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COMMENTS ON THE SECOND REPORT OF THE MARYLAND ATTORNEY GENERAL'S RESEARCH WORKING GROUP

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I. INTRODUCTION

The Maryland Attorney General's Research Working Group (Research Working Group), in its Second Report recommending legislation for regulating research with decisionally incapacitated individuals, has produced a path-breaking document.¹ It makes a major contribution to the debate over a complex, difficult, and controversial topic. My comments on the recommended legislation draw on my experience over the past six years as a member of the institutional review board (IRB) for the intramural research program of the National Institute of Mental Health. The IRB reviews and approves research that involves patients with Alzheimer's disease and severe psychiatric disorders, including schizophrenia.

II. SCOPE OF WORKING GROUP'S PROPOSED LEGISLATION CONCERNING DECISIONALLY INCAPACITATED SUBJECTS

The Legislative Findings of the proposed legislation state that "[r]esearch involving decisionally incapacitated individuals may be essential under some circumstances if science is to understand and ultimately combat diseases of the brain, including Alzheimer's Disease, severe psychiatric disorders, severe trauma, stroke, and other causes of decisional incapacity."² This suggests that the recommended legislation be intended to encompass research involving patients with a broad range of conditions, including "severe psychiatric disorders" such as schizophrenia. Overall opinion would concur that patients

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1. Jack Schwartz, Office of the Md. Att'y Gen., Second Report of the Attorney General's Research Working Group (May 1997) [hereinafter Second Report] (the Second Report is reprinted in the appendix to this issue of the *Journal of Health Care Law & Policy*).

2. Second Report, *supra* note 1, at A-4 (§ 20-501(c) of the draft legislation; reprinted in Appendix A to the Second Report).

with the dementing condition of Alzheimer's disease lose decision-making capacity as the disease progresses. Considerable controversy, however, surrounds the question of whether patients with severe psychiatric disorders, such as schizophrenia and profound depression, are decisionally incapacitated with respect to research participation.³ For the past 20 years, many caretakers and researchers working with the mentally ill have claimed that mentally ill persons are capable of informed consent.⁴ Therefore, some psychiatric investigators⁵ have resisted more stringent requirements for mentally ill research subjects.⁶

We should not presume that, as a class, patients with schizophrenia or severe depression lack decisional capacity. Nor should we presume that such patients are just as capable of giving informed consent for participation in research as normal volunteers or patients with non-psychiatric medical disorders. The meager data from empirical studies, although subject to conflicting interpretations, raise concerns about the decision-making capacity of severely ill patients with schizophrenia.⁷ In general, diagnostic categories do not reliably indicate whether or not individual patients are incapable of giving informed consent to participate in research.⁸ Rather, it is necessary to assess the patients' ability to understand the nature of a specific study, what participation involves, the risks and potential benefits to participation, and the alternatives to research participation. Along with these con-

3. See Barbara H. Stanley & Michael Stanley, *Psychiatric Patients in Research: Protecting their Autonomy*, 22 COMPREHENSIVE PSYCHIATRY 420, 420-21 (1981).

4. See *id.* at 421.

5. The draft legislation defines "investigator" as a person who conducts research by means of: (1) physical procedures by which data are gathered from a living individual; (2) manipulation of an individual or the individual's environment; (3) communication or interpersonal contact between an investigator and individual; or (4) gathering individually identifiable private information, including information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public. Second Report, *supra* note 1, at A-3 (§ 20-501(1)(1)-(4) of the draft legislation).

6. A number of mental health professionals feel a protective stand is unwarranted. See Stanley & Stanley, *supra* note 3, at 421.

7. See Thomas Grisso & Paul S. Applebaum, *Comparisons of Standards for Assessing Patients Capacities to Make Treatment Decisions*, 152 AM. J. PSYCHIATRY 1033, 1035 (1995); see also Paul S. Applebaum, *Rethinking the Conduct of Psychiatric Research*, 54 ARCHIVES GEN. PSYCHIATRY 117, 118 (1997); William T. Carpenter, Jr. et al., *The Rationale and Ethics of Medication-Free Research in Schizophrenia*, 54 ARCHIVES GEN. PSYCHIATRY 401, 405 (1997); Joseph J. Fins & Franklin G. Miller, *The Call of the Sirens: Navigating the Ethics of Medication-Free Research in Schizophrenia*, 54 ARCHIVES GEN. PSYCHIATRY 415, 415-416 (1997).

8. See Carpenter, Jr. et al., *supra* note 7, at 405.

siderations, researchers must assess the patients' ability to voluntarily agree to enroll in the study.

