

Unresolved legal and ethical issues in research of adults with severe traumatic brain injury: Analysis of an ongoing protocol

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Abstract—This paper synthesizes federal and state laws and bioethics literature with observations from an ongoing research protocol to identify, define, and clarify the unresolved legal and ethical issues regarding research involving adults with traumatic brain injury (TBI). Solutions that protect rights and minimize unnecessary impediments to valuable clinical and scientific inquiry are also illustrated using the same protocol. Research was performed at intensive care, inpatient rehabilitation, and long-term acute chronic hospitals. Our research protocol identified five areas of law impacting adults with TBI: advanced directives, healthcare surrogacy acts, probate acts, power of attorney acts, and the Health Insurance Portability and Accountability Act. The published bioethics literature and responses from local Human Subject Institutional Review Boards (IRBs) suggest that some of the unresolved ethical issues in research include defining vulnerability, defining informed voluntary consent, determining competency and/or decision-making capacity, using caregivers as subjects, and conducting multisite cooperative studies. Collaboration with IRB members and administrators as well as legal and research ethic scholars developed procedures that protect rights while avoiding unnecessary impediments to research. Investigations of persons with TBI and other cognitive impairments are governed by

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complicated and inconsistent regulations within the Common Rule and federal and state statutes. A need for clear and consistent regulatory guidance regarding multisite studies of TBI persists. In lieu of regulatory guidance, carefully researched solutions for critical peer review are needed to guide future multisite investigations of TBI.

Abbreviations: CFDA = Catalog of Federal Domestic Assistance, CFR = Code of Federal Regulation, DoD = Department of Defense, HIPAA = Health Insurance Portability and Accountability Act, IHCSA = Illinois Health Care Surrogacy Act, ILWA = Illinois Living Will Act, IPAA = Illinois Power of Attorney Act, IRB = Institutional Review Board, LTF = losses to follow-up, MHCDA = Minnesota Health Care Directives Act, NBAC = National Bioethics Advisory Commission, ORCA = Office of Research Compliance and Assurance, OPRR = Office for Protection from Research Risks, OPRS = Office for the Protection of Research Subjects, PI = principal investigator, TBI = traumatic brain injury, USC = United States Code, VA = Department of Veterans Affairs.

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INTRODUCTION

Research involving persons with traumatic brain injury (TBI) is essential if we hope to address questions regarding rehabilitation effectiveness and outcomes, but unresolved legal and ethical issues about involving cognitively impaired persons in research place the scientist in a situation that could impede and/or dissuade valuable scientific inquiry. An ongoing multisite research protocol, involving persons with severe TBI, is described in this paper as a means to examine unresolved legal and ethical issues throughout the continuum of recovery from TBI. The scientific aspects of the research protocol are presented in abstract format in **Figure 1**, and the research protocol is referred to, from this point forward, as “the protocol.”

FEDERAL AND STATE LAWS AND REGULATIONS GOVERNING RESEARCH WITH HUMAN SUBJECTS

This section provides background regarding the laws and regulations that must be followed to protect the rights of human subjects during the process of obtaining informed volitional consent. Each of the three subsections summarizes different aspects of the federal and state laws and regulations governing research with human subjects. Federal regulations governing federally funded research, generally called the “Common Rule,” and the origins of these regulations are summarized in the

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first subsection [1]. The next subsection is titled “Informed Voluntary Consent for Vulnerable Populations” and examines and illustrates the unresolved issues impacting research involving persons with TBI at the federal level. The third subsection titled “The Common Law and State Statutes” examines the same issues, but at the state level. The protocol is used throughout the second and third subsections to illustrate the unresolved legal issues. It is also used to highlight the observation that even if the existing laws and regulations were clear and consistent, pertinent ethical issues would remain unresolved.

The first issue examined in the second and third subsections relates to the federal definition of vulnerability and how the federal definition influences a local institution’s capacity to protect the rights of persons with TBI to informed voluntary participation. The concept of voluntary consent leads to related issues including unintended coercion and therapeutic misconception. Therapeutic misconception relates to perceived benefit and this leads to issues related to “minimal risk” versus “more than minimal risk” as well as issues specific to military subjects. The stipulation that consent must be informed leads to issues related to the use of the terms “competency” versus “capacity.” Another issue arises from the state of medical science; that is, insufficient evidence exists to have a standard definition for clinical consciousness. The last issue relates to informed consent for caregivers. Solutions addressing the unresolved issues include customized proxies and a project oversight committee. These and other solutions are described later in the results section of this paper.

Federal Regulations and the Common Rule

Federal departments and agencies that fiscally support research with human subjects have adopted a Common Rule outlined in Title 45 Part 46 (Subpart A) of the Code of Federal Regulations (CFRs) protecting the rights of human subjects [1]. The adoption of these regulations can be traced back to the Nuremberg Military Tribunal following World War II, where Nazi physicians were convicted of crimes against humanity for their role in wartime medical experiments. The tribunal drafted the Nuremberg Code stipulating that research with humans must be guided by basic ethical principles including a person’s right to make an informed decision to voluntarily participate in research. The U.S. Surgeon General stipulated in 1966 that oversight and enforcement of

PROTOCOL ABSTRACT

Problem Statement

The absence of a reliable and valid measure of neurobehavioral functioning in unconscious persons has impeded the identification of prognostic indicators of neurological recovery following severe traumatic brain injury (TBI). A neurobehavioral measure needs to be sufficiently sensitive for detecting subtle indices of and changes in functioning. The research objectives of the protocol are to (1) construct a neurobehavioral measure of functioning in unconscious persons that is sensitive to changes in neurobehavioral functioning over time and (2) identify the factors likely to influence functional recovery.

Study Design

Longitudinal observational validation and outcomes study.

Study Sample

Persons 18 years of age or older who incurred a severe TBI and who are unconscious at the time of protocol enrollment. The sample comprises active duty military personnel, veterans, and civilians.

Settings

One neuro/spine intensive care unit, two in-patient rehabilitation hospitals, and one long-term acute chronic hospital.

Instrumentation

The Disorders of Consciousness Scale (DOCS) and the Glasgow Coma Scale (GCS) are used to measure neurobehavioral integrity.¹ The DOCS and GCS are noninvasive bedside evaluations employing sensory stimulation to elicit behavioral responses as indicators of neurobehavioral functioning. Functional outcome is measured using three questionnaires: the Satisfaction with Life Scale (SWLS),² the Craig Handicap Assessment and Reporting Technique (CHART),³ and the Functional Independence MeasureTM (FIM).⁴

Methods

The DOCS and GCS evaluations are repeated every 7 days for at least 3 weeks while the subject is in the hospital and/or until she or he recovers consciousness.¹ During hospitalization, research staff observe each subject weekly for indications of consciousness. This observation takes 10 to 15 minutes, and it is conducted during the subject's routine medical care.

