2017

Guardianship and Clinical Research Participation: The Case of Wards with Disorders of Consciousness

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GUARDIANSHIP AND CLINICAL RESEARCH PARTICIPATION: THE CASE OF WARDS WITH DISORDERS OF CONSCIOUSNESS

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Abstract:

We review relevant federal law about research on human subjects and state laws on guardian authority to determine whether guardians can consent on behalf of their ward to participation in research. The Common Rule is silent on the issue as are most state guardianship laws. Our analysis shows significant variation in guardians' decision-making authority in the states that do regulate wards' participation in research.

We consider how the appointment of guardians for patients with disorders of consciousness (DOC) impacts such patients' access to research. We assert that it is important that such persons be permitted to participate in research, so that their conditions and potential medical interventions can be studied, and that those with similar conditions can benefit from the knowledge gained from these studies. We argue that state guardianship laws should be adopted to specifically give guardians the authority to consent to research on behalf of wards who may be able to regain decisional capacity.

Incapacitated adults with a legally appointed guardian or conservator may also be recruited for, or involved with medical, behavioral, or social science research. Much of the research in which such persons participate is aimed at evaluating medical interventions for, or contributing to general knowledge about disorders from which they may suffer. In this paper we will consider how the appointment of guardians for patients with disorders of consciousness (DOC), severe brain injuries that affect a patient's level of arousal and ability to interact (Giacino et al. 2014), impacts such patients' access to research.

Such persons may be under guardianship because they have lost decisional capacity (i.e., those in a coma or vegetative state), or may have severely impaired decisional capacity (i.e., those in a minimally conscious state). Guardians are judicially appointed to ensure that such persons have their basic needs, including health care, taken care of and that their finances and property are well managed. Guardians are necessary to ensure that the interests of persons with DOC are protected (Fins and Pohl in press).

Persons in a minimally conscious state (MCS) have intermittent conscious awareness and behaviors associated with such awareness (Giacino et al. 2002, 351). Patients in a MCS have the prospect of recovery (Giacino et al. 2002; Schiff, Giacino, and Fins 2009; Giacino et al. 2014; Fins 2015; Fins and Pohl in press; Nakase-Richardson et al. 2012), but much research remains to be conducted to determine how to adequately diagnose and treat such persons (Giacino et al. 2002, 352; Schiff, Giacino, and Fins 2009; Giacino et al. 2014). Given that persons under guardianship have had their decisional authority transferred to a guardian, it is necessary to determine the scope of the guardian's authority to consent to this research, which may be the

only path toward recovery for a person in a MCS and the only way to increase scientific knowledge about a condition which does not have a clear animal correlate.[1]

This paper will focus on the permissibility of research participation of persons with DOCs under guardianship by examining how law enables or constrains a guardian's authority to consent to the research on behalf of the incapacitated person. First, this paper will examine how the federal Common Rule treats research on those whom the law designates as "incapacitated" or "incompetent." Second, we will examine state guardianship laws that have implications for human subjects research. Third, we will analyze the implications of these guardianship laws for research on those with brain injuries and DOC. Finally, we will propose alternatives to existing guardianship laws in order to ethically serve the interests of persons with DOC so they can participate in, and benefit from, research while concurrently being protected from exploitation.

COMMON RULE AND RESEARCH ON INCOMPETENT OR INCAPACITATED PERSONS

The Common Rule is a set of federal regulations governing research on human subjects (45 C.F.R. § 46) that has been adopted by 18 federal agencies (HHS 2015). The Common Rule does not specifically address research on incapacitated adults under guardianship. That is, incapacitated adults under guardianship are not specifically recognized as a "vulnerable group" such as prisoners (45 C.F.R. §§ 46.301-306), pregnant women (45 C.F.R. §§ 46.201-207), neonates (45 C.F.R. §§ 46.201-207), or children (45 C.F.R. §§ 46.401-409),[2] although adults under guardianship share features of vulnerability of impaired decisional capacity, and are often institutionalized.

[1] That is, it is not possible to study human consciousness in animals.

[2] Scholars and the National Bioethics Advisory Commission (NBAC) have offered some guidance about involving persons with decisional impairment in research (NBAC 1998; Michels 1999; Fins and Miller 2000). These recommendations have not made it into federal regulations, however.

Although not explicitly mentioned in the Common Rule (OHRP 2011c; New York State Task Force on Life and the Law 2014), research on incapacitated adults is most strongly implicated in sections of the Common Rule on selection of subjects and informed consent. The Common Rule directs Institutional Review Boards (IRBs) to be "cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons" (45 C.F.R. § 46.111(3)).[3] In this section, the Common Rule expands upon what is considered a vulnerable population, and if not considered an exhaustive list, then IRBs may be sensitive to the special circumstances of incapacitated adults under guardianship. Furthermore, persons with a DOC would fall into the category "mentally disabled persons." Additionally, when instructing investigators of the necessity of informed consent, a potential subject's "legally authorized representative" is referenced (45 C.F.R. §§ 46.102, 111(4), 116), which in some cases would include a guardian.