III. COMMENTS ON DRAFT LEGISLATION

A. Terminology

There are some minor points to discuss to clarify the definition of terms. First, the term "monitor" in the proposed legislation seems inappropriate.⁹ A monitor is someone who is designated to carry out an activity to make sure the rules are being followed.¹⁰ However, the role of the monitor in this law includes giving consent when neither a research agent, health care agent, nor surrogate are available to speak for the potential research patient who lacks decisional capacity.¹¹ Giving legally valid consent is a function that, strictly speaking, lies outside the scope of monitoring. Moreover, the term connotes a policing role, and thus may provoke resistance on the part of investigators. It would be desirable, therefore, to formulate a more fitting term for this role. Likewise, the definition of "monitor" should give some indication of the functions included in this important role.

The definition of "surrogate" refers the reader to another part of the law, not included in the Second Report.¹² If the Final Report is intended as a document to be used by investigators and IRBs, then all the important terms should be defined and provided. This is especially significant for "surrogate" since it is possible that this term might be confused with "health care agent."¹³

B. Research Involving More than Minimal Risk

The two sections in the draft legislation concerning what counts as research posing more than minimal risk merit critical scrutiny. For example, section 20-504(d)(3) states that:

An IRB may not determine that research presents a minimal risk if the research would expose the class of subjects who are

9. See Second Report, *supra* note 1, at A-4 (§ 20-502(o) of the draft legislation).

10. See *id.*

11. See *id.*

12. See *id.* at A-5. Pursuant to the Annotated Code of Maryland, "surrogate" means an adult authorized to make health care decisions for an individual. MD. CODE ANN., HEALTH-GEN. 1 § 5-605 (1994).

13. Surrogates are more limited than are health care agents in their ability to consent for decisionally impaired individuals. The proposed legislation defines a "health care agent" as appointed by an individual under an advance directive and authorized under the Health Care Decisions Act to make health care decisions for the individual. Second Report, *supra* note 1, at A-2 (§ 20-502(f) of the draft legislation).

intended to be enrolled in the research to a loss of dignity greater than ordinarily experienced by individuals who are not decisionally incapacitated during the performance of routine physical or psychological examinations or tests.¹⁴

In principle, it seems appropriate to include consequences to a person's dignity within the scope of risk assessment for research. However, it is far from clear what is meant by "loss of dignity." Clarifying this phrase by providing examples would aid IRBs in determining what type of research crosses the "minimal risk" threshold.

The draft legislation further stipulates in section 20-504(d)(4) that:

An IRB may not certify research as presenting a minimal risk or a minor increase over minimal risk if the research would expose the class of subjects who are intended to be enrolled in the research to the reasonable possibility of: (i) severe or prolonged pain or discomfort; or (ii) deterioration in a medical condition.¹⁵

Interpretation of this provision presents some potentially serious problems. What does "reasonable possibility" mean? What makes a possibility reasonable, as opposed to unreasonable? Is a certain minimal probability of serious harm what is contemplated by "reasonable possibility"? If a minimum probability of serious harm is the proper meaning then this should be made explicit.

Problems of interpreting what constitutes a "minimal risk" or a "minor increase over minimal risk" within the terms of the proposed legislation can be illustrated by focusing on two common types of studies in psychiatric research: challenge studies and studies using positron emission tomography (PET) scans. Challenge studies involve administering drugs or procedures likely to provoke characteristic symptoms of psychiatric disorders for the purpose of investigating the pathophysiology of these disorders under controlled conditions.¹⁶ These studies are not therapeutic and present no prospects of direct medical benefit to the patients who participate in them.¹⁷ The symptoms provoked are usually relatively mild and not prolonged.¹⁸ How-

14. Second Report, *supra* note 1, at A-7.

15. *See id.*

16. Franklin G. Miller & Donald L. Rosenstein, *Psychiatric Symptom-Provoking Studies: An Ethical Appraisal*, 42 *BIOLOGICAL PSYCHIATRY* 403, 403 (1997).

17. *See id.* at 404.

18. *See id.* at 405-06.

ever, in published reports of challenge studies,¹⁹ provoked symptoms for some patients have been more severe and long lasting.²⁰

Challenge studies with decisionally incapacitated patients may qualify as more than a minor increase over minimal risk, even if the symptoms they produce are not severe or long-lasting. A typical paradigm for schizophrenia research is to administer a psychostimulant, such as methylphenidate, which provokes psychotic symptoms in schizophrenic patients. The symptoms of distorted thought and mood provoked in this type of research may, or may not, be considered "severe" or as causing prolonged discomfort. In any case, they are likely to be familiar to the patients, since they are characteristic of their disorder. Despite differences of opinion concerning the seriousness of the symptom provocation,²¹ it is arguable that to produce by means of research interventions the symptoms of a disease in patients who suffer from that disease would be to cause a "deterioration in a medical condition." The patient is made worse, even if only for a short time.

