various jurisdictions may have slightly different definitions, most refer to capacity as “the ability to understand relevant information, appreciate the present situation and its consequences, and the ability to manipulate information rationally.”¹ These standards were developed initially with a focus on the capacity to consent to treatment, not research, and are consistent with the definition of capacity in the United States. This may be due to a number of factors such as the presence of ICU acquired delirium, coma, the need for sedation, or underlying critical illness. Conversely, the presence of one or more of these characteristics does not automatically designate a potential subject as lacking capacity to provide their own informed consent. For example, a patient with respiratory failure from pneumonia, who is awake but requires mechanical ventilation for respiratory support and does not need sedation for comfort, may possess adequate capacity to understand the risks, benefits, and alternatives to participating in a clinical research trial, thus, allowing him or her to provide their own informed consent for the study. Such is not always the case, as mechanically ventilated patients are commonly

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sedated in an effort to maintain comfort, or are comatose due to their underlying critical illness.

Physicians caring for critically ill patients in ICUs often directly approach a loved one or designated surrogate decision maker for clinical management decisions, rather than attempting to discuss the situation with the patient themselves. In the case in which a patient is mechanically ventilated but is awake, interactive, and non-verbal the dilemma exists as to whether the patient actually has the capacity to provide full informed consent from a research and clinical management perspective. Because of the potential vulnerability of these critically ill patients, it is important to ensure that all aspects of the study are fully understood by the patient to avoid exploitation of this vulnerable population – and further avoid the potential for suspect research misconduct, a likened to the Willowbrook Experiments, the Tuskegee Syphilis study and the World War II Nuremberg trials.

Given the high morbidity, mortality and financial burden associated with mechanically ventilated, critically ill patients,^{2,3} clinical research on this population is necessary in order to determine management strategies and therapeutic modalities to improve outcomes. When including mechanically ventilated, critically ill patients who are supposedly able to provide their own informed consent for research studies, the investigator must use a method insuring capacity and understanding are present in the potential subject. Such strategies will be discussed in detail, including the advantages and disadvantages as well potential ethical questions that may exist when using such methods to ensure capacity and understanding when obtaining informed consent.

OBTAINING CONSENT FOR RESEARCH IN CRITICALLY ILL SUBJECTS

As mentioned, obtaining informed consent for clinical research from critically ill patients is often difficult, due to various reasons. Thus, frequently consent is obtained from a surrogate decision maker or legally authorized representative (LAR) who exercises “substituted judgement” to make decisions that they believe would be consistent with what the patient would have chosen in a given situation.⁴ A unique, often under recognized situation is the difficult task of obtaining informed consent for critical care research from the patient who is critically ill, but awake, interactive but non-verbal due to mechanical ventilation. Communication with these patients is frequently difficult, often relying on the patient writing on paper. Oftentimes, when patients are also unable to write, it may be necessary to communicate with closed ended questions requiring “yes” or “no” answers as means of communicating. This is a problem in particular for patients who were independent community dwellers who maintained a high level of functional independence in society, in contrast to institutionalized or chronically ill patients who reside in nursing homes or long-term care facilities. The resident of a nursing home or long-term care facility who becomes critically ill, may need medical assistance daily in addition to help with their basic needs, and may be limited with their ability to communicate at baseline. These patients are in contrast to the community dwellers who assumedly possessed the ability to communicate prior to critical illness.

