

1 Appendix I. HISTORY OF REGULATORY EFFORTS IN THE UNITED
2 STATES

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4 When the National Commission was created in 1974, the decisionally
5 impaired were among the special populations that it intended to consider, partly
6 because of the controversy about lobotomy. In its 1978 *Report and*
7 *Recommendations on Research Involving Those Institutionalized as Mentally*
8 *Infirm*,¹ which came at the very end of its tenure, the National Commission
9 rejected both the Nuremberg Code's complete ban and the 1964 Declaration of
10 Helsinki's limitation on the involvement of incapable subjects in research. The
11 members of the National Commission believed a less restrictive approach was
12 justified to avoid indirect harm to incapable persons by crippling research
13 efforts designed to yield potential treatment for these persons' conditions. They
14 introduced this idea as follows:

15 [S]ince some research involving the mentally infirm cannot be
16 undertaken with any other group, and since this research may
17 yield significant knowledge about the causes and treatment of
18 mental disabilities, it is necessary to consider the
19 consequences of prohibiting such research. Some argue that
20 prohibiting such research might harm the class of mentally
21 infirm persons as a whole by depriving them of benefits they
22 could have received if the research had proceeded.²

23 This concept marked an important turning point in the social philosophy
24 underlying the regulation of human subjects research, in that benefits to others

¹National Commission, *Report and Recommendations, Research Involving Those Institutionalized as Mentally Infirm* (hereinafter *Report on Institutionalized Persons*) (Washington, DC: Department of Health, Education and Welfare [DHEW], 1978), pg. no.

²*Ibid.* , 58.

1 (particularly others who now or may in the future suffer from the same
2 disorder) who were not participating in a particular research protocol could now
3 be given more weight. The National Commission concluded that the dual goals
4 of benefiting mentally infirm persons and protecting individual subjects from
5 undue harm could be met by a third approach: incapable subjects could be
6 involved in studies offering them potential direct benefit, as well as studies that
7 did not offer potential direct benefit, as long as the burdens and risks of
8 research participation did not exceed a certain level.

9 Based on this general approach, the National Commission created a
10 framework for evaluating research involving incapable subjects. Its proposals
11 regarding children and institutionalized persons with mental impairments were
12 similar, though with some variation, and had several elements in common: a
13 requirement to justify the involvement of these subject groups rather than
14 alternative but less vulnerable subject populations; a hierarchy of research
15 categories establishing more rigorous substantive and procedural standards for
16 proposals presenting more-than-minimal risk to incapable subjects; and a
17 mechanism for incapable subjects to provide input in the form of "assent" or
18 objection to study participation—that is, a simple yes or no when questioned
19 about willingness to be in a study.

20 Differences in the recommendations on children and institutionalized
21 persons were based on the National Commission's recognition that some adults
22 institutionalized as mentally infirm retain the ability to give an informed and
23 voluntary decision. Because of concerns about the vulnerability of
24 institutionalized persons, however, the National Commission recommended that
25 IRBs be given discretion to appoint "an auditor to observe and assure the
26 adequacy of the consent process for research" that presents greater-than-
27 minimal risk. Moreover, the National Commission believed such auditors

1 should be *required* in projects presenting no prospect of direct benefit and
2 more-than-minimal risk to subjects. Their proposals also gave incapable adults
3 more authority than children to refuse study participation.³ Finally, because
4 incapable adults usually lack the legal guardian that most children have, the
5 National Commission noted that in some cases a court-appointed guardian
6 would be required to authorize research participation.