Other federal regulations provide further guidance to IRBs and investigators if one analogizes the position of adults under guardianship to that of children. Both groups lack the capacity to consent to research, but the Common Rule specifies a discrete tiered relationship between risk and consent for children's research participation, which may be useful as a framework for determining whether and how adults under guardianship might participate in research. The regulations about research on child subjects discuss the relationship between risk levels and the prospect of direct benefit to the subjects (45 C.F.R. §§ 46.404-407). For research not involving more than minimal risk, a child's parent or legal guardian can consent on behalf of the child (45 C.F.R. § 46.404). For research involving greater than minimal risk, but the

[3] See also 45 C.F.R. § 46.111(7)(b), Michels (1999), and Silverman, Luce, and Schwartz (2004).

prospect of direct benefit, a child's parent or legal guardian can consent on behalf of the child as long as the research risk-benefit ratio is appropriate (45 C.F.R. § 46.405). For research that is greater than minimal risk with no prospect of direct benefit, a child's parent or legal guardian can consent as long as the research is only "a minor increase over minimal risk" and there is the prospect of generalizable knowledge about a particular condition the child research subject has (45 C.F.R. § 46.406). Research that is not approvable under any of the previous regulations may be approved if it "presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children" (45 C.F.R. § 46.407).[4] The Common Rule strictly limits research on child wards of the state, however, and wards of the state upon whom research is conducted are required to have a special advocate appointed for them to act in their best interests throughout the duration of the research (45 C.F.R. § 46.409). Importantly, in all of these regulations, the assent of the child is also required, if the child is developmentally able to provide assent. If IRBs consider adults under guardianship to be similar to children, they could conceivably use these risk-benefit guidelines.

There are reasons not to analogize adults under guardianship to children, however. One significant difference between the two groups is that adults under guardianship may have had capacity at one point whereas children have never had legal capacity. Indeed, adults with DOC under guardianship likely had capacity prior to their severe brain injury. Given prior capacity, these persons likely had preferences about whom they would like to act as their surrogate decision maker whether or not they formalized their preference in an advance directive. Persons

[4] Empirical research has demonstrated variability in how IRBs assess risk in research on children (Shah et al., 2004). This may mean that the same research on child subjects would be approved at one institution, but not another. Despite the lack of clear guidance of what constitutes "minimal risk" or "minor increase over minimal risk," some IRBs feel confident that they can easily assess risk on a case-by-case basis. For example, Cornell IRB documents state: "Procedures that exceed the limits of minimal risk may be difficult to define in the abstract, but should not be too difficult to identify on a case-by-case basis" (Cornell University Office of Research Integrity and Assurance Human Research Participant Protection Program 2010, 5).

with prior capacity may also have had preferences about participating in research and what they would be willing to risk for a particular prospect of benefit.

While not having the force of law, the U.S. Department of Health and Human Services has published guidance on conducting research on those with diminished capacity, although none of it addresses adults under guardianship specifically. For example, in the Office for Human Research Protections (OHRP) FAQ, there is guidance about what constitutes a "legally authorized representative" (LAR). According to the OHRP, this is determined by the law of the state, and yet paradoxically most states have no such law about who constitutes such a person when it comes to consenting to another's participation in human subjects research (New York State Task Force on Life and the Law 2014). Any relevant legal guidance likely comes from law about surrogate consent for medical treatment, and if the research is related to a particular medical treatment, then these laws may be applicable (OHRP 2011a; New York State Task Force on Life and the Law 2014; Saks et al. 2008). The OHRP guidance directs IRBs to consult with legal counsel to determine who an appropriate LAR is (OHRP 2011a); yet, there is still likely to be confusion about who an appropriate LAR might be (Saks et al. 2008; New York State Task Force on Life and the Law 2014).

The OHRP FAQ offer further guidance for adults with decisional impairment, whether "temporary, progressive, or permanent," and state that only a LAR can consent on their behalf (OHRP 2011b). Additionally, the FAQ note that IRBs are required to have professional competence in assessing research on persons with decisional impairment, and if they do not, to retain the help of consultants with such expertise (OHRP 2011c).

STATE GUARDIANSHIP LAWS ABOUT RESEARCH ON INCOMPETENT

OR INCAPACITATED PERSONS

Given the silence of the Common Rule about research on incapacitated adults under guardianship, much of the regulation of such research is left to states and individual IRBs, and thus can be idiosyncratic. An examination of individual IRB polices[5] and state-level laws on human subjects research, informed consent, advance directives, and institutionalized patients' rights is beyond the scope of this paper .[6] Rather, given our focus on DOC, this section will examine existing state guardianship laws about research on incapacitated persons who once had decisional capacity which was lost or highly impaired following brain injury (we thus exclude guardianship laws on the developmentally disabled).

In 2014, one of us (MW) searched WestLaw, a legal database, for each state's guardianship laws, and identified states that addressed incapacitated persons' participation in medical or behavioral research. Then another author (MU) repeated the search a year later to ensure that guardianship statutes were still current.[7]

We initially grouped the different state regulatory approaches into three categories. The first category is the absence of regulation on guardians' ability to consent to research on behalf of their ward. The second category consists of statutes that regulate guardians' ability to consent to experimental medical procedures or medication for their ward, which have the prospect of being therapeutic. The final category consists of statutes that regulate guardians' ability to

[5] For a description of local IRB variation in permitting surrogate consent for research, see New York State Task Force on Life and the Law (2014, 7).

[6] We only studied guardianship laws, and not state-specific human subjects research protection laws. For more information on state human subjects research protection laws and proxy consent, see Saks et al. (2008). We also did not study state advance directive laws. Some persons may name a durable power of attorney that could make healthcare or research participation decisions on their behalf in case of incapacity. Many persons do not engage in such advance planning (Rao et al. 2014), however, especially as it pertains to future research participation (Fins and Miller 2000; Muthappen, Forster, and Wendler 2005). Guardianship is thus a post hoc remedy, which is why it is the focus of our paper. Furthermore, there is variation in how states treat the authority of guardians compared to healthcare agents to make decisions for a ward (ABA Commission on Law and Aging 2015).

[7] Saks et al. (2008) also compiled state statutes on proxy consent. The differences between our tables are due to statutes that have changed since they published their research.

consent to any sort of experiment—medical or behavioral—on behalf of their ward. See Table 1 for a list of which states belong to each category, and sample statutes for the latter two categories.