If the interpretation of challenge studies as presenting more than a minor increase over minimal risk is correct, then, according to the draft legislation, such studies with decisionally incapacitated patients could only be conducted under the very restrictive conditions of § 20-510 which addresses "no expected benefit research."²² These conditions require that the patient, while capacitated, prepare an advance directive authorizing participation in the very sort of research protocol under consideration—to be confirmed by a monitor. In addition, the research agent²³ who understands the goals and risks of the research also to be confirmed by the monitor—determines that the patient would consent to participate in this study if capable of giving informed consent.²⁴ Whether this constitutes a desirable or undesirable limitation of potentially promising research needs to be carefully considered. Challenge studies in psychiatric research with decisionally incapacitated patients are morally problematic but justifiable, provided that the challenge studies have scientific merit and adequate safeguards in place. If the law makes challenge studies by their very

19. *See id.*

20. *See id.* at 406.

21. *See id.* at 405-06.

22. Second Report, *supra* note 1, at A-14.

23. "Research agent" is defined in § 20-502(r) of the draft legislation as "an adult who, under an advance directive authorizing research participation, is expressly authorized to make decisions regarding an individual's participation in research, whether or not the research agent is also a health care agent or surrogate." *Id.* at A-5.

24. *Id.* at A-15 (§ 20-510 of the draft legislation).

nature more than a minor increase over minimal risk, investigators will have a very strong incentive to circumvent legal restrictions by taking the stance that all patients involved in these studies are fully capable of giving informed consent.

Similarly, under the draft legislation, the interpretation of research involving PET scans may involve more than a "minor increase over minimal risk." PET scans, described simplistically, involve taking a "picture" of activity in the brain with the use of injected radioactive substances.²⁵ PET scans are common tools of neurological and psychiatric research and are typically employed in studies that are not therapeutic and pose no direct medical benefits to the subjects.²⁶ Does a PET scan count for more than a minor increase over minimal risk? Out of a few thousand PET scans performed at NIH, complications have occurred in a few patients connected with arterial lines used in the scanning procedure—complications that have required surgery to correct. Thus, although the risk is slight, it would seem that a "reasonable possibility" exists of "severe or prolonged pain or discomfort" or "deterioration in a medical condition" resulting from a PET scan.²⁷ Furthermore, the use of radiation might be considered to make these studies more than minimal risk. Although there is no documented evidence of harm caused by exposure to the amount of radiation produced by PET scans, it is possible that low doses of radiation can cause serious harm. Given the theoretical risk, differences of opinion are likely concerning whether the use of radiation in these studies expose the subjects to the "reasonable possibility" of a "deterioration in a medical condition."²⁸ It would be quite unfortunate if the powerful research tool of PET scans were interpreted as posing more than a "minor increase over minimal risk." Unless the language of section 20-504(d)(4) of the draft legislation is changed, research using PET scans is arguably vulnerable to being placed in the most restrictive class of research.

These reflections lead to the more philosophical question of whether it is a good idea to specify in law what counts as greater than minimal risk research. A consideration in favor of such specification is the fact that the concept of minimal risk is otherwise vague and elastic. It can be stretched to fit diverse research procedures, provided that investigators and IRB members think the research is justified. Yet the potential problems posed by applying the Research

25. MARVIN LICKEY & BARBARA GORDON, *MEDICINE AND MENTAL ILLNESS* 71-72 (1991).

26. *Id.*

27. Second Report, *supra* note 1, at A-7 (§ 20-504(d)(4) of the draft legislation).

28. *Id.*

Working Group's effort to specify criteria for research that is more than minimal risk raise doubts about the wisdom of such specificity in these regulations. The federal regulations, following the recommendations of the National Commission for the Protection of Human Subjects, define "minimal risk" but do not stipulate criteria for research that is greater than minimal risk.²⁹ Judgments about this are left to the discretion of IRBs.³⁰ A compromise position is to translate the *rules* stipulating conditions that make research more than minimal risk into *guidelines*, specifying criteria for risk assessment, to be used by IRBs in determining when research poses greater than minimal risk. Two corrective changes are suggested. First, clear language should replace the ambiguous term "reasonable possibility." Second, the Research Working Group should consider qualifying the phrase "deterioration in a medical condition" by indicating that the deterioration exceeds some threshold level of minimal severity and by introducing a time factor, for example, a deterioration that is more than transient.

C. *The Scope of Expected Benefit Research*

Turning to section 20-507(a)(1), "expected benefit research," it is misleading to describe this research as pertaining to "the *class* of decisionally incapacitated individuals who have been authorized by an IRB to be enrolled in research."³¹ The presumption is that "class" refers to refer to the specific group of subjects to be enrolled in a research protocol. But the term "class" might be interpreted much more broadly to include all those persons subject to the disorder under study. Whereas non-therapeutic studies, by definition, have no expected benefit for the subjects of the study, they may in the future lead to benefit for the "class" of patients with a particular disorder. The latter interpretation of "class" would allow research normally having "no expected benefit" to be construed as "Expected benefit research." It is therefore important to make perfectly clear that the prospect of direct medical benefit pertains only to the subjects of a specific protocol.