Research procedures conducted after hospital discharge depend on the subject's state of consciousness when discharged. If the subject is not conscious when discharged from the hospital, then research staff contact the participant's legal representative once a month, up to 12 to 15 months after the date of the subject's injury to determine if the subject is showing signs of consciousness. Monthly phone calls last approximately 10 to 15 minutes. The last phone call is made 12 to 15 months after the subject's date of injury, and it includes the questions from the FIM and CHART. If the subject has recovered consciousness at the time of this final phone interview and is able to participate, then the SWLS is also administered. During this final interview, research staff speak with the subject's primary caregiver. The caregiver is the person who the legal representative identifies as knowing what the subject is and is not able to do for her- or himself. The caregiver may, for example, be the legal representative, someone the legal representative has hired, a family member, and/or a friend; this interview takes approximately 30 minutes.

Risks and Burden

Risk is minimal to the patient and burden is minimal to the legal representative and/or primary caregiver. Discomforts for the subject may include frustration, agitation, physical discomfort, and fatigue in response to stimulation, and a burden to the legal representative and/or primary caregiver includes answering questions about the subject.

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Figure 1.

Measurement, treatment effectiveness, and outcomes after severe brain injury.

these principles, for any research funded by the Public Health Service, are to be conducted by local institutions and committees. This policy was codified in 1974 in the Department of Health, Education and Welfare as regulations known as 45 CFR 46 [1,2].

Authority for medical studies involving human subjects in the military is through 45 CFR 46, but is accompanied by additional Department of Defense (DoD) directives on the implementation of 45 CFR 46 at U.S. Code (USC) 10, Section 980 [3]. The Department of Veterans Affairs (VA) has also concurred in 45 CFR 46; additional information and clarification specific to the VA are described in the VA M-3 manual, Chapter 9 [4].

At the time the protocol was implemented, the Office for Protection from Research Risks (OPRR) served as the oversight office for the Department of Health and Human Services. Since that time, a new office has been established to replace the human studies protection function of OPRR. The new Office for Human Research Protections monitors programs for the protection of human subjects at universities, hospitals, and other medical and behavioral research institutions with federally funded research. The VA also has an established oversight office called the Office of Research Compliance and Assurance (ORCA). ORCA is charged with advising on matters affecting research integrity in the protection of humans and animals, promoting enhancements in the ethical conduct of research in conformance with regulations and policies, and investigating any allegations of research improprieties and misconduct.

Regulations and Laws Governing Informed Voluntary Consent for Vulnerable Populations

The sample in the protocol is specified by federal regulations to be a vulnerable population because the participants have mental impairments (45 CFR 46, Subparts B, C, and D) [5]. Unconscious persons are vulnerable because their medical decision-making capacity is compromised. The subject is unconscious at time of protocol enrollment and the concept of vulnerability should, therefore, also encompass the subject's legally authorized representative. This is complicated further because a state of altered consciousness can be a chronic condition and/or a transition during recovery. If a subject recovers consciousness, she or he is likely to have residual memory and cognitive impairments that fluctuate throughout recovery [6-8]. Cognitive impairments have been

described by Moreno et al. as existing by varying degrees [9], but it is the fluctuation throughout recovery from TBI combined with the nature of the residual memory and cognitive impairments that set TBI apart from other cognitive impairments. Persons with TBI are vulnerable and need extra protection and the magnitude of vulnerability fluctuates throughout recovery, but the end point of recovery is unknown and/or nonexistent.

The magnitude of vulnerability is different throughout the recovery process and different for each of the subgroups making up the sample. Active duty military personnel and their legal representative (surrogate) may be vulnerable because they may consider the preferences of commanders when making decisions and because a soldier's ability to refuse some medical procedures is restricted.* The military subject's legal representative may feel pressured to provide surrogate consent if she or he believes that medical research participation is mandatory. This confusion may arise from mandated medical procedures (e.g., anthrax vaccine) prior to military deployment. The subject's legal representative may not understand the distinction between medical research and mandatory military medical procedures. These conditions also present the possibility of unintended coercion, and for this reason, the DoD revised Army regulations (ARs) covering medical subjects (AR 40-38) to state that commanders and other supervisors must not be in the room when a study is being explained to a potential subject and/or legal representative [10]. It is also likely that veterans who served in the armed forces for numerous years and their legal representatives may be susceptible to unintended coercion given long-term exposure to regimented conditions. Furthermore, veterans who obtain healthcare services from the Veteran Health Administration and who have no alternative source of medical care may have an unfounded fear of losing health benefits. The veteran's legal representative may also have this fear. These conditions may create unintended coercion to provide consent with veterans. Unintended coercion may also arise with civilians, soldiers, and veterans because of a sense of desperation given the seriousness of the injury.

*See for example., U.S. Air Force vs. Washington, 54 Military Justice (MJ) 936 (2001), in which the U.S. Air Force court of criminal appeals upheld a bad conduct discharge for willful disobedience of a superior officer's order to be inoculated with the anthrax vaccine.

Therapeutic misconception may also represent unintended coercion and, therefore, must be considered important when benefits and/or potential benefits are explained to the surrogate and/or subject. The Institutional Review Boards (IRBs) required that the researcher specifically state that direct benefit cannot be promised because the legal representative may feel a sense of desperation given the seriousness of the brain injury.* Legally authorized representatives may be hopeful that the subject will benefit from research participation and, despite explanations from researchers, may be more likely to consent to participation on behalf of the severely brain injured patient. Therapeutic misconception may persist even after the investigator explains to the surrogate that direct benefits for the subject should not be anticipated (45 CFR 46.111a) [1]. Paradoxically, the military site's IRB required the researcher to demonstrate how the research would benefit *all* subjects. This explanation was required because there is a federal regulation requiring research to have intent to benefit the subject [3], interpreted locally as demonstration of intention to benefit subjects. The benefit does not need to be actually realized, but it must be demonstrated to be intended. Therefore, at the nonmilitary sites, the investigator clearly must not promise direct subject benefit or potential benefit, but at the military site, the investigators must explain and even promise potential *direct subject benefit*. The latter interpretation placed the scientist in a position of conflict, and the principal investigator (PI) was not able to conceive of a reasonable solution that did not violate basic ethical principles. The project, at the military site, was tabled because of this issue and because of funding issues.