Relatively few states regulate surrogate consent, by a family member for example, for participation in research (Silverman, Luce, and Schwartz 2004; Saks et al. 2008). Furthermore, after reviewing each state's laws on guardianship, it is clear that few states regulate guardians' authority specifically to consent to their ward's participation in medical or behavioral research.

Thirty-eight states (75 percent) do not regulate by statute guardians' authority to consent to their ward's participation in research. This lack of regulation does not necessarily imply that guardians actually are empowered and have authority to provide research consent.[8] Given that guardianship is the domain of state probate courts, where opinions are not readily accessible, it is impossible to determine whether issues of incapacitated persons participating in research have found their way to the courts unless these cases are appealed to a trial court. There have been no trial court cases on this issue in the past ten years.[9] Thus, it is unclear whether probate judges have limited or expanded guardians' authority in this domain in particular states that lack statutes regulating this. Any such probate court cases, however, are highly fact-specific and thus have no precedential value; that is, there is no generalizable case law on this issue. It may be the case, however, that when guardians are charged generally with acting in their ward's best interest, and are faced with the decision of whether to consent on behalf of the ward to therapeutic research that has the prospect of direct benefit, guardians in such states do provide such consent. In some cases, it may be unclear what is in the ward's best interest or whether the research will provide a

[8] See also Saks et al. (2008).

[9] We did a Westlaw search of all federal and state cases using "guardian," "consent," and "research" or "experimentation" in the same paragraph. In Saks et al. (2008) review of the case law, they likewise did not find more than one relevant case.

therapeutic benefit. In such cases, the law's lack of guidance may be problematic for guardians attempting to make the best decisions under conditions of uncertainty.

Twelve states and the District of Columbia (25 percent) do regulate by statute guardians' authority to consent to their ward's participation in "experimental treatment," "experimental medical procedures," "medical experiments," or "experimental behavioral procedures." It is unclear what exactly these statutes are attempting to regulate—research or treatment. For statutes that reference only "experimental treatment" or "experimental medical procedures," we assume that this also includes clinical research, although we realize that medical treatment and research differ.[10]

Six of these states regulate guardians' ability to consent to experimental medical treatment or medication. Alaska's statute is typical for this group of states:

> "A guardian may not: (4) consent on behalf of the ward to the performance of an experimental medical procedure or to participation in a medical experiment not intended to preserve the life or prevent serious impairment of the physical health of the ward" (Alaska Stat. § 13.26.150(e)).

In Alaska, there must be a prospect of direct benefit to the person under guardianship in order for their guardian to consent to participation in research regardless of the level of risk. The kind of experimental medical procedure must also be related to prevention of a serious health risk. This could be interpreted to mean that persons under guardianship in Alaska may not participate in phase I trials, which are toxicity studies not designed to provide direct benefit to participants.

[10] Some have defined the difference between research and treatment in the following way: "*Research* and *experiment*, employed interchangeably in the literature, are distinguished from *treatment* by the respective absence or presence of a benefit accruing to the subject/patient. This benefit is calculated by applying predictions made in accordance with established standards of medical practice" (Tomossy and Weisstub 1997, 114). See Saks et al. (2008) for a description of how the distinction between treatment and research is blurred in the laws. Kansas' statute clearly regulates persons under guardianship participating in research, for example, but it is not as clear whether the statute also regulates experimental treatment (for text of statute, see Table 3).

Seven other states regulate by statute a ward's participation in experimental medical treatment and also regulate whether incapacitated persons can participate in behavioral or social science research. Florida offers one example of this type of regulation:

> "Without first obtaining specific authority from the court, as described in s. 744.3725, a guardian may not: (b) Consent on behalf of the ward to the performance on the ward of any experimental biomedical or behavioral procedure or to the participation by the ward in any biomedical or behavioral experiment. The court may permit such performance or participation only if: 1. It is of direct benefit to, and is intended to preserve the life of or prevent serious impairment to the mental or physical health of the ward; or 2. It is intended to assist the ward to develop or regain his or her abilities" (Fla. Stat. Ann. § 744.3215(4)).

Many of these statutes use similar language to the statutes that regulate only incapacitated person's participation in medical research. The regulation is arguably stricter in nature, however, as it excludes all kinds of research participation rather than just medical research. Additionally, it is important to note that in Florida's statute, a court can permit the ward to participate in research, but the guardian cannot without going to the court for permission; that is, there is a distinction between what is legally permissible and what is within the bounds of a guardian's authority. Florida's statute also permits experimental medical procedures not just to save a ward's life or prevent impairment (like Alaska's statute), but also to restore functioning and health, which means experimental procedures designed to rehabilitate are permissible.

When states regulate guardians' authority to consent to research on their wards, about half distinguish between non-therapeutic and therapeutic research on those under guardianship.[11] See Table 2. Therapeutic research offers the prospect of direct benefit to those being studied, whereas non-therapeutic research has no such prospect but rather contributes to general knowledge.

[11] See also Saks et al. (2008).

There is confusion on the topic of the boundaries between therapy and research, which has been described as "therapeutic misconception," where research is misunderstood as therapy (Appelbaum, Roth, and Lidz 1982; Saks et al. 2008). In this context both guardians and investigators can suffer from misconstrual. "Therapeutic research" is a vague term, which captures the ambiguity and perhaps ambivalence of the research endeavor and is oxymoronic in early stages where research activities are more investigational than therapeutic. It becomes a more cogent concept in later stages of research, such as phase III research where a therapeutic concept is tested against standard therapy. Such definitional clarity is not captured in the law, and the ambiguity could be construed as legislative or statutory therapeutic misconception.