7 In response to the National Commission's work, the Department of
8 Health, Education and Welfare (DHEW) proposed regulations to govern
9 research on the two populations. Those affecting children were adopted by the
10 Department of Health and Human Services (DHHS) in June 1983,⁴ but those
11 affecting persons institutionalized as mentally disabled never were.⁵ The
12 Secretary of DHHS attributed the government's failure to do so to "a lack of
13 consensus" on the proposed regulatory provisions and to a judgment that the
14 general regulations governing human subjects' participation sufficiently
15 incorporated the National Commission's recommendations.⁶ Robert Levine
16 blames the reported lack of consensus on DHEW's earlier failure to adhere to
17 the National Commission's recommendations.⁷ DHEW's proposed regulations
18 indicated that consent auditors might be mandatory for all research involving

³The National Commission required explicit court authorization to involve an objecting institutionalized person in research. In contrast, the group recommended that parents be permitted to authorize research over a child's objection if the study presented a prospect of direct benefit to subjects not available outside the research context.

⁴"Protection of Human Subjects, Additional DHHS Protections for Children Involved as Subjects in Research" 48 no. 9818 (8 March 1983): pg. no. . microfiche.

⁵"Protection of Human Subjects, Proposed Regulations on Research Involving Those Institutionalized as Mentally Disabled," *Federal Register* 43 no. 53950 (17 November 1978): pg. no. . microfiche.

⁶President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, *Implementing Human Research Regulations* (Washington, DC: Government Printing Office, 1983): 23–9.

⁷R.J. Levine, "Proposed Regulations for Research Involving Those Institutionalized as Mentally Infirm: A Consideration of Their Relevance in 1996," *IRB* (September-October 1996): 1; see also R. Bonnie, "Research with Cognitively Impaired Subjects," 107. Bonnie also refers to opposition to special regulations for persons with mental illness on grounds that such an approach would foster negative stereotypes about such individuals.

1 institutionalized mentally disabled persons, and suggested that the authorization
2 of an additional person assigned the role of independent advocate might be
3 necessary before an incapable person could become a research subject. During
4 the public comment period, many respondents objected to these additional
5 procedural requirements, presumably on the belief that they were unnecessary
6 and overly burdensome to research.⁸

7 With the exception of the Institutionalized as Mentally Infirm
8 recommendations, the 1981 DHHS rules largely followed from the National
9 Commission’s work. In 1991, these rules were codified for 16 federal agencies
10 that conduct or sponsor research with human subjects and are now known as the
11 “Common Rule.”⁹ The regulations authorize IRBs to institute additional but
12 unspecified safeguards for research involving vulnerable groups, including the
13 mentally disabled.¹⁰ These safeguards could involve consultation with
14 specialists concerning the risks and benefits of a procedure for this population,
15 or special monitoring of consent processes to ensure voluntariness. It is not
16 known how frequently IRBs actually implement such measures.¹¹

17 In the United States today, research involving adults diagnosed with a
18 condition characterized by mental impairment is governed by no special
19 regulations, but falls instead under the Common Rule, in which a few provisions
20 address research involving persons with mental disabilities. First, the Rule
21 identifies "mentally disabled persons" as a vulnerable population, and directs
22 institutional review boards to include "additional [unspecified] safeguards . . . to

⁸Ibid.

⁹“Federal Policy for the Protection of Human Subjects: Notices and Rules,” *Federal Register* 56 nos. 28002–32 (18 June 18, 1991): pg. no., microfiche.

¹⁰Ibid.

¹¹National Institutes of Health Panel Report, *Research Involving Individuals with Questionable Capacity to Consent: Ethical Issues and Practical Considerations for Institutional Review Boards (IRBs)* (27 February 1998), pg. no. The report indicated that IRBs regularly exercise this authority.

1 protect the rights and welfare" of mentally disabled research subjects. It also
2 advises IRBs to ensure that "subject selection is equitable," and that mentally
3 disabled persons are not targeted for involvement in research that could be
4 conducted on a less vulnerable group.¹² Finally, "[i]f an IRB regularly reviews
5 research that involves a vulnerable category of subjects, such as . . . mentally
6 disabled persons, consideration should be given to the inclusion of one or more
7 individuals who are knowledgeable about and experienced in working with
8 these subjects."¹³ The Common Rule allows an incapable individual's "legally
9 authorized representative" to give valid consent to the individual's research
10 participation,¹⁴ but provides no definition of incapacity, no guidance on the
11 identity or qualifications of a subject representative beyond "legally
12 authorized," and no guidance on what ratio of risks to potential benefits is
13 acceptable.