The regulatory guidelines defining "informed consent" stipulate that informed consent is a "legally effective" document (45 CFR 46.116) [1,8,11,12]. The language "legally effective" has lead local IRBs to multiple interpretations of what constitutes legally effective informed consent. Some IRBs interpret the regulations as requiring "competency" on behalf of the subject or the legally authorized representative, and some IRBs require documentation of "capacity." The terms "competency" and "capacity" are not defined in the federal regulations

and guidelines. Therefore, local IRBs look to other federal and state laws and its own guidelines to determine an individual's competency and/or capacity [9,13,14]. While the VA stipulates use of the term "competency" in the VA M-3 policy manual [4], other institutions and agencies look to the federal and state policy and laws overseeing their institution/agency to determine which term to employ and how to define it. The law stipulates that a person is competent unless proven to be otherwise. A court determines legal incompetence. While the National Bioethics Advisory Commission (NBAC) [15] report addresses issues only related to persons with mental disorders, these definitions are relevant to the TBI population, in that this report discusses how decisional impairment refers to a limitation that is not part of normal growth and development. The report discusses how the term "capacity" is more specific than the term "competent" because it specifies abilities to understand a condition and to know when action is necessary. Capacity is task specific, and when using this term, the researcher is obligated to specify the criteria being used to assess capacity, but no standard exists for assessing a person's capacity to consent or refuse research participation [16]. The NBAC report does discuss options for assessing capacity in the mentally disordered population [15, p. 17–20], but acknowledges that no standard exists for assessing capacity to consent or refuse research participation for any population [16–18]. The procedures for assessing capacity for persons with mental disorders may not be relevant to the TBI population because the selected threshold, for what is or is not capacity, will differ given that the origins of the decisional impairment are different. In 1998, the National Institute of Health commissioned further clarification from the NBAC [19], and these clarifications were published in 1999 [15], but issues related to the assessment of capacity pertinent to head trauma remain unresolved [9,17,18,20].

To further complicate this issue, a person who incurs a severe TBI will lose consciousness for a period of time; this could be a chronic or transient condition [21]. While the subject is in a comatose or vegetative state, his or her decision-making capacity is clearly compromised, but research distinguishing between minimal consciousness and consciousness poses additional unresolved issues because the *clinical criteria determining consciousness* are not universally agreed upon [22–24]. Research studying the recovery of consciousness must include criteria defining consciousness and when or if a participant

*An IRB is the institutional review mechanism for research projects that involve human subjects, and an alternative name used within the Veterans Health Administration is Human Studies Subcommittee.

recovers consciousness. The process of evaluating competency or decision-making capacity must be initiated at this point. Organic memory disorders subsequent to severe TBI will, however, pose problems to the evaluation. A study participant may, for example, verbally reiterate the definition of voluntary participation or recite the risks just told to him or her, but 1 hour or 1 minute later, the subject may not recall the conversation.

Those subjects in the protocol who survived up to 1 year after severe TBI and received caregiving support services served to highlight two additional issues related to the right to informed voluntary consent. At 1 year after injury, the participant may or may not be able to participate in an outcomes interview. If the participant is able to participate in the interview, then research staff attempt to include the participant. But to collect accurate data, research staff must confirm the data with the participant's primary caregiver. For the IRB, the PI defines the caregiver as the person who the participants' legal representative identifies as knowing what the participant is and is not able to do for him or herself. The *first issue* is that the participant's legal representative must identify the caregiver and provide permission for research staff to speak with the caregiver about the participant. The *second issue* relates to interviewing the caregiver about the participant. The caregiver is being drawn into the research, and therefore, she or he must be willing to participate in the research. The solutions addressing both of these issues, as well as other issues raised in this article, are discussed under the results section of this paper.

Common Law and State Statutes

The doctrine of informed consent in medical treatment has been well established in the common law (e.g., *Cruzan vs. Director, Missouri Department of Health* 497, U.S. 261 [1990]). This doctrine has been extended to protect the rights and privacy of an incapacitated subject by allowing a legal representative to make a medical decision for the subject on the basis of the subject's known beliefs and wishes. As state judiciaries began to develop standards that would allow a legal representative to make medical decisions on behalf of an incapacitated person, the system became confusing and unwieldy. Family and friends were often obligated to go through the court system to make any decision for an incapacitated individual. In addition, the courts from state to state enforced idiosyncratic requirements for both the decision-making standards and the burden of proof required for the legal

representatives when making a healthcare decision, which created delays, confusion, and insufficient guidance.

The legislature in a majority of states responded to these problems by enacting advanced directives, including living will statutes and health care power of attorney statutes. A living will allows a subject to delineate his or her desires for end-of-life care in the event that he or she is incapacitated at the time. A health care power of attorney is more flexible than a living will because it allows an individual to appoint an agent to make medical decisions in the case of incapacitation, and it allows for more unforeseen circumstances than does a living will. These instruments must be properly executed before the subject becomes incapacitated; if not, then these instruments are not legally effective. Unfortunately, most people do not execute either instrument. The family then must go back to the courts, unless the state has passed a surrogate decision-making statute for healthcare.

Surrogate statutes assign a priority status for the appointment of a legal representative to make healthcare decisions for a subject without having to go through court proceedings. Approximately 25 states have adopted healthcare surrogacy statutes. Although the National Conference of Commissioners on Uniform State Laws developed a Uniform Health Care Decisions Act (the "Uniform Act") in 1993, not every state has followed all of the provisions of the Uniform Act when enacting surrogacy legislation. Therefore, even among the states with surrogacy statutes, the requirements for surrogacy decision-making may vary. Further variation by institutions within the same state is also possible. An institution may, for example, not interpret a healthcare surrogacy statute as encompassing clinical or health-related research. A discussion of two state's statutes (Illinois and Minnesota) is used to illustrate the conflicts and distinctions among jurisdictions (see **Table**).

Illinois Statutes Regarding Informed Consent

In Illinois, the Medical Patient Rights Act (the "Act") affirms federal law by requiring that healthcare providers obtain informed consent before providing any non-emergency healthcare to patients [25]. The Act stipulates that informed consent must be received from a patient who is the subject of a research program or experimental procedure. When determining an individual's capacity to consent, medical providers and scientists should, for the purposes of clarity, follow the statute with the narrowest definition of decisional incapacity, and in Illinois, the

Table.
Statutes and consenting procedures for hospitals in Minnesota and Illinois.

Legal Topic	Illinois	Minnesota
Advanced Directive Acts	Living Will Act (1984) Illinois Power of Attorney Act (1987)	Minnesota Health Care Directive Act (1999) Minnesota Living Will Act (1999)
Health Care Surrogate Statute	Illinois Health Care Surrogate Act (1991)	None
Probate Act	Probate Act (1975)	Minnesota Probate Code
Narrowest Definition of "Capacity"	"The ability to understand and appreciate the nature and consequences of a decision regarding medical treatment or forgoing life-sustaining treatment and the ability to reach and communicate an informed decision in the matter, as determined by the attending physician and supported by one other physician." [*]	"Decision-making capacity" as "the ability to understand the significant benefits, risks, and alternatives to proposed health care and to make and communicate a health care decision." [†]
Persons Legally Recognized to Evaluate Patients Healthcare Decision-making Capacity	<ul style="list-style-type: none"> • Power of Attorney Act specifies a physician. • Illinois Health Care Surrogate Act: Concurring opinions of two physicians who assesses the patient's decisional capacity. 	<ul style="list-style-type: none"> • Not specifically stated in Patient Bill of Rights Act, Minnesota Health Care Directive Act, or the Minnesota Living Will Act. • The patient bill of rights states only that reasonable attempts must be made to determine if a patient has an advanced directive.
Criteria for Determination of Capacity Approved by Human Subjects Review Boards	<ul style="list-style-type: none"> • The attending physician is the designated person for defining initial decision-making capacity. • A qualified healthcare provider, other than a physician, can determine return to previously defined capacity. 	<ul style="list-style-type: none"> • Two concurring physicians during hospitalization and one after discharge are designated as the persons qualified to evaluate decision-making capacity. • After discharge, a mental health provider can evaluate and determine decision-making capacity; evaluation and determination should be documented in medical chart.
Narrowest Surrogate Hierarchy Approved by Human Subjects Review Boards	<ul style="list-style-type: none"> • Power of attorney • Court-appointed guardian • Patient's spouse 	<p>Obtaining permission of the surrogate to willingly act as legal research agent is required.</p> <ul style="list-style-type: none"> • Power of attorney • Healthcare surrogate designated by patient • Patient's spouse