Confusion on this issue can be seen in the wide array of statutory schema across jurisdictions. The District of Columbia, for example, prohibits the guardian to consent to the ward's participation in any experimental procedures without regard for whether there may be the prospect of benefit, in contrast to the Alaska and Florida statutes described above, which consider therapeutic intent and the severity of harm prevention sought by clinicians or researchers. Laws that do not distinguish between therapeutic and non-therapeutic research mean that a guardian's possible "therapeutic misconception," will not have an impact on the ward's research participation, which is not permitted.

We also categorized the "gradient" of a guardian's authority to consent to experimental procedures or research on their wards for those states that have statutes addressing such authority. See Table 3. That is, some states prohibit guardian consent to experimental procedures in all cases without a court order, which is the most restrictive category. For example, North Dakota's statute reads:

> "Notwithstanding general or limited authority to make medical decisions on behalf of the ward, no guardian may consent to … experimental treatment of any

> kind unless the procedure is first approved by order of the court" (N.D. Cent. Code Ann. § 30.1-28-12 (5-312)(4)).

There are no exceptions for the seriousness of the situation a ward may face.

Some states do make exceptions for emergency contingencies and in cases where the preservation of the ward's life is at stake, making these formulations less restrictive than an outright prohibition on a guardian's provision of consent. For example, Oklahoma's statute reads:

> "Except in an emergency and only as necessary to preserve the life of the ward, no guardian shall have the power to consent on behalf of the ward to … performance of any experimental biomedical or behavioral procedure, or participation in any biomedical or behavioral experiment, except with specific authorization of the court having jurisdiction of the guardianship proceeding" (Okla. Stat. Ann. Tit. 30, §3-119(3)).

While this statute recognizes the importance of preservation of life, it does not allow exceptions for potentially rehabilitative experimental interventions or procedures.

Other states not only recognize that experimental procedures may be necessary to save the life or prevent harm to the ward, but that there may be some experimental procedures that help the ward regain lost abilities. These states thus permit guardians to consent on behalf of the ward to such rehabilitative procedures. For example, Kansas' statute uses the phrase "and is intended to preserve the life or health of the ward or to assist the ward to develop or regain skills or abilities" (Kan. Stat. Ann. § 59-3075(e)(6)(A)). This category is more permissive.

The most permissive, even altruistic, category is exemplified by Wisconsin, which allows guardians to consent on behalf of the ward to any research the ward would have chosen to participate in, even if there is no prospect of direct benefit to the ward. The statute reads:

> "The power to authorize the ward's participation in research that might not help the ward but might help others even if the research involves greater than minimal risk of harm to the ward if the guardian can establish by clear and convincing

> evidence that the ward would have elected to participate in such research" (Wis. Stat. Ann. § 54.25(2)(d)).

California is also in this category, and is arguably more permissive than Wisconsin in that it does not have the evidentiary standard of "clear and convincing" evidence of the ward's wishes, but instead states:

> "Surrogate decisionmakers described in this section [including guardians or conservators] shall exercise substituted judgment, and base decisions about participation in accordance with the person's individual health care instructions, if any, and other wishes, to the extent known to the surrogate decisionmaker. Otherwise, the surrogate decisionmaker shall make the decision in accordance with the person's best interests. In determining the person's best interests, the decisionmaker shall consider the person's personal values and his or her best estimation of what the person would have chosen if he or she were capable of making a decision" (Cal. Health & Safety Code § 24178(g)).

Some states, while not addressing the issue of surrogate consent to research through law, have nonetheless addressed the issue through state task forces. For example, in New York it is legally permissible for those who lack consent capacity to participate in research, but there is little legal guidance about how to involve and adequately but not overly protect (to the point of exclusion) such participants. The State Task Force on Life and the Law[12] wrote a report aimed at IRBs, researchers, and surrogate decision-makers with recommendations for incapacitated individual's participation in research (New York State Task Force on Life and the Law 2014).[13] The report only briefly addresses guardians and consent, arguing that in several research scenarios (with varying levels of risk and prospect of direct benefit), court-appointed guardians are often inappropriate persons to give surrogate consent because they probably could not exercise substituted judgment (New York State Task Force on Life and the Law 2014, 44).

[12] One author is a member of the Task Force, but is speaking in their individual capacity in this paper and not as a representative of the Task Force.

[13] The recommendations are too numerous to list in this paper. For a brief summary of the report, see Koch and Han (2014) and Koch (2014).

IMPLICATIONS OF GUARDIANSHIP LAWS FOR RESEARCH ON THOSE WITH BRAIN INJURIES AND DISORDERS OF CONSCIOUSNESS

Persons with brain injuries and subsequent DOC may be deemed "incompetent" by a court and placed under guardianship. Persons with a DOC may be able to recover over time, and in fact 21% regain functional independence (Nakase-Richardson et al. 2012), but in order to determine how best to aid them in this process, scientists and clinicians need to be able to conduct research on them given that there is still much that is unknown about some DOCs (Giacino et al. 2014).

In particular, there is much that is unknown about the MCS (Giacino et al. 2014; Fins 2015). At this time, although there has been demonstration of proof of principle of some potentially therapeutic interventions, much of the research on the MCS remains in phase I and is greater than minimal risk (Schiff et al. 2007; Schiff, Giacino, and Fins 2009) and requires surrogate consent because the nature of the MCS means the person can give, at most, assent to participate in the research. This investigatory research, such as the proof of principle that deep brain stimulation (DBS) can lead to improvement for a person in a MCS (Schiff et al. 2007; Schiff, Giacino, and Fins 2009), offers ex ante "the prospect of direct medical benefit in the sense that there is a chance, though small, that some subjects will receive clinically significant improvement" (Fins and Miller 2000, 34). Similarly, other human subjects research on the MCS has moved beyond phase I to assess efficacy, side effects, and safe dosages of drug therapies (Giacino et al. 2012).

