

Justice, Clinical Research and the Minimally Conscious State

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I. Introduction

Madam Chair and Commission Members, I am honored to be here today as the Commission considers Federal guidelines for research and questions of justice.

I would like to focus my remarks on research on subjects who lack decisional capacity, the Common rule and research that represents more than a minor increase over minimal risk without the prospect of direct benefit to individual subjects. Before I begin, let me state that I am a member of the New York State Task Force on Life and the Law and that the Task Force is considering many of these same issues. My comments today are mine alone and do not represent that body. I will provide the Commission a full copy of my remarks.

II. Research in Subjects with Disorders of Consciousness

My comments will be informed by my participation in investigative work involving patients with disorders of consciousness, namely the vegetative and minimally conscious states. I served as one of the four lead investigators of the 2007 *Nature* study of the first use of deep brain stimulation in the minimally conscious state, and in my role as a physician-ethicist helped to design the ethical framework for that trial.^{i ii iii}

I have also been involved with neuroimaging studies seeking to understand the ethical implications about emerging knowledge about the biological substrate of these conditions, mechanisms of recovery and efforts to improve diagnosis, prognostication and ultimately treatment.^{iv} I am currently completing a book on neuroethics and disorders of consciousness, to be published by Cambridge University Press, which is

based on my participation in this work as a co-investigator as well as in-depth interviews of family members of patients with disorders of consciousness.

Because brain states like the vegetative state and minimally conscious states can be confused – either through errors of omission or commission as during the Schiavo debate, let me seek to lay out a few key definitions when I speak about them.^{v vi} The vegetative state, first coined as a "syndrome without a name" by the Scottish neurosurgeon Bryan Jennet and --my teacher – the late Fred Plum in 1972 is a state of "wakeful unresponsiveness" -- an eyes-open state in which there are sleep-wake cycles but no response to the environment beyond those that are reflexive.^{vii} Biologically, this state has been understood as a functional brainstem in the absence of higher cortical function. Prominent legal cases such as Quinlan, Cruzan and Schiavo have featured patients who were permanently vegetative.

The diagnostic criteria for MCS called the Aspen Criteria were first published in 2002 and have allowed -- and indeed promoted -- diagnostic refinement between these two brain states.^{viii} The minimally conscious state, in contrast to patients who are vegetative are conscious, albeit "minimally" so. MCS patients respond to their environment. They may show intention, attention, and memory. They may track a visitor to their room, grasp for a ball or even say their name or respond to a command. The problem is that these patients only demonstrate these behaviors episodically and intermittently. This poses a huge clinical problem because when these behavioral manifestations of consciousness are not demonstrated the patients are easily confused with those who are vegetative.

Indeed, a recent study revealed that 41% of patients diagnosed as vegetative were in fact minimally conscious when properly assessed using a validated neurobehavioral rating scale.^{ix} We know of the locked-in syndrome, this – as others have said – is the locked out syndrome.^x

Forty one percent is an error rate that would be unconscionable in any other area of medicine and reflects the marginalization of this MCS population that has suffered from what I have described as a societal *neglect syndrome*, invoking the neurological analogy of patients with parietal lobe lesions who neglect part of their visual field. These patients have been out of our gaze amidst polemics and notions of futility that lead to the mistaken belief that nothing can or should be done to ameliorate their condition.

But, they make a justice claim on our health care system as conscious beings who have been labeled as permanently unconscious left to linger in their nursing home beds. They also make a justice claim on neuroscience research to be able to partake in the benefits of new technologies, which might restore or augment their abilities. And finally, for this to occur, this population makes a justice claim on us to figure out novel ethical and regulatory constructs that would allow surrogates to authorize their participation in research that is more than minimal risk and may not offer the prospect of direct medical benefit.

There is a sound scientific predicate to this argument. Biologically, the minimally conscious state is distinguished from the vegetative state by its functional integration of neural networks. While the vegetative brain is functionally disconnected from itself and *dis-integrated*,^{xi} the MCS brain works integrally. Multiple studies have shown the ability of MCS patients to activate integrated neural networks in response to language.^{xii xiii xiv xv}

This is in contrast to the VS brain, which only activates primary sensory areas in response to language or sound.^{xvi}

This distinction provides the biological *context*, which is central to the question of ethics and justice. Brains, which are, or have the capacity for functional integration, are amenable to interventions that might harness this latent capacity and restore functional communication and an ability to interact with others. This was the case with our work with deep brain stimulation in the minimally conscious state, which I would like to briefly describe.