^{*}Illinois Health Care Surrogate Act, effective 1991, Ch. 755 40/1 to 40/55 (1999).

[†]Minnesota Health Care Directive Act, 145C.01(1b) (1999).

most explicit and narrowest definition of incapacity is found in the Illinois Health Care Surrogate Act (IHCSA) (e.g., it does not necessarily follow, for example, that a person who has been adjudged disabled under the Probate Act is necessarily lacking in "decisional capacity" under the IHCSA) [26–28]. The IHCSA distinguishes between medical and medical research activities and defines "decisional capacity" as "the ability to understand and appreciate the nature and consequences of a decision regarding medical treatment or forgoing life-

sustaining treatment and the ability to reach and communicate an informed decision in the matter as determined by the attending physician" [29]. Under the IHCSA, getting a judicial determination of incapacity (the IHCSA eliminates the need for judicial involvement in the personal decision-making process and to protect the subject's privacy) is not necessary [30]. The attending physician only needs to determine that the subject lacks decisional capacity. At least one other qualified physician must concur in the determination that a subject lacks

decisional capacity, and the determination must be documented in the subject's medical record.

When a patient is determined to lack decisional capacity to consent regarding healthcare, four Illinois statutes govern how to determine who should be allowed to make healthcare decisions for the incapacitated person. The Illinois Power of Attorney Act (IPAA) [31], the IHCSA, the Probate Act [28], and the Illinois Living Will Act (ILWA) control surrogate designation in Illinois [32]. The IPAA allows a person (the principal), while he or she still has full capacity, to appoint an agent to make healthcare decisions for him or her (with or without some limitations) should the principal become incapacitated. The IPAA states "when a health care provider believes a patient may lack capacity to give informed consent to health care which the provider deems necessary, the provider shall consult with any available health care agent known to the healthcare provider who then has the power to act for the patient under a healthcare agency" [33]. Therefore, under the IPAA the healthcare provider has a duty to determine if the principal has already appointed an agent.* The ILWA allows a principal with full capacity to make a written declaration instructing an agent and/or physician how to make decisions concerning life-sustaining treatment when the principal is terminally ill. (Since a living will only pertains to end-of-life decisions, it is not relevant to this discussion.) The IHCSA statutorily appoints a surrogate to make certain decisions about healthcare in the case that no surrogate or agent has been appointed by the principal before he or she becomes incapacitated. Finally, the Probate Act allows a court to determine that a person is incapacitated for certain functions, such as healthcare decision-making, and to appoint an agent to make those decisions for that person.

An agent appointed under the IPAA may have the broadest range of decision-making powers of any legal representative for healthcare in Illinois, including a court-appointed guardian under the Probate Act. Unless the subject revokes an agency under the IPAA, even a court cannot grant another guardian powers that are already possessed

by an agent under a durable power of attorney for healthcare [34]. Also, an agent under an IPAA is not required to get a court order declaring the principal incompetent before exercising the delegated powers, but an attending physician must certify the patient as incompetent [35].

If no agent has been appointed under the IPAA, the scientist should then determine whether a guardian has been appointed by the courts specifically for this type of healthcare decision. If so, the guardian may consent to the procedure for the principal (subject). If no agent or guardian exists, then the scientist should look to the IHCSA to determine who may act as a surrogate medical decision-maker for the patient. Surrogates are appointed in the following designated order of priority:

1. The subject's guardian of the person.
2. The subject's spouse.
3. Any adult son or daughter of the subject.
4. Either parent of the subject.
5. A close friend of the subject.
6. The subject's guardian of the estate [36].

If two or more surrogates are in the same category, then those surrogates must make reasonable efforts to reach a consensus. If they disagree, a majority of the persons in the category "control," unless the minority initiates a guardianship proceeding [36]. The statute does not state what to do if no majority exists, although it provides for obtaining a guardian to break a tie [36,37].

Minnesota

Minnesota has a Subjects Bill of Rights requiring that written, informed consent be obtained before subjects participate in experimental research [38]. Subjects have the right to refuse participation, and both consent and refusal must be documented in the individual care record [39]. Under the Subject Bill of Rights, if a subject enters a healthcare facility unconscious or unable to communicate, the facility must make reasonable efforts to determine if the subject or resident has executed an advance directive regarding healthcare decisions [40].

The Minnesota Health Care Directives Act (MHCDA) is the main Minnesota statute governing surrogate healthcare decision-making [41]. The MHCDA allows a principal with full capacity to execute a written healthcare directive if he or she loses decision-making capacity [42]. A healthcare directive may include healthcare instructions to direct providers, family, and a healthcare agent. It may also include a healthcare power of attorney to appoint an agent to make healthcare decisions

*Also see The Federal Patient Self-Determination Act, 42 USC 1396(a) (2000). This Act requires health care providers to document, in a subject's medical record, whether the subject executed an advance directive. Health care providers must ask whether a subject signed a durable power of attorney for health care, a living will or any other type of advance directive for health care in order to be in compliance with this federal law.

for the principal when the principal, in the judgment of the principal's attending physician, lacks decision-making capacity. A healthcare directive may include a statement of the circumstances under which the directive becomes effective other than upon the judgment of the principal's attending physician [43].

The MHCDA defines "decision-making capacity" as "the ability to understand the significant benefits, risks, and alternatives to proposed healthcare and to make and communicate a healthcare decision" [44]. Since this definition is narrower than the definition of incapacity under the Minnesota Probate Code, this should be the definition that healthcare professionals use to determine incapacity for medical decision-making.

Minnesota has no surrogacy law to appoint and guide the identification of the legally recognized surrogate decision-maker if the subject has not executed an advance directive. In that case, family and friends of the subject must petition the courts to have a guardian or conservator appointed to make healthcare decisions for the subject.