While guardianship may be necessary to protect the interests of persons in a MCS given their irregular periods of behavioral evidence of consciousness, guardianship may also be an obstacle to conducting research—both therapeutic and non-therapeutic—on this population

(Giacino et al. 2014; Fins 2015; Fins and Pohl in press).[14] As can be seen from Table 2, five states and the District of Columbia would prohibit all such research on persons in a MCS under guardianship, even if it offered the prospect of a direct benefit. Seven other states may require evidence of direct benefit before such persons could access an experimental medical procedure. These laws would thus eliminate the possibility of brain injured persons with DOC under guardianship in these states from being enrolled in phase I clinical trials where, even if a researcher has "therapeutic intent," the purpose of the research is not to improve a person's recovery (Fins and Miller 2000, 34), but which are important for continuing to obtain information about this population.

As Michels (1999, 1427) notes:

> "There is agreement that research on human subjects requires informed consent but that, at the same time, we must learn as much as possible in order to improve the care of those who suffer from diseases that impair their capacity to provide informed consent. How do we proceed when these goals are in conflict, when conducting research on those who cannot themselves consent to participate in it is the route to improving their care?"

In this respect, although guardianship is meant to protect these persons, it may also impede their recovery (Giacino et al. 2014). As noted above, twenty-one percent of persons with DOC currently regain functional independence (Nakase-Richardson et al. 2012), and it is possible that even greater numbers of persons would achieve higher levels of independence if they had access to experimental medical procedures of therapeutic clinical research. Moreover, for minimally conscious persons under guardianship, it may be difficult once they recover and regain capacity to reverse the guardianship decision or to exercise autonomy in decision-making, including consenting to research or treatment on their own behalf, especially if they live in a state where

[14] See also Michels (1999, 1430), Fins and Miller (2000, 33), and Saks et al. (2008) for a description of how protections for the vulnerable may obstruct research that may help them.

statutory guidance on restoration of wards' rights is lacking (Giacino et al. 2014; Fins and Pohl in press; Cassidy 2013).

PROPOSED ALTERNATIVES TO EXISTING GUARDIANSHIP LAWS

Both advisory groups and scholars have called for more uniformity in the regulation of human subjects research (e.g., NBAC 2001; Silverman, Luce, and Schwartz 2004; Wright and Robertson 2014). There have also been recent calls for more uniformity in guardianship law with respect to guardian decision-making (Cohen et al. 2015). We likewise propose uniform laws and guidelines for research on persons with brain injury and DOC under guardianship, so that similarly situated persons can be treated the same. As the state of guardianship law currently stands, access to research for persons under guardianship depends on the state in which they live, the IRB approving the research, or the probate judge interpreting an ambiguous guardianship statute.

First, we recommend that guardians of persons who may regain decisional capacity be expressly permitted by state guardianship laws to consent to experimental medical procedures and IRB-approved clinical research on behalf of the incapacitated person after carefully considering the potential risks and benefits, and using the values of their ward to guide the decision. Additionally, all guardianship laws should use conceptually clear language, making sure to distinguish experimental medical procedures from clinical research should states choose to permit one but not the other, so that there is no ambiguity about what is permissible for guardians to consent to on behalf of their wards. Finally, guardians should receive education or training about research on human subjects and on persons with DOC.

We limit our recommendation to guardians of wards that may regain decisional capacity because it may only be through access to experimental medical procedures or clinical research that such capacity may be regained. Given that many advocate for guardians to help wards regain capacity (National Conference of Commissioners on Uniform State Laws 1997, 1-4), a law that prohibits or through its silence may discourage guardians from consenting to such procedures or research on behalf of their ward is in conflict with this duty.

Assuming the person with a DOC has not previously indicated their disinclination to participate in research in an advance directive, guardians should be permitted to consent to clinical research on behalf of a person with a DOC as their LAR even if the study has no prospect of direct benefit, as long as the study has been approved by an IRB competent to evaluate medical research on persons with DOC and as long as there are safeguards in place.[15] This proposal may make it less likely that clinician-investigators will misconstrue research as therapy in order to obtain "therapeutic" consent from a guardian when the intervention is still unproven and investigational (Fins and Miller 2000, 39). An appropriate IRB committee for studies of persons in a MCS would ideally include reviewers who were family members of persons with brain injuries and DOC or other persons who have provided support to this population.[16]

Another safeguard may be using a consensus decision-making model outlined in Fins and Miller (2000) wherein the LAR, treating physician, clinical investigator, and lay volunteer MCS advocate all must come to consensus about the person in the MCS participating in research that is greater than minimal risk. The person in the MCS would provide assent if possible, and their

[15] See also Saks et al. (2008) and OHRP (2011c).
[16] See also Michels (1999, 1429) for a similar recommendation for IRB approval of psychiatric research.

dissent, if any, should be respected.[17] As noted by the proponents of this model, it "draws upon the skills, expertise, and experiences of each of these interlocutors while attempting to counterbalance the biases and motivations of each" (Fins and Miller 2000, 40). In this case, guardian consent would be necessary but not sufficient for the person in the MCS to participate in the research.