OBTAINING CONSENT FROM CRITICALLY ILL, MECHANICALLY VENTILATED PATIENTS – POSSESSING CAPACITY AND THE ACCURACY OF A SURROGATE

It has been recommended that investigators who conduct trials involving critically ill, mechanically ventilated patients should assess potential subjects' capacity to make their own decisions,^{5,6} as well as comprehension of their participation in the study.⁷ This task often falls on the investigator during their initial screening evaluation of the subject for eligibility. Thus, it is necessary for the investigator to be completely objective when performing his or her assessment potential subjects' possession of capacity. In addition to close monitoring by institutional review boards, as well as the requirement of clinical trials to have oversight by data safety monitoring committees, many study enrollment protocols which involve critically ill patients include a tool to assess capacity. These tools are used with every potential subject to be enrolled in a study. The tools usually incorporate a short series of probing, open ended questions. Such questions may include: 1) "Can you tell me what will happen if you decide to be in this study?" 2) "How will being in this study help you?" 3) "Can anything bad happen to you by being in the study?" 4) "What do you need to do (who do you talk to) if you do not want to be in this study?". The use of such tools allows the investigator to make an objective assessment of capacity. The main issue with the use of such tools to assess capacity and formal understanding of their requirements of involvement in a research protocol is that the patient may not be able to verbally express their concerns or easily ask questions regarding the protocol because of their mechanical ventilation requirements. Although this may complicate the procurement of informed consent from a mechanically ventilated patient, if the patient apparently maintains capacity to provide consent to participate in a study (i.e. written, or on a tablet computer), the approval should be valid.

The enrollment of critically ill patients receiving mechanical ventilation may pose another problem, as their ability to freely verbalize and answer open ended questions may be limited and not truly reflective of their capacity. Although some physicians may seek to obtain consent for clinical decisions or research studies from a surrogate or a LAR, who supposedly acts in the best interest of the patient, the means of obtaining the patient's true perception of the research study at hand is through direct consent of the patient if they possess capacity. Despite some patients needs for mechanical ventilation, renal replacement therapy, vasopressor agents and/or other life sustaining modalities, patients suffering from critical illness are not necessarily incapacitated.

Recent studies demonstrate greater than half of the patients admitted to an intensive care unit receiving mechanical ventilation are able to conduct meaningful communication, if assisted with communication tools, such as a pen and paper or a whiteboard.⁸ In the case of a clinical trial, meaningful communication is the patients' ability to comprehend what the investigator explaining to them – including study risks, potential benefits, and what the potential subject needs to do if they wish to withdraw from the study. Thus, it is conceivable that the majority of patients admitted to an ICU could provide their own consent for research studies. If an investigator attempts to obtain consent from a critically ill patient who can provide their own

informed consent, the onus falls on the investigator to ensure the risks, benefits, study activities and patient responsibilities are clearly and unequivocally understood by the patient as a potential study participant. If a patient can give informed consent, but not physically sign the consent form, a witness's signature for informed consent can be obtained, with the requirement that the patient sign the consent form when they are able. Such is standard practice for investigators enrolling critically ill patients per most institutional review boards. In cases that are not straightforward, with even slight uncertainty existing as to whether a critically ill subject possesses capacity to make their own decisions, a qualified professional - usually a psychiatrist or psychologist - should be should assess the potential subjects' decision-making ability.⁹ These specialized professionals will not only assess for capacity, but also test for neuropsychological impairments and other psychiatric etiologies which may elucidate reasons for limited capacity.¹⁰

PROBLEMS WITH SURROGATE INFORMED CONSENT

Although seemingly a quick and easy solution for the investigator, the incorporation of proxy consent into a study of intubated, mechanically ventilated patients may not necessarily be the best consent process for the patient. This may be due to reality that despite the LAR being a spouse, close relative or friend of the patient, the LAR cannot know with 100 percent accuracy the patient's true preferences with respect to their views on participating in a proposed study at the time. One study noted surrogate decision makers for critical-care research resulted in false-positive consent rates of 16 to 20.3%, depending on the risk of the study (low vs. high).¹¹ These discrepancies between have been shown to increase depending on the risk of the study, with higher risk studies resulting in more surrogate and patient discrepancies.¹²