29. 45 C.F.R. § 46.102(i). The regulations define minimal risk as "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." *Id.*

30. ROBERT J. LEVINE, *ETHICS AND REGULATION OF CLINICAL RESEARCH* 248 (1986).

31. Second Report, *supra* note 1, at A-10.

D. Research with Individuals Who Have Never Had Decisional Capacity

Another potential problem with the draft legislation is that it may be interpreted as excluding "no expected benefit research" for subjects who have never had decisional capacity. The stipulations for all three categories of "no expected benefit research" seem to require that the research agent, health care agent, surrogate, or monitor determine that the subject without decisional capacity would consent to participate in research if able to give informed consent.³² Is it possible to make such a determination in the case of someone who has never had decisional capacity — for example, an individual with profound mental retardation? It is suspected that it may often, if not always, be a fiction to make a judgment that an individual who never had capacity would consent to participation in research if capacitated. For on what basis would the judgment be made? Is it the intent of the Research Working Group to rule out all "no expected benefit research" for subjects who never had decisional capacity? Would this be desirable?

Explicit attention to research with subjects who have never had decisional capacity seems warranted. Greater restrictions on research with these subjects may be justified, since they lack the ability to specify in an advance directive or express verbally their preferences concerning participation in research. Perhaps such subjects should be enrolled in no expected benefit research only if it poses no more than minimal risk.³³

E. Loss of Decisional Capacity During Research

Finally, the law as currently drafted does not seem to provide any clear provision for the case of a subject who gives informed consent to enter research but becomes incapacitated during the course of a study. It would be desirable to have a section explicitly devoted to

32. *Id.* at A-12 (§ 20-508 of the draft legislation).

33. A more recent draft reflects this concern. The proposed statute states in pertinent part: "No legally authorized representative other than a research agent or health care agent may consent to a decisionally incapacitated individual's participation in [no expected benefit, minor increase over minimal risk] research." Jack Schwartz, Office of the Md. Att'y Gen., Third Report of the Attorney General's Research Working Group (August 1, 1997) [hereinafter Third Report] (the Third Report is reprinted in the appendix to this issue of the *Journal of Health Care Law & Policy*). Moreover, for research which is no direct benefit and more than a minor increase over minimal risk, the draft permits only research agents to consent, and only when, among other requirements, a monitor confirms that "the research is unambiguously included in the individual's advance directive authorizing research participation." *Id.* at A-22 (§§ 20-516(b)(1)(I)(d) of the draft legislation; reprinted in Appendix A to the Third Report).

substitute decision-making by a "legally authorized representative" in this situation. Furthermore, for certain types of research, it is predictable that some of the subjects will lose capacity during the course of the research. For these studies, the IRB should require that the subjects designate in advance a research agent to make decisions concerning continued participation of the subject in case of decisional incapacity.

IV. CONCLUSION

In sum, I recommend five changes for the proposed Maryland legislation governing research with decisionally incapacitated patients. One, the definitions should explain the role of the monitor and what is meant by a surrogate, as distinct from a health care agent. In addition, a more fitting label than "monitor" should be adopted.³⁴ Two, the sections stipulating what counts as more than minimal risk should be transformed into guidelines for IRBs to assess the risk level of prospective studies.³⁵ Furthermore, examples of loss of dignity should be indicated,³⁶ "reasonable possibility" should be replaced by a clearer term,³⁷ and "deterioration in a medical condition" should be qualified both with respect to degree and duration.³⁸ Third, the misleading term "class" should be omitted from the provision stipulating the scope of "expected benefit research."³⁹ Fourth, guidelines for research with subjects who have never had decisional capacity should be included, and finally, the law should address substitute decision making for patients who lose decisional capacity in the course of research.

34. Second Report, *supra* note 1, at A-4 (§ 20-502(o) definition of "monitor" in the draft legislation); *accord id.* at A-5 (§ 20-502(s) definition of "surrogate"); *id.* at A-2 (§20-502(f) definition of "health care agent").

35. *Id.* at A-5 (§ 20-504 of the draft legislation).

36. *Id.* at A-7 (§ 20-504(d)(3) of the draft legislation).

37. *Id.* (§ 20-504(d)(4) of the draft legislation).

38. *Id.* (§ 20-504(d)(4)(ii) of the draft legislation).

39. *Id.* at A-10 (§20-507(a)(1) of the draft legislation).