The Minnesota Probate Code allows a court to appoint guardians and conservators to make healthcare decisions for an incapacitated person [45]. A guardianship or conservatorship *of the person* generally gives authority over healthcare decision-making, and a guardian or conservator of the person generally has the power to give any necessary consent for medical treatment [45]. The guardian or conservator must be made aware of any healthcare directive. Unless the principal has otherwise specified in the directive, the appointment of the healthcare agent in a healthcare directive is considered a nomination of a guardian or conservator of the person for the Probate Code [46].

RESULTS

Procedures for obtaining informed volitional consent need to be approved. Based on this need, the goal of each review board was to develop documentation and procedures for obtaining consent that protect subjects' rights to informed voluntary consent throughout their participation in the research protocol. The goal of the scientist was to protect rights while minimizing impediments and undue expense to the successful and rigorous conduct of the protocol. Following a review of the Common Rule, state statutes, and local IRB responses, the procedures

described in the following paragraphs were developed and revised after each IRB review. After each IRB from the Illinois and Minnesota hospitals approved the proposed procedures, subject enrollment was initiated.

As part of each IRB application, a procedure for *defining* and *determining lack of capacity* and *return to capacity* was proposed. The PI developed and revised the procedures with guidance from a local IRB panel member, local IRB administrators, a disabilities research ethics scholar, and a health-law expert. The health-law expert retains appointments within academic and private institutions, so the health-law expert was able to guide the PI for all three states because law students assisted with legal research.

The approved procedures included one critical form referred to as the "Consent of Proxy Form" (**Figure 2**). It is called this because it comprises the procedures that must be followed when informed voluntary consent is obtained and when surrogate or proxy decision-makers are involved. In hindsight, a more representative name would be the "proxy form," and it is referred to as such from this point forward. The Illinois and Minnesota IRBs both required Sections 1 and 2 of the proxy form. Each IRB follows different state statutes, and the content of these sections, as illustrated in **Figure 2**, was customized according to each IRB's requirements. Section 1 specifies a method for determining capacity upon admission of subject to the protocol, whereas Section 2 specifies the methods to be used for assessing capacity if a subject recovers consciousness after hospital discharge and/or during the follow-up phase of the study. The Minnesota IRB required two additional sections (3 and 4). Section 3 specifies a hierarchical procedure for identifying the legally recognized surrogate decision-maker and Section 4 specifies a procedure for determining the surrogate's willingness to act as the subject's legally recognized surrogate.

The first section of the proxy form comprises procedures for determining decision-making capacity that are specific to the protocol. As illustrated in **Figure 2**, two attending physicians determine incapacity upon hospital admission. This procedure was routine for each of the participating hospitals, and it was adopted for the protocol. The second section provides criteria for when capacity should be reevaluated and who can determine return to capacity. The proxy form for the Illinois and Minnesota sites stipulates that allied health professionals directly involved in the subject's medical care are only determining return to capacity if the subject had been

ILLINOIS	MINNESOTA
Section 1. Determination of Research Decision-Making Capacity: In-Patient Hospitalization	
<p>I am the Subject's attending physician. I have examined the Subject and have determined that the Subject does/does not (<i>clearly circle one</i>) have the capacity to consent to participation in the Study.</p>	<p>I am the Patient's attending physician. I have examined the Patient and have determined that the Patient does not have the capacity to consent to participation in the Study.</p>
<p>_____ Signature of Clinician with Credentials</p> <p style="text-align: right;">____/____/____ Date</p>	<p>_____ Signature of Attending Physician</p>
<p>_____ Signature of Witnessing Physician</p> <p style="text-align: right;">____/____/____ Date</p>	<p>I am a physician licensed in the state of Minneapolis. I do/ do not (<i>clearly circle one</i>) concur with the attending physician's determination of incapacity.</p> <p>_____ Signature of Witnessing Physician</p>
Section 2. Determination of Research Decision-Making Capacity: After In-patient Discharge	
<p>I am a _____ (<i>write in clinical profession</i>). I have examined the Subject and have determined that the Subject does/does not (<i>clearly circle one</i>) have the capacity to consent to participation in the study. I verbally explained, in person to the Subject, the purpose of the research, the Subject's expected participation, the risks, and the benefits. The following information was read to the Subject. Responses are recorded below: The risks of this Study are—</p> <ol style="list-style-type: none"> 1. Frustration and agitation in response to the questions. 2. Emotional upset. 3. That your information, like all of your medical information, could be disclosed in legal proceedings. 4. That other unknown side effects could occur. <p>There may be no benefits to you from the study. If you do not wish to be in this study, you will continue to receive care as provided by your physician. Do you wish to participate in this study of your own free will?</p>	<p>I am a _____ (<i>write in clinical profession</i>). I have examined the Patient and have determined that the Patient does/does not (<i>clearly circle one</i>) have the capacity to consent to participation in the Study. I verbally explained, in person to the Patient, the purpose of the research, the Patient's expected participation, the risks, and the benefits. The following questions were asked and the Patient's responses are recorded below:</p> <ol style="list-style-type: none"> 1. What does voluntary mean? 2. What will happen if you decide to not participate? 3. What will we ask you to do for the research? 4. What are the risks of participation? 5. Will you benefit? 6. Are there any benefits to the study 7. Other observations:
<p>_____ Signature of Clinician with Credentials</p> <p style="text-align: right;">____/____/____ Date</p>	<p>_____ Signature of Clinician with Credentials</p> <p style="text-align: right;">____/____/____ Date</p>
<p>_____ Signature of Witness</p> <p style="text-align: right;">____/____/____ Date</p>	

Figure 2. Consent of proxy: Substantive content (continued on next page).

ILLINOIS	MINNESOTA
<p>Section 3. Identification of Proxy</p> <p>NA</p>	<p>Informed consent to participate in the Study may be given for the Patient by a Proxy,” or substitute decision-maker. A Proxy may be any of the following individuals listed in paragraph A, in the order of priority listed, if no individual in a prior class is reasonably available, willing, or competent to act.</p> <p>A. Review the following list and write “Proxy” in the space provided to indicate the relationship of the individual who will provide informed consent for the Patient. If an individual with a higher priority exists but is not reasonably available, willing, or competent to act, indicate in the spaces provided the reason that the person is not available and make a note of any contact attempts by staff.</p> <ol style="list-style-type: none"> 1. Healthcare surrogate designated by Patient 2. The judicially appointed guardian of the Patient, who has been authorized to consent to medical treatment: 3. The Patient’s spouse. 4. A parent of the Patient. 5. An adult child of the Patient, or if the Patient has more than one adult child, a majority of the adult children who are reasonably available for consultation. 6. The adult sibling of the Patient or, if the Patient has more than one sibling, a majority of the adult siblings who are reasonably available for consultation. 7. An adult relative of the Patient who has exhibited special care and concern for the Patient and who has maintained regular contact with the Patient and who is familiar with the Patient’s activities, health, and religious or moral beliefs. <p>B. Informed Consent must be based on the Proxy’s Informed Consent and on the decision the Proxy reasonably believes the Patient would have made under the circumstances.</p>
<p>Section 4. Proxy Consent</p> <p>NA</p>	<p>I am over the age of 18 and willing and competent to make healthcare decisions for the Patient, including the decision to enroll the Patient in the Study. I have reviewed the attached Informed Consent to participate in the Study and have had the opportunity to ask any questions regarding the Patient’s participation. I certify that signing this Informed Consent to enroll the Patient in the Study described is not contrary to</p>

Figure 2.