14 In the 1980s and 1990s, numerous groups and individuals expressed
15 dissatisfaction with gaps in the existing regulations. After the Advisory
16 Committee on Human Radiation Experiments reviewed eight studies conducted
17 in the early 1990s involving adult subjects with uncertain decisionmaking
18 capacity, and found that four of the studies required subjects to undergo
19 diagnostic imaging that offered them no prospect of direct benefit and that two
20 appeared to present greater-than-minimal risk to the subjects, it noted, "there
21 was no discussion in the documents or consent form of the implications for the
22 subjects of these potentially anxiety-provoking conditions. Nor was there
23 discussion of the subjects' capacity to consent or evidence that appropriate
24 surrogate decision makers had given permission for their participation."¹⁵

¹²45 CFR 46.111(a)(3), (b).

¹³*Ibid.*, 107(a).

¹⁴*Ibid.*, 116.

¹⁵ACHRE, *Final Report*, 706–7.

1 Inquiries into studies involving rapid medication withdrawal from persons
2 diagnosed with schizophrenia have also raised questions about the adequacy of
3 current federal policy and the ethical acceptability of certain existing research
4 protocols.¹⁶

5 We are not aware of strong evidence that IRBs are actively using, or not
6 using, their existing discretionary authority when reviewing protocols involving
7 individuals with mental or brain disorders. Although IRBs currently have
8 authority to monitor research in progress, including research involving persons
9 with mental disorders, it does not appear that such monitoring routinely occurs,
10 possibly because institutional and other resources have not been devoted to this
11 critical activity. Observers of the review process agree that although the
12 workload of many IRBs at some of the largest research centers has greatly
13 increased in recent years, the institutional support for IRB activities has often
14 not kept pace.¹⁷ While some institutions have responded to this increase by
15 establishing more than one board, the practice may not be widespread enough.
16 According to the report of the DHHS Office of the Inspector General,
17 monitoring of a protocol's progress after its initial approval is practically
18 nonexistent apart from investigators' routine filing of annual progress reports.
19 After the initial stages, local review has only minimal impact on actual research
20 practices.¹⁸

21 The lack of more specific federal guidance on research involving persons
22 with mental disorders has also meant that research not under federal jurisdiction
23 has gone its own way, or rather at least 50 different ways, because laws and

¹⁶A. Shamoo, "Ethical Concerns."

¹⁷Department of Health and Human Services, Office of the Inspector General, *Institutional Review Boards: Their Role in Reviewing Approved Research* (Washington, DC: DHHS, 1998).

¹⁸U.S. General Accounting Office, *Continued Vigilance Critical to Protecting Human Subjects*, report to the Ranking Minority Member, Committee on Governmental Affairs, U.S. Senate, Scientific Research (Washington, DC: Government Accounting Office, 1996).

1 regulations vary widely; most states have no rules that specifically apply to
2 research involving this population while some states have quite restrictive
3 regulations. Several states currently prohibit certain types of research on
4 persons with mental disorders, research which presents greater than minimal
5 risk and from which subjects are not likely to benefit.¹⁹ This suggests that both
6 IRBs and researchers may have trouble identifying (and thus following) the
7 procedures and standards that are requisite to ethical and legal investigations
8 involving persons with mental disorders, even in states that have attempted to
9 provide the badly needed guidance.