Another problem with obtaining informed consent from a patient's LAR is that the surrogate may be psychologically or emotionally distressed by the ordeal of having a loved one in the ICU. Thus, the reasoning and thought process that led to the decisions made by the surrogate on behalf of the patient may have been affected by the mental stress or anxiety of the situation. The psychological stress of having a loved one admitted as a patient in an intensive care unit has been shown to result in anxiety and depression (in 73.4% and 35.3% of family members, respectively),¹³ as well as learned helplessness,¹⁴ and acute post-traumatic stress disorder.¹⁵ These psychological states are not only the direct result of having a loved one as a patient in an ICU, but also arise from other various factors such as poor communication by the physicians caring for the patient,¹⁶ leading to heightened uncertainty and anxiety regarding the patients prognosis, and sleep deprivation leading to cognitive impairment and disruptions in daily routines which can further influence the decision making process.¹⁷ Thus, given the potential for cognitive impairment and impaired decision making process, investigators must be cautious when obtaining consent form surrogate consent from LARs in the research involving critically ill subjects, as the rationale and capacity of the surrogate themselves may be impaired.

Even if informed consent is obtained from an LAR, allowing a patient to participate in a research study, some potential problems can arise later in the course of their enrollment, particularly if, upon regaining capacity, the patient decides they do not wish to participate in

the study despite the initial consent provided by the LAR. This situation presents a dilemma as now the question emerges as to what to do with the patient's study information or data. It can be argued that the collected data should be discarded - as if the patient never gave informed consent - and that the patient should be counted as screened but not consented. This situation, however, would result in wasted resources in the form of study personnel, intervention treatments/drugs, and investigators time, depending on the design of the research study. Then the question arises as to whether the subject was improperly enrolled into the study, or if improper conduct of research was committed. In the most extreme cases, if an invasive intervention is required in a study, the possible subject of coercion or criminal battery may be called into question. Such are the reasons that justify full institutional review board (IRB) evaluations of protocols to ensure safety of participants in human subjects' research, and prevent the unethical conduct of research like the Willowbrook Experiments, the Tuskegee Syphilis study and the World War II Nuremberg trials - trials which vulnerable populations were harmed or had treatment withheld intentionally (mentally retarded children infected with hepatitis B, impoverished negro males infected with syphilis and not treated with penicillin, prisoners of war subjected to unsubstantiated "medical procedures").

PROCEEDING WITH OBTAINING INFORMED CONSENT FOR CRITICALLY ILL PATIENTS' PARTICIPATION IN CLINICAL TRIAL RESEARCH

In summary, from an ethical standpoint, it is clear that the most straightforward method to obtain informed consent for clinical trials involving critically ill patients is from the patient themselves, regardless if they are intubated and mechanically ventilated or not. Although this method is the most time consuming in the intubated mechanically ventilated patient due to the verbal communication limitations, it will avoid any uncertainty in patients' willingness to participate, in addition to preventing potential discrepancies that may arise when an LAR gives surrogate consent for participation in studies for patients lacking capacity. Alternatively, in patients who clearly lack capacity to give their own informed consent, the permission to participate in a study can be granted by an LAR on behalf of the patient, but the investigator needs to be aware of potential issues with consenting the surrogates as 1) the LAR themselves may have their decision making capacity impaired due to the emotional and/or psychological stress of having a loved one admitted to an ICU,¹⁸⁻²¹ 2) the potential disqualification of the patient if/when they regain decision making capacity if they decline to give informed consent and, although less likely, 3) the possibility of reprimand or disciplinary action if the investigator is found to be responsible for research misconduct, specifically coercion or undue inducement.²² The importance of human subjects' research of critically ill patients cannot be emphasized enough, however, moving forward in this field of science should not come at the expense of not properly obtaining informed consent from critically ill patients that are willing and able, emphasizing "proper" to include disclosure, understanding, voluntariness, and competence of the potential subject.²³ Ideally, a uniformly accepted procedure for consenting critically ill patients who are mechanically ventilated, but maintain the ability to communicate should be adopted for all investigators performing clinical research on critically ill patients.

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