Consent of proxy: Substantive content (continued on next page).

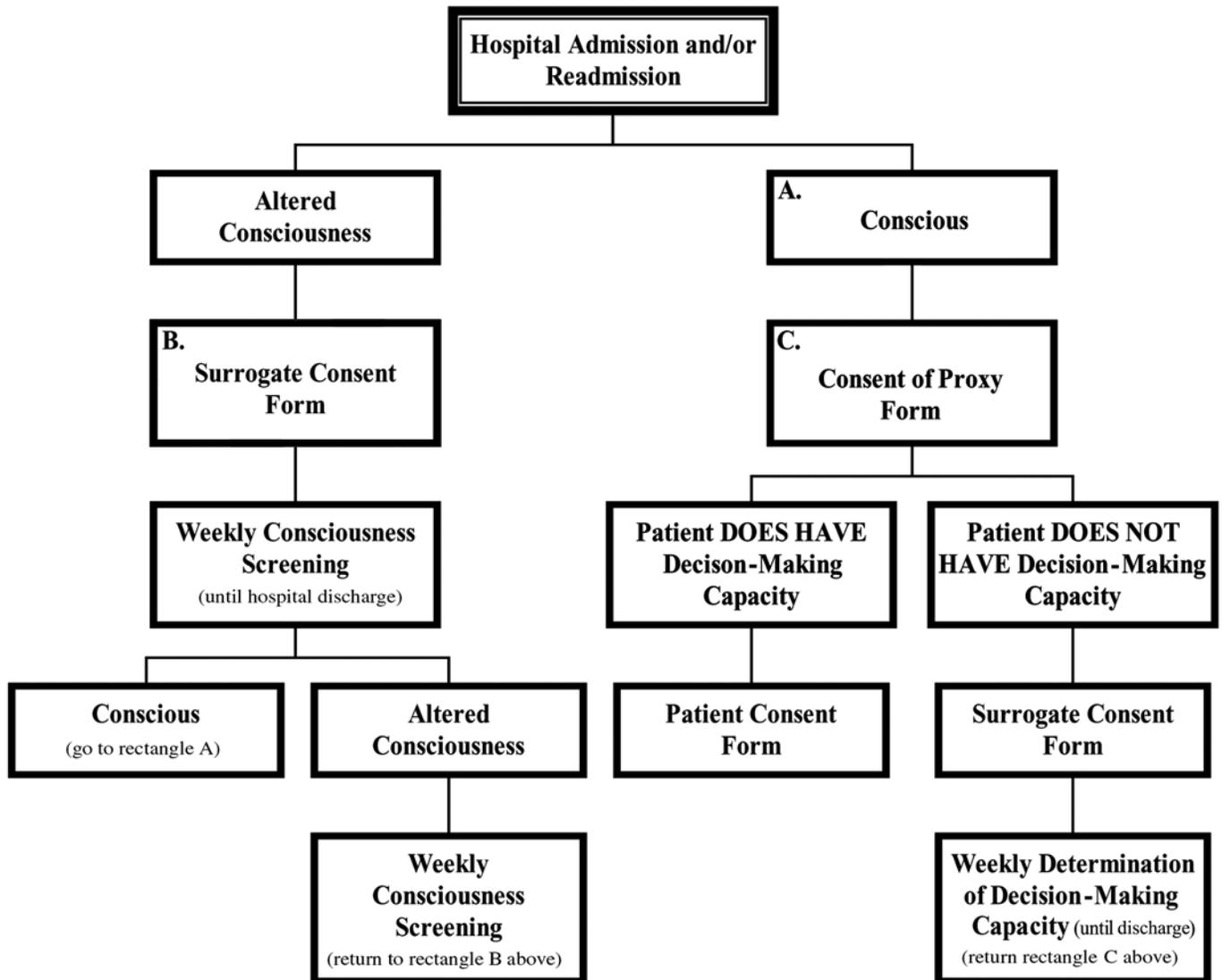


Figure 3.
In-patient consenting procedures.

consent form, completes this phase of the process of obtaining informed voluntary consent.

Procedures for obtaining informed voluntary consent must account for the fluctuating nature of TBI recovery. When subjects are enrolled into the protocol, they are unconscious and do not demonstrate capacity to provide informed voluntary consent, but during recovery, they may regain this capacity (return to capacity). Therefore, procedures for obtaining informed voluntary consent include methods for identifying *when* a subject's capacity should be reevaluated.

Capacity to provide informed voluntary consent requires, at a minimum, that the participant be conscious, but the state of science is that there is no agreement on what does or does not constitute consciousness. Therefore, unconsciousness is defined by research criteria as not demonstrating functional communication, functional use of an object, and/or a behavioral manifestation of a sense of self. Recovery of any one of these skills means that the participant has recovered consciousness. The research protocol aims to identify when the participant meets this definition (time to consciousness is one of the