While some might be skeptical that a consensus-based decision-making model would be practical given that large-scale studies involve multiple independent parties, there is evidence of its feasibility in clinical decision-making (Herr and Hopkins 1994; Sadovnikoff and Jurchak 2007), which is indirect evidence that the model may work in the research context as well. Furthermore, while many parties may be involved in executing the research, only four are required by this model to achieve consensus, which reduces the perceived administrative burden of this model. Any burdens on the research team, however, are far outweighed by the procedural safeguards provided by this model. The alternative may simply be not conducting the research, which is ultimately problematic for both researchers and patients. Our proposal is a pragmatic response to a complicated issue, and is designed to address the needs of the incapacitated person while still providing access to research.

For concerns about researchers downplaying the risks of the research to avoid any difficulties in achieving consensus, we note that the incentive for researchers to downplay risks is present for all types of research. If researchers do downplay risks, this is integrity-compromising, and researchers may be subject to sanctions from their professional associations, employers, or affiliated university. The IRB will also review the research protocol for any sign of downplaying risks.

[17] See also Saks et al. (2008).

Returning to the federal regulations on research involving child subjects may be useful in thinking about what situations guardians could provide surrogate consent to research participation for a person in a MCS (45 CFR §§ 46.404-407). These guidelines may be useful in instances in which persons with a DOC have not indicated at an earlier point, for example in a research advance directive, that they would not desire to participate in the proposed research study. These regulations provide guidelines for the relationship between risk levels of research, the prospect of direct benefit, the prospect of generalizable knowledge about particular conditions, and consent/assent. For experimental phase II or III procedures involving the prospect of direct benefit to a person in a MCS, the guardian should be able to consent on their behalf, with the assent of the minimally conscious person if possible. For investigational phase I experimental procedures that are potentially greater than a minor increase over minimal risk and offer no prospect of direct benefit but have the possibility of yielding generalizable knowledge about MCS not obtainable by any other means, a guardian should be permitted to consent to the experimental procedure on behalf of the person in the MCS, with the assent of the minimally conscious person if possible. In this latter instance, however, the burden is on the investigators to demonstrate the importance of their research, that they cannot conduct the research in any other way than with persons in a MCS, that they have taken all possible steps to minimize risks, that there is clinical equipoise, and that the guardians do not have a therapeutic misconception; such studies should also be carefully scrutinized by the IRB approving the study protocol.[18]

The guardianship laws should be written in such a way as to require the use of substituted judgment whenever possible when making the decision on behalf of the ward whether to consent

[18] See also Saks et al. (2008) for a discussion of the importance of the IRB review.

to experimental treatment and research.[19] This may mean, however, that even if the experimental treatment may be in the incapacitated person's best interest from an objective point of view, if it conflicts with their values or beliefs, a guardian may not consent to it on their behalf.[20] Previous empirical studies suggest, however, that most people would be inclined to participate in research that has the prospect of therapeutic benefit (Muthappen, Forster, and Wendler 2005).

The above recommendation presupposes that the guardian is a family member or close friend of the person in a MCS. However, not all guardians know their wards prior to their appointment as guardian. For these professional guardians, we propose an additional safeguard, similar to that found in the federal regulations concerning research on child wards of the state (45 CFR § 46.409), which require that IRBs appoint an advocate for the ward for the duration of the research process to make sure that participating is in the ward's best interests.[21] If the person in a MCS has a guardian *ad litem*, this person is naturally suited to be such an advocate.

[19] We recognize that proxies do not always know their charge's wishes about research participation (Muncie et al. 1997), but still advocate for the use of substituted judgment instead of a best interests or reasonable person standard of decision-making when the ward's values and beliefs are known.

[20] Wisconsin's statute provides an interesting model of taking into consideration the ward's wishes about participating in research. "(c) The power to authorize the ward's participation in research that might not help the ward but might help others even if the research involves greater than minimal risk of harm to the ward if the guardian can establish by clear and convincing evidence that the ward would have elected to participate in such research; and the proposed research was reviewed and approved by the research and human rights committee of the institution conducting the research. (d) Unless it can be shown by clear and convincing evidence that the ward would never have consented to any experimental treatment, the power to consent to experimental treatment if the court finds that the ward's mental or physical status presents a life-threatening condition; the proposed experimental treatment may be a life-saving remedy; all other reasonable traditional alternatives have been exhausted; 2 examining physicians have recommended the treatment; and, in the court's judgment, the proposed experimental treatment is in the ward's best interests" (Wis. Stat. Ann. § 54.25(2)).

[21] "…the IRB shall require appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or in loco parentis. One individual may serve as advocate for more than one child. The advocate shall be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization" (45 C.F.R. § 46.409).

Additionally, the ability of guardians to consent on behalf of their wards to participation in research necessitates at least a minimal understanding of the research process and of DOC. We recommend that guardians be court-ordered to receive training on human subjects research and on DOC when they are appointed guardians of a person with a DOC.

Second, we recommend that guardianship appointments for those with brain injuries and DOC be time-limited rather than indefinite and revised over time to meet the evolving needs of a person in a MCS.

The initial guardianship order for a person possibly in a MCS should be for a period of no longer than a year, and then such order of guardianship should be revisited by the court regularly in a more than cursory manner so that the minimally conscious patient who recovers[22] can exercise autonomy to the degree to which they are able.[23] Current OHRP guidance documents explicitly acknowledge the possibility that a research participant's capacity to consent can change over the course of research. The guidance gives examples on research on progressive disorders or aging, wherein subjects may be competent to consent at the beginning of the research, but lose capacity over the course of the study. The guidance directs such persons to designate a LAR who can represent them throughout the study in the case of lost capacity (OHRP 2011c). What the guidance does not seem to envision, however, is capacity changes in the other direction, e.g., recovery. That is, a situation wherein a subject is not competent at the outset of the study, but regains capacity or cycles in and out of competence, a situation that is possible for a person in a MCS or other conditions such as bipolar disorder, formerly known as manic depression.