Bilateral central thalamic DBS electrodes were implanted in a 38-year-old man who had been MCS for six years after severe traumatic brain injury following an assault.^{xvii} He has an initial Glasgow Coma Scale of 3 and had been vegetative for about 3 months before becoming MCS with having the ability of simple command following and visual pursuit. He had shown no incremental improvement for years. The results of a six-month double-blind cross over study showed an increased level of arousal, ability to eat by mouth and a regained ability to communicate up to six to seven word sentences. He could say the first 16 words of the Pledge of Allegiance and tell his mother that he loved her. Additional details of this complex study can be found in the materials I previously provided the Commission.

III. Surrogate Consent in Historical Context

It is well appreciated here that subjects who cannot provide autonomous consent constitute a vulnerable population, open to exploitation, unable, as they are to protect their interests or defend themselves against unwanted and unconsented to interventions.

This inability to provide consent for research participation may either displace authorization to surrogates or lead to a protectionist ethic that excludes this population from research of more than minimal risk without the prospect of direct benefit. Or it can lead to distortions, or confusion, in what is meant by the prospect of direct benefit and confusion about early phase research itself, which is primarily concerned about safety and not efficacy.

It is important to bring these issues about consent forward at this time because the recent news about the unethical Public Health Service activities in Guatemala decades ago remind us of the impetus for the original National Commission's charge from Congress under the National Research Act of 1974, just after the revelations about the Tuskegee Syphilis Study.

The National Commission given its historic moment made human subjects protections its primary focus. As outlined in the Belmont Report and elsewhere, your predecessor Commissioners, stressed three principles, the centrality of respect for persons, beneficence, and justice and the associated applications of these principles in the process of informed consent, risk-benefit assessment, and selection of subjects.

But given the shocking revelations of Tuskegee, the National Commission's appropriately focused on human subjects protections and not the promotion of access to research. When it came time to consider the question of justice, the emphasis was that the *burden* of research be properly and fairly distributed across society. Vulnerable populations should not shoulder a disproportionate share of the load simply because they were available for research. And given the legacy of cases like the Jewish Chronic Disease Hospital and Willowbrook here in New York, when and if research was to be

conducted in vulnerable populations, appropriate justification would need to be presented to IRBs before approval could be given.

Having said this, it is also important to note that the National Commission wrote a congressionally mandated report on psychosurgery in the year prior to Belmont in which they outlined a mechanism for surrogate consent in research and practice. I have noted previously^{xviii}:

Attempting to balance “access to potentially beneficial therapy” against the coercion or a breach of voluntariness, the Commission outlined a complex regulatory approach that required, among other strictures, that the proposed national psychosurgery advisory board determined that the specified psychosurgical procedure had a demonstrable benefit for the patient’s condition and that if the operation were to be performed as an element of a research protocol that these efforts be in compliance with the recommendations on research involving the institutionalized mentally infirmed.^{xix} (26330)

These recommendations were never put into law.

Restrictions on research for vulnerable subjects, including those with decisional incapacity, were further enumerated in the Common Rule. The closest we get to a standard for research without the direct prospect of benefit is the -- more liberal-- category of 46.406 in the children’s section of the Common Rule, which asserts, most notably in part (c) that:

6.406 Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.

HHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject, only if the IRB finds that:

- (a) The risk represents a minor increase over minimal risk;
- (b) The intervention or procedure presents experiences to subjects that are

reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;

(c) The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and

(d) Adequate provisions are made for soliciting assent of the children and permission of their parents or guardians, as set forth in 46.408.

To address these issues, the Clinton-era National Bioethics Advisory Commission relied upon a regulatory distinction between research that does and does not offer the prospect of direct medical benefit, which has a significant bearing on required safeguards.^{xx} Whereas phase III clinical trials, assess efficacy -- and can be understood as having the prospect of direct medical benefit -- the categorization of other types of clinical research is less clear. In fact, the line between beneficial and non-beneficial research can be blurred, especially at the frontiers of clinical investigation.