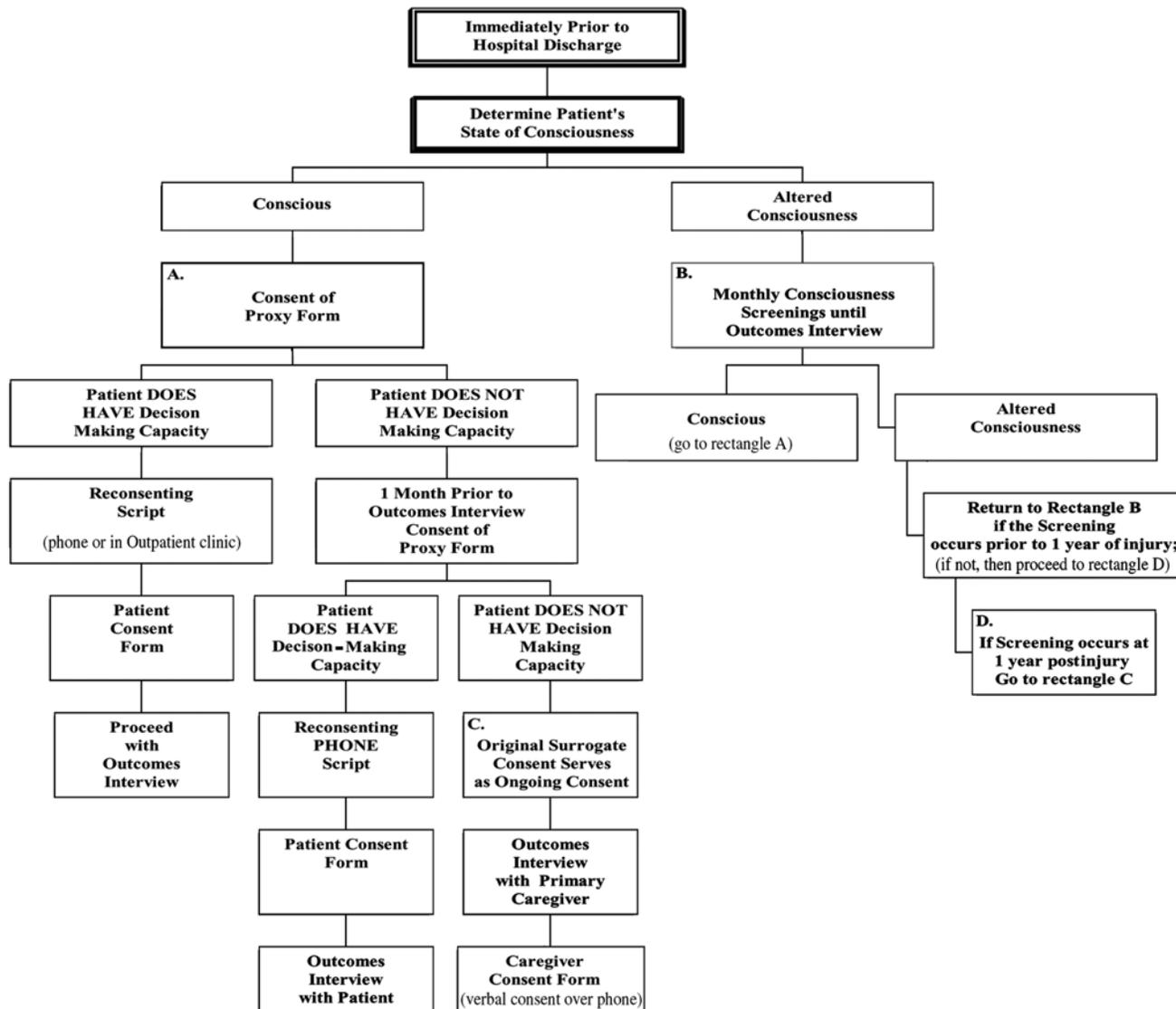


Figure 4.
Consenting procedures after hospital discharge.

outcomes); therefore, research staff conduct routine screenings for indications of consciousness. The IRB approved a screening form for this purpose. If the subject meets the research criteria for consciousness during any of these routine screenings, then the IRB approved that this could indicate that it is time to reevaluate the participant's decision-making capacity. If it is determined that the subject is conscious, then *nonresearch* staff must determine whether the participant has *recovered* decision-making capacity by completing the second section of the proxy form. This is conducted by mailing the proxy form to the participants attending physician with a

cover letter. An allied health professional directly involved in the participant's medical care can also complete the form. These two options provide the researcher with more flexibility to obtain a timely response and avoid undue LTF. The forms are mailed with a copy of the original surrogate consent 1 to 2 months before the final outcomes interview (12 months postinjury), which allows for determining capacity to be made shortly before the final outcomes interview.

The Subject Patient Consent Form was approved for use in the situation when the subject is determined to have recovered decision-making capacity. The IRBs also

developed and approved a Reconsenting Phone Script. This script allows researchers to contact the subjects who have been reported to have (i.e., with the proxy form) recovered decision-making capacity. The script dictates how research staff should explain the research project to the TBI subject. If at the end of the script the subject verbally agrees to continue participation, then the Subject Patient Consent Form is mailed to the subject with a cover letter and a self-addressed stamped envelope. The cover letter explains and provides examples of who can sign as a witness and also explains that research staff may call two to three times to remind the subject to mail the consent form back to the research office. The IRB also approved the cover letter.

The protocol procedures stipulate that if the subject is not conscious and/or not able to participate in a phone interview at the time of the 1-year outcomes interview, then the subject's primary caregiver is to be interviewed about the subject's functional status. The IRBs approved the use of language in the surrogate consent form informing the surrogate that she or he is consenting to the caregiver's role as the participant's proxy at 1-year postinjury. When the caregiver is someone different than the person who signed the surrogate consent form, then the IRBs approved the use of a Caregiver Telephone Consent Form. The IRBs approved, in other words, a waiver of written informed consent because the caregiver is providing information about the subject. However, by using the approved "telephone consent form," the caregiver is providing verbal informed consent for their participation in the protocol. The caregiver being interviewed must be fluent in English unless (1) the caregiver consent form was translated into another language, (2) the IRBs approved that translation, and (3) the person conducting the interview is fluent in the same language. If not, then another English speaking person must be interviewed and verbally consented.

The approved procedures for obtaining informed voluntary consent just described have been implemented for 20 months, and additional burdens to the research protocol included LTF, additional costs, and additional staff time for reconsenting procedures and IRB management. LTF have been primarily due to physicians not affiliated with the research hospitals not returning the completed proxy form, with only one participant not providing permission at the time of reconsent. When the consent of proxy form is completed in person with the physician, the

LTF are minimized, but this can be impractical and costly.

An additional solution enacted by the PI was to form a project oversight committee composed of a research ethicist, a medical ethics scholar, a professor of sociology, a sociology of religion professor, an administrator, a lawyer, a lay person who incurred a coma and has recovered decision-making capacity, and the PI. The members serve at no cost to the project and meet biannually either in person or via conference calls. This solution is possible because the study is conducted within an academic milieu and pervasive interest throughout the academic institution is palpable. While members willingly serve on the committee, assembling the committee took about 1 1/2 years and coordinating a scheduled time to meet can be problematic but is alleviated if administrative assistants are assigned this task. This oversight committee oversees all sites and identifies, defines, and proposes solutions to unanticipated ethical issues as they arise in the conduct of this research protocol, but it does not interpret regulations for the local IRBs. One issue with which the committee assisted the investigator is the Health Insurance Portability and Accountability Act (HIPAA) requirements [47]. The committee advised the investigator to develop a HIPAA preauthorization and an authorization form for release of protected health information, which the IRBs approved. The HIPAA does not require the HIPAA preauthorization, but since it is a multisite study and subject recruitment is conducted by nontreating clinicians, consent to release the name of a potential subject to research staff is obtained by the treating physician prior to giving identifying information to research staff. The research staff then approach the surrogate to talk about the study and the patient's possible participation.

The PI aims to conduct research while protecting subjects rights, but this dual goal has an inherent conflict and the oversight committee was developed to address this conflict. The committee provides objective observers who understand the protocol and are skilled at identifying and defining ethical issues as they arise. Naturally, the local IRB is presumed to serve as the objective observing body, but given the demands currently placed on local IRBs, this is not a feasible solution. The oversight committee will facilitate successful protocol completion, but paying members and/or reimbursing them for incurred expenses would make coordinating routine meetings easier.