[22] The typical adult placed under guardianship is not expected to recover (Fins and Pohl in press), and most guardianships end when the ward dies (Cassidy 2013, 123). For persons with DOC under guardianship who are recovering, however, hospitals may wish to alert the probate courts of this fact, at which time the court can determine whether continued guardianship is in the person's best interest.

[23] Such limited duration guardianship orders may also save money on guardianship fees.

However, there is OHRP guidance on what happens when a child enrolled in a study becomes an adult through the course of the study, and the guidance directs the researchers to obtain consent again from the person now that parental/guardian consent is no longer sufficient (OHRP 2011d). If we analogize incapacitated persons who regain some decisional capacity during the study to children who become adults during the study, then this guidance would suggest that consent be obtained from the person being studied rather than their guardian.[24] If it is not possible to gain consent from a person in a MCS, but assent is possible, then assent should be obtained;[25] if assent is refused, then the subject should be not be enrolled in or should be disenrolled from the study. That is, a guardian's consent in this situation is necessary, but not sufficient when assent from the incompetent person is possible.

With time-limited guardianships and frequent reports to the court, this may mean that guardianship orders may be altered over time consistent with changes in the patient. For some patients with DOC, this may mean that their guardian starts with a general order of guardianship, giving the guardian all decision-making authority, but that as the incapacitated person recovers, the guardian's authority over certain decisions is removed, and the guardianship becomes more limited (e.g., authority for medical decisions or experimental treatment decisions is removed from the guardian, but authority for decisions about property is retained).[26] Such limited and individually tailored guardianships are consistent with the position of the 1997/1998 Uniform Guardianship and Protective Proceedings Act drafting committee's views on guardianship as a

[24] The New York State Task Force on Life and the Law (2014) also discusses how informed consent should be obtained prior to the study and then when risk and benefits significantly change or "when new scientific information becomes available" (34). We would include "regaining consciousness" or "regaining capacity" as part of "new scientific information." The Task Force report also notes that a common reason for withdrawing consent is regaining decisional capacity (37), which raises troubling questions for surrogate decision-making (if such a reason is common, it is unlikely that the surrogate is making the decision using the "substituted judgment" standard of decision-making).

[25] See Schiff et al. (2007), Schiff, Giacino, and Fins (2009), and Fins (2015) for an example of how assent for continued treatment was obtained from a person in a MCS while enrolled in a phase I DBS study.

[26] See also Bach and Kerzner (2010) for a discussion of supported decision-making as patient regains legal capacity.

last resort, limited to only the rights a ward cannot exercise, and aimed at assisting the ward in regaining capacity (National Conference of Commissioners on Uniform State Laws 1997, 1-4; Cassidy 2013).

It may also be that guardianship of any sort is inappropriate as a person with a DOC recovers, and that instead the Supported Decision-Making model is used, in which the ultimate decision-maker is the person with a disability, but they are offered help from family members, friends, and professions in understanding their choices (Burton Blatt Institute 2014). If guardianship is inappropriate, it is necessary for states to have clear procedures for restoration of the ward's rights (Cassidy 2013).

CONCLUSION

Many have offered recommendations for how best to involve persons with decisional impairments in research studies. While obtaining voluntary informed consent of research participants is important, so is equitable selection of subjects. Thus, some have argued that vulnerable groups—such as those without consent capacity—should not be excluded from research, but instead the research should be designed to minimize risks to them (NBAC 2001). Others have also called for inclusion of those with decisional impairments, but with additional safeguards once research involves more than minimal risk (Fins and Miller 2000; Silverman, Luce, and Schwartz 2004; New York State Task Force on Life and the Law 2014).[27]

We assert that it is important for those with brain injury and DOC to not be excluded from research solely because they are under guardianship. Instead, it is important that such persons be permitted to participate in research, so that their conditions and potential medical

[27] For a critique of additional safeguards for those with impaired decisional capacity, see Michels (1999, 1428).

interventions can be studied, and that those with similar conditions can benefit from the knowledge gained from these studies (Fins and Miller 2000; Saks et al. 2008; New York State Task Force on Life and the Law 2014; Fins 2015). Such persons also need access to experimental medical procedures, which may aid them in their recovery and in regaining decisional capacity.

The Common Rule is silent on whether those under guardianship can participate in clinical research, and only a few states regulate it. We propose that states adopt uniform laws, which can be written by the Uniform Law Commission,[28] explicitly permitting guardians to offer surrogate consent, and giving guidance to guardians on how to do so appropriately. We also propose that probate courts adopt guardianship practices that protect the autonomy and promote the wellbeing of persons with DOC, and allow for data collection and research on an important and neglected population.

[28] We recognize that not all laws drafted by the Uniform Law Commission are widely adopted by the states. The 1997 Uniform Guardianship and Protective Proceedings Act, for example, has only been adopted by five states and the District of Columbia. There is also a recent discussion in *JAMA* about uniform guardianship laws (Cohen et al. 2015) and difficulty in enacting them (Gillick 2015). If a draft of a uniform law was accompanied by state legislative lobbying around the issue of persons under guardianship having access to therapeutic research, however, it may be more widely adopted. It certainly would also have expressive value (Sunstein 1996), and may be incorporated into probate court decision-making even if not adopted by a state legislature.