10 Uncertainty about legal and ethical norms can contribute to an
11 adversarial tone in public discourse about this kind of research. Indeed, as
12 events in New York State illustrate, advocacy of sharply differing ethical

¹⁹Those states are Alaska. See, e.g., Alaska Stat. §47.30.830 (Michie 1996) prohibiting experimental research on state mental health patients that involve “any significant risk of physical or psychological harm”; Delaware Code Ann. tit. 16, §51.75(f) (1995) prohibiting any resident of a state mental hospital from being approached “to participate in pharmaceutical research if [the] patient is incapable of understanding the nature and consequences of [the] patient’s consent”); Delaware Code Ann. tit. 16, §51.74 (1995) prohibiting certain classes of mental hospital residents, regardless of competency, from participating in pharmaceutical research; 405 Illinois, Comp. Stat. Ann. 5/2-110 (West 1993) providing that parent or guardian cannot consent to ward’s participation in any “unusual, hazardous, or experimental services” without approval by court and determination that such services are in the “best interests” of the ward); Massachusetts Regs. Code tit. 104, §13.01-.05 (1995) prohibiting research on patients in mental facilities that will not provide direct, therapeutic benefit and prohibiting research on patients with mental disabilities where the risk is more than minimal and exceeds the benefit to the subject; Missouri Ann. Stat. §6.30.115 (8) (West Sup. 1997) preventing state mental health patients from being “the subject of experimental research,” with exceptions, and prohibiting biomedical or pharmacological research from being performed on any individual with mental disabilities if that research will have no direct therapeutic benefit on the individual research subject; Diane E. Hoffman and Jack Schwartz, *Proxy Consent to Participation of the Decisionally Impaired in Medical Research*, Maryland’s Policy Initiative, I J. Health Care Law and Policy 136, nos. 9 and 12 (1997) citing state statutes which provide restrictions for research on the decisionally impaired; John C. Fletcher and Alison Whitman, *A New Consent Policy for Research with Impaired Human Subjects*, *Psychopharmacology Bulletin* 23 (1987): 382. Virginia’s state statute also [to be completed]. Washington State’s statute (RCA 7.70.065) permits consent on behalf of an incompetent subject by (1) the appointed guardian, (2) the person to whom the subject has given a durable power of attorney including the authority to make health care decisions, (3) the subject’s spouse, (4) the adult children of the subject, (5) the parents of the subject, and (6) the adult siblings of the subject, in that order of priority. According to this statute, a legally incompetent subject for research purposes is one who is incapable of providing informed consent by reason of unconsciousness, mental illness, developmental disability, senility, excessive use of drugs, or other mental incapacity (RCA 11,88.010).

1 perspectives can result in litigation. In a case called *T.D. v. New York State*
2 *Office of Mental Health*, several individuals and organizations challenged
3 regulations of the New York State Office of Mental Health with respect to
4 participation in greater than minimal risk research by minors and persons who
5 lacked the capacity to give informed consent. In 1995, the trial court invalidated
6 the regulations on the grounds that the Office of Mental Health lacked statutory
7 authority to adopt them.²⁰ The next year, the intermediate appellate court in
8 New York agreed with the trial court's conclusion but added a far more wide-
9 ranging critique of the regulations, opining that they violated both constitutional
10 due process rights and substantive protections granted these research subjects
11 under New York's statutory and common law.²¹ Finally, however, New York's
12 highest court narrowed the judicial holding to the original decision of the trial
13 court.²²

14 Cognizant of New York's imbroglio, officials in Maryland have
15 undertaken a less adversarial process of policy formulation. A working group
16 under the auspices of the Maryland Attorney General has, over more than two
17 years, produced a series of reports culminating in a proposed state statute that
18 would govern the substantive and procedural aspects of research involving
19 "decisionally incapacitated individuals."²³

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²⁰*Case name?*, 626 N.Y.S. 2d 1015, N.Y. Sup. Ct. 1995.

²¹*Case name?*, 650 N.Y.S. 2d 173, N.Y. App. Div. 1996.

²²*Case name?*, 690 N.E. 2d 1259, N.Y. 1977. According to the New York Court of Appeals, the intermediate appellate court's discussion of constitutional, common law, and other statutory issues was "an inappropriate advisory opinion."

²³Office of the Maryland Attorney General. *Final Report*.