DISCUSSION

Multiple Site Research Implications

Meritorious research of severe TBI requires subject recruitment from multiple sites and throughout the continuum of care. When studying the severe TBI population, researchers need to accrue a sample from multiple sites because of the low absolute incidence rate of severe TBI [48], relative to all TBI, and because persons with severe TBI are not centrally located within the healthcare continuum [49–52]. The protocol was, therefore, by necessity reviewed by six Human Subjects IRB and/or Human Studies Subcommittees governing the practice of research at each participating hospital located in Illinois, Minnesota, and the District of Columbia; five IRBs approved the protocol and one tabled the protocol because of the issues related to funding as well as issues related to perceived benefit for the participant. The protocol initially started recruiting subjects in Illinois and Minnesota. The protocol has recently been funded to expand subject recruitment to Florida but has not been funded in the District of Columbia. Each of the respective IRBs reviewed the protocol, and at the time of writing this article, subjects were recruited from four veteran and private hospitals in Minnesota and Illinois, but they were not recruited from a military hospital.

Federal regulations do provide a mechanism to avoid duplication and undue impediments in multicenter cooperative protocols. Under the Common Rule, participating institutions can enter into a joint review arrangement or rely upon the review of another qualified IRB, which would avoid duplication and undue impediments to research (45 CFR 46.114) [1]. The IRBs did not, however, classify the protocol as a cooperative project because, while the regulations allow for cooperative agreements, the regulations also stipulate that each institution is responsible for ensuring that the rights and welfare of human subjects are safeguarded at their own institution (45 CFR 46.114) [1]. Each institution is also mandated to ensure that the cooperative research is consistent with its local laws, institutional policies, professional and community standards, and population differences (45 CFR 46.103(d), 46.107(a), and 46.111(a)(3)) [5]. Each of the participating institutions' IRBs determined that this multisite cooperative protocol did not qualify for joint review. Cited reasons included—

1. The local boards have greater familiarity with the actual conditions surrounding the conduct of research.
2. The lack of familiarity with the other participating sites.
3. The IRBs aim to have intimate familiarity with any research conducted in their own hospital.
4. The perceived diminished authority of each IRB for approving and monitoring the research protocols and to avoid the image of a “rubber stamp.”
5. That each institution has developed expert review panels, entrusted with protecting the rights of the subjects within the respective institutions.

Therefore, while the Common Rule allows consolidation of the IRB review effort, the decisions of the local IRBs, the cited reasons, and the other written regulations cause researchers to question the practical application of 45 CFR 46.114 as an effective means of reducing impediments to scientific inquiry of multisite cooperative studies, which are essential to the study of TBI.

Meritorious research of TBI requires multiple subject recruitment sites. Multisite studies can be designed to recruit subjects while protecting their rights, but because obtaining IRB approval is so cumbersome, the costs for managing and overseeing the use of human subjects in a multisite study may at some point become cost-prohibitive. Three guidelines were useful to the authors and may prove useful for other researchers working with incapacitated research TBI subjects: (1) when developing and evaluating a process for obtaining informed voluntary consent, consult with a health-law expert and a disability research ethics scholar; (2) collaborative and ongoing communication between the IRBs, administrators, IRB reviewers, the project PI, and local PI is essential as the process of obtaining informed voluntary consent is a fluid process; and (3) use of the narrowest (most conservative) definitions when variability between IRBs exists.

Implications for Research and Researchers, and Need for Further Resolution

The movement of biomedical research ethics to the center stage in society is due, in part, to the advancement of scientific knowledge and medical technology. Ironically, this same technology has increased our chances of surviving a severe TBI; thus we have a growing number of persons living after a severe TBI. These advancements provide society with options and choices, but the corollary is that there must be a basis for making ethical choices [53]. While researchers are conducting the scientific investigations that ultimately advance scientific knowledge and medical technology, the Common Rule

serves as the basis for making ethical choices. The Common Rule when combined with state statutes inadvertently leads, however, to confusion and multiple interpretations when researchers study TBI and especially when researchers study TBI in multiple sites.

While a comprehensive examination of the larger ethical issues that are unresolved is not the focus of this paper, it is important that a distinction be made between the ethical and legal issues because significant ethical issues remain unresolved. The issue of capacity, for example, is confusing because the concept encompasses determining the appropriate legal definition to be applied, determining who is qualified and reasonably available to evaluate a subject's decision-making capacity, and determining how and when that person should evaluate the subject for capacity. While legal definitions of capacity were adopted for the protocol, the approved procedures and definitions highlight unresolved ethical questions. Why are attending physicians rather than other professionals (e.g., treating therapists, ethicists, psychologists) legally identified as the persons to determine decision-making capacity? Does conflict of interest exist for the treating physician? Does the family become confused if the treating physician is involved in determining capacity and does this confusion increase the chances of therapeutic misconception and/or unintended coercion? Are there methods that can be used to enhance capacity (e.g., writing consents for TBI, e.g., www.ncddr.org/du/products/focus/focus1/consent.html; repetition; and multimodal presentations of same information) [54]? Furthermore, are the legal definitions of capacity adequate for persons with TBI given common residual deficits such as organic memory disorders and executive functioning impairments? Further, the concept of decision-making capacity does not address the transient and sporadic nature of the cognitive (e.g., executive function) and organic memory deficits acquired after a TBI. The nature of the memory and of cognitive impairments after TBI raises questions about the notion of sufficient capacity for persons with transient recall of details who are required to make an informed decision. [20].

The variability in interpretation of state statutes complicates and perhaps obscures another ethical issue, which is the accuracy of surrogate decision-makers in predicting what patients would actually want. The appointment of a legally authorized agent or representative to provide informed consent on behalf of the unconscious patient assumes inherent accuracy by using

substituted judgment. The protocol highlights this unresolved ethical issue because we use substituted judgment, but using this mechanism does not mean that we can be overly confident that we are indeed acting on behalf of the patient's true wishes [55–59].

CONCLUSIONS

This paper has focused on the issues and difficulties faced in meeting the existing legal standards, and the synthesis of these federal regulations and state statutes suggests that the existing policies and laws do not sufficiently guide research scientists in the area of TBI. The ethical and legal discourse in the next decade should focus on refining and/or clarifying the federal policy and state laws that govern meritorious research of TBI. The NBAC has provided recommendations that should continue the dialogue [15,19], but suggested revisions and/or clarifications include that the Common Rule (1) be written in a language that circumvents variable interpretations and/or misinterpretations, (2) succinctly summarize the guidelines for use as a reference, and (3) minimize unnecessary barriers to meritorious research. Scientists should also publish their creative solutions that protect rights and minimize research barriers. A comprehensive body of peer-reviewed literature could be a supplemental source of guidance for investigators and review boards.

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