Phase I trials offer the prospect of medical benefit in the sense that there is a chance, though small, that some subjects will receive clinically significant improvement. But fundamentally, the purpose of early stage of research is to assess the safety of treatments by determining the maximum tolerated dose of experimental medications -- and the safety of devices in the case of DBS. Because research classified as having a prospect of benefit may require less stringent regulatory safeguards there might be the tendency to overemphasize potential benefits to phase I studies so as to facilitate the work.^{xxi xxii} This is problematic because it could distort the informed consent process, foster therapeutic misconceptions and violate notions of equipoise.

IV. Ethical Analysis and Recommendations

Clearly the conduct of research without consent or over the objections of a competent individual is an ethical lapse without justification. But this does not translate into making research authorized by surrogates suspect. This is paternalistic and robs the surrogate of an important decision-making role. Through my interviews with families with loved ones with disorders of consciousness, I have come to appreciate the burdens they have assumed and strongly believe that with this assumption of responsibility should come additional authority to consent to research with appropriate IRB oversight.

Nor should research without autonomous consent be problematic when the object of the intervention – as in the case with our work with DBS in MCS – the object of our work was the restoration of functional communication and the restoration of some degree of personal agency.

This was indeed what was observed in our DBS study. Although the subject was mute prior to implantation, with the stimulator in place he has been able to voice preferences when asked whether he wants to continue with a physical therapy session. As I have noted previously¹⁷:

His responses while seemingly routine are in fact demonstrative of a restitution of elements of his decision-making capacity. While they remain at the level of assent, and do not reach the level of formal consent, this degree of improvement is ethically noteworthy. In our view this progress is a further validation of the philosophical and regulatory arguments mustered to utilize a surrogate decision maker, the patient's legally authorized representative (LAR) -- to authorize enrollment in this protocol approved by three institutional review boards and granted a investigational new device exemption (IDE) by the Food and Drug Administration (FDA).^{1 xxiii xxiv xxv xxvi xxvii xxviii xxix xxx} By asserting such a role for surrogate authorization, given the subject's inability to provide consent because of his disorder of consciousness, we have been able to restore a modicum of

personal agency and patient self-determination. This degree of autonomy has allowed him a degree of new found control over his environment and facilitated engagement with others, an outcome we take as a moral good.

To allow work such as this to continue and to fulfill the justice claims, indeed meet the civil rights of those individuals whose expression of consciousness is dependent upon others or a prosthetic intervention, I would make the following six recommendations to facilitate surrogate consent:

1. Despite the recent historical revelations about Guatemala, avoid the temptation to respond with additional prohibitions on appropriate and sound surrogate research. Do not respond to these egregious and horrifying findings by further excluding a population in need of research participation.
2. Create a fourth category in the Common Rule for research that involves more than a minor increment over minimal risk without the prospect of direct benefit and stipulate the conditions when surrogate consent would be permissible.
3. Appreciate that the Belmont Report's commentary about equitable distribution of the burdens of research could equally be argued as suggesting a fair distribution of the *benefits* of research. And with that appreciation, once and for all, unequivocally, enshrine in Federal law a role for the legally authorized representative (LAR) to consent to research of more than a minor increment over minimal risk without the prospect of direct medical benefit with appropriate IRB review. This can be facilitated by a consensus model of consent, which involves the LAR, patient's physician, investigator

and a community member, Research Subject Advocate familiar with the patient's condition, which I previously described.²⁸

4. Avoid the temptation to create a super IRB as originally proposed by Jay Katz and the Psychosurgery Report in 1977 to tackle the difficult cases. This will prove unworkable and displaces problems better resolved locally with sufficiently skilled IRBs.

5. Endorse a mechanism for prospective authorization of research advance directives but do not rely upon this approach at the exclusion of empowering the LAR as above.

6. Make a recommendation to President and Congress for additional (or the reallocation) of resources to support research compliance and research ethics programs in intra-mural and extra-mural programs necessary to support these recommendations.

Thank you very much for the privilege of being with you this afternoon. I would welcome any questions.

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