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Table 1: State Laws on Guardian's Decision-Making Authority with Respect to Consenting to Incapacitated Persons Participation in Research

No Regulations on Research Participation[29]	Regulate Participation in Experimental Medical Procedures or Experiments Only	Regulate Participation in Experiments Generally (Medical and Behavioral Research)
	Alaska Stat. § 13.26.150(e): A guardian may not: (4) consent on behalf of the ward to the performance of an experimental medical procedure or to participation in a medical experiment not intended to preserve the life or prevent serious impairment of the physical health of the ward.	Fla. Stat. Ann. § 744.3215(4): Without first obtaining specific authority from the court, as described in s. 744.3725, a guardian may not: (b) Consent on behalf of the ward to the performance on the ward of any experimental biomedical or behavioral procedure or to the participation by the ward in any biomedical or behavioral experiment. The court may permit such performance or participation only if: 1. It is of direct benefit to, and is intended to preserve the life of or prevent serious impairment to the mental or physical health of the ward; or 2. It is intended to assist the ward to develop or regain his or her abilities.

[29] Some of these laws have complex exceptions or intersect with guardian's power to make healthcare decisions for an incapacitated person, which may have implications for the incapacitated person's participation in research, if the intervention is described as "therapeutic."

Alabama	Alaska	D.C.
Arizona	Arkansas	Florida
Colorado	California	Kansas
Connecticut	Minnesota	Nevada
Delaware	New Hampshire	Oklahoma
Georgia	North Dakota	Pennsylvania
Hawaii		Wisconsin
Idaho		
Illinois		
Indiana		
Iowa		
Kentucky		
Louisiana		
Maine		
Maryland		
Massachusetts		
Michigan		
Mississippi		
Missouri		
Montana		
Nebraska		
New Jersey		
New Mexico		
New York		
North Carolina		
Ohio		
Oregon		
Rhode Island		
South Carolina		
South Dakota		
Tennessee		
Texas		
Utah		
Vermont		
Virginia		
Washington		
West Virginia		
Wyoming		

Table 2: State Guardianship Laws on Therapeutic Experimental Intervention

Distinguish Therapeutic from Non-Therapeutic Research	Do Not Distinguish Therapeutic from Non-Therapeutic Research
Nev. Rev. Stat. Ann. § 159.0805(1): Except as otherwise provided in subsection 2, a guardian shall not consent to: (a): The experimental medical, biochemical or behavioral treatment of a ward; (c): The participation of a ward in any biomedical or behavioral experiment (2): The guardian may consent to and commence any treatment or experiment described in subsection 1 if the guardian applies to and obtains from the court authority to consent to and commence the treatment or experiment. (3): The court may authorize the guardian to consent to and commence any treatment or experiment described in subsection 1 only if the treatment or experiment: (a): Is of direct benefit to, and intended to preserve the life of or prevent serious impairment to the mental or physical health of, the ward; or (b): Is intended to assist the ward to develop or regain the ward's abilities.	D.C. Code Ann. § 21-2047.01: A guardian shall not have the power: (2) To consent to convulsive therapy, experimental treatment or research, or behavior modification programs involving aversive stimuli, unless the power to consent is expressly set forth in the order of appointment or after subsequent hearing and order of the court
Alaska California Florida Kansas Nevada Oklahoma Wisconsin	Arkansas D.C. Minnesota New Hampshire North Dakota Pennsylvania

Table 3: The Gradient of Guardian Consent Authority

Prohibit Consent to Experimental Procedures	Restrict Consent to Experimental Procedures to Cases of Preserving Life or Preventing Harm	Permit Consent to Experimental Procedures in Cases of Preserving Life, Preventing Harm, and Rehabilitation	Permit Consent to Experimental Procedures in Cases in which Ward would have Consented
N.D. Cent. Code Ann. § 30.1-28-12 (5-312)(4): Notwithstanding general or limited authority to make medical decisions on behalf of the ward, no guardian may consent to psychosurgery, abortion, sterilization, or experimental treatment of any kind unless the procedure is first approved by order of the court.	Okla. Stat. Ann. Tit. 30, §3-119(3): Except in an emergency and only as necessary to preserve the life of the ward, no guardian shall have the power to consent on behalf of the ward to an abortion, psychosurgery, removal of a bodily organ, performance of any experimental biomedical or behavioral procedure, or participation in any biomedical or behavioral experiment, except with specific authorization of the court having jurisdiction of the guardianship proceeding;	Kan. Stat. Ann. § 59-3075(e): A guardian shall not have the power [to consent to]: (6) performance of any experimental biomedical or behavioral procedure [or experiment] on the ward…without the prior review and approval of such by either an institutional review board…[or] review committee established…[to determine] whether the proposed procedure or experiment: (A) Does not involve any significant risk of harm to the physical or mental health of the ward, or the use of aversive stimulants, and is intended to preserve the life or health of the ward or to assist the ward to develop or regain skills or abilities; or (B) Involves a significant risk of harm to the physical or mental health of the ward, or the use of an aversive stimulant, but that the conducting of the proposed procedure or experiment is intended either to preserve the life of the ward, or to significantly improve the quality of life of the ward, or to assist the ward to develop or regain significant skills or abilities, and that the guardian has been fully informed concerning the potential risks and benefits of the proposed procedure or experiment or of any aversive stimulant proposed to be used, and as to how and under what circumstances the aversive stimulant may be used, and has specifically consented to such;	Wis. Stat. Ann. § 54.25(2)(d): Guardian authority to exercise certain powers. (c) The power to authorize the ward's participation in research that might not help the ward but might help others even if the research involves greater than minimal risk of harm to the ward if the guardian can establish by clear and convincing evidence that the ward would have elected to participate in such research; and the proposed research was reviewed and approved by the research and human rights committee of the institution conducting the research.
Arkansas District of Columbia Minnesota New Hampshire North Dakota Pennsylvania	Alaska Oklahoma	Florida Kansas Nevada	California Wisconsin