Are the rules for research with subjects with dementia changing?

Views from the field

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Abstract—Deliberative bodies have recommended additional protections for persons with dementia included in clinical trials. This survey of experienced dementia researchers revealed that 45 to 64% considered that specific ones of these recommendations would increase subject protection, and 40 to 86% considered they would make research less feasible. The real tradeoff between protection and difficulty in conducting research on devastating illnesses needs to be confronted when new regulations in this area are debated.

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The complex issues involved in conducting research with persons with impaired decision-making capacity have been widely explored.[1,2] How best to ensure adequate protection of these persons while allowing promising research to go forward has been addressed by several bodies, perhaps most prominently by the National Bioethics Advisory Commission (NBAC), but including important statements by the Alzheimer's Association and the American Geriatrics Society.[3-5] The recommendations of these groups and their shared concerns have been, and will continue to be, the starting point for deliberative bodies considering regulations for the protection of human subjects.[6]

We sought the opinions of researchers experienced in studying persons with Alzheimer's disease (AD) about how much additional protection a subset of these recommendations might provide and the effect they might have on the conduct of future research.

This study is part of a larger project that included a structured review of a sample of articles reporting research with persons with AD.[7] The sample of articles was derived from a Medline search using AD and dementia as key words, limited to all variants of clinical trials conducted in the USA and published between 1992 and 1998. Half (125) of the resultant articles were selected for the structured review. The corresponding authors of these studies comprised the sample for the survey reported here.

Methods. There were 97 different corresponding authors identified by the 125 articles.

The survey directed the respondent's attention to the study (the Reference Study [RS]) reported in the sampled article. The RS were all published after the enactment of the Common Rule, which reconciled human subject protections required by 17 US government departments (1992) and before the publication of the NBAC report (December 1998) recommending augmenting those protections. Two open-ended questions asked how capacity to give consent was assessed and how proxies were identified. Two closed-ended questions asked whether a mildly impaired person would have been enrolled without proxy involvement and whether the trial was considered to have greater than minimal risk. These questions were repeated, asking how responses might differ were the trial to be initiated now (2002). Fixed-choice questions asked about new procedures suggested by NBAC and others[3-5] (a standard procedure for independent assessment of decision-making capacity, a procedure for identifying proxies, a method of instructing proxies, and a procedure for obtaining prospective authorization) and about any experience with these recommended changes. The last set of closed-ended questions asked about changes in institutional review board (IRB) procedures, the effect of specific changes on the feasibility of initiating studies "similar to the Reference Study," and an assessment of the protection each change might provide.

Questionnaires were initially distributed by overnight delivery; two follow-up mailings were sent to nonrespondents by first class mail. The final attempt was by e-mail. This project was reviewed and approved by the IRB of the Biological Sciences Division of the University of Chicago.

See also pages 1645 and 1662

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Table 1 *Implementation of new procedures*

	No. (%), n = 38
New procedures for subject capacity assessment	3 (7.8)
Have or are developing new process to obtain prospective authorization	5 (13.1)
Yes, have had experience with prospective authorization	2
Have or are developing new materials to educate proxies	6 (15.7)
IRB requires more precise documentation of protections	28 (73.6)
More ongoing oversight by IRB during the conduct of research	28 (73.6)

IRB = institutional review board.

Results. Of the 97 authors to whom we distributed surveys, 1 was deceased and 6 were lost to follow-up. Thus, there were 90 surveys that might have reached the target respondent; of these, 38 (42.2%) were returned completed. Fifteen surveys were returned, indicating refusal to participate; five refusing authors specified that they were unfamiliar with recruitment and consent procedures in the RS. We received no response from 37 corresponding authors. The type of research, source of research funding, and our assessment of the risk level of the trials reported did not differ between responding authors and nonresponders.

The RS of the 38 respondents were published in 28 different journals. Twenty-four of the respondents (63%) were currently conducting research with subjects of questionable decision-making capacity; four were developing such projects. Ten respondents (26%) were not currently involved in such research.

Twelve respondents reported that the RS was regarded as having greater than minimal risk when the study was conducted and would be so judged now; two thought that their previously minimal risk studies would now be considered more than minimal risk. Eleven respondents would have enrolled a mildly impaired subject without proxy involvement when the RS was done; six would do so now.

Reports of how capacity to consent was assessed for the RS varied widely from short phrases to full descriptions of medical and neuropsychological testing. Thirteen respondents gave these answers about assessment. Six others simply reported, for example, "all participants had milder dementia," without mentioning how this was determined. Five reported that subject capacity had been assessed for another circumstance, for example, "on record from clinical assessment." Twenty respondents noted that proxies (caretakers, family members) also (or only) gave permission or consent responding to our question about subject capacity assessment.

Few respondents reported procedural innovations since the RS was conducted. However, five reported new procedures for assessing competence: three mentioned more structured consent interviews, and two mentioned new requirements for proxy designation.

Responses about proxy selection for the RS also varied widely from informal designations (e.g., family members or caretakers) to legal definitions. No one reported that the procedures for identifying proxies had changed, although two had clearly delineated such changes in response to the question about capacity assessment.

Nearly three-quarters of respondents did, however, discern changes in requirements from their IRB (table 1).

Table 2 *Expected effects of proposed protections*

A. Please indicate how much effect you think each of the following would have on the feasibility of initiating studies similar to the Reference Study today.

	No effect no. (%)	Slightly less no. (%)	Much less no. (%)	Not feasible no. (%)
Independent capacity assessor	8 (22.2)	10 (27.6)	15 (41.7)	3 (8.3)
Independent consent monitor	5 (14.3)	12 (34.3)	16 (45.7)	2 (5.7)
Independent participation monitor	6 (19.4)	10 (32.3)	13 (41.9)	2 (6.5)
Prospective authorization	9 (27.3)	5 (15.2)	6 (18.2)	13 (39.4)
Periodic reconsenting	18 (56.3)	8 (25.0)	3 (9.4)	3 (9.4)
Standardized proxy selection	21 (60.0)	9 (25.7)	4 (11.4)	1 (2.9)

B. How much additional protection do you think each of the following would offer for decisionally incapacitated candidates for research participation?

	No increase no. (%)	Slight increase no. (%)	Great increase no. (%)
Independent capacity assessor	14 (38.9)	19 (52.8)	3 (8.3)
Independent consent monitor	13 (37.1)	20 (57.1)	2 (5.7)
Independent participation monitor	17 (54.8)	12 (38.7)	2 (6.4)
Prospective authorization	14 (42.4)	13 (39.3)	6 (18.1)
Periodic reconsenting	12 (35.3)	17 (50)	5 (14.7)
Standardized proxy selection	18 (51.4)	13 (37.1)	4 (11.4)

Percentage base for items differs because of item nonresponse.

Table 3 *Changes since the Reference Study*

A. In your experience, has the IRB at your institution become more exacting in its requirements for research involving decisionally incapacitated individuals since the time you conducted the Reference Study?	No. (%)
No, the same	4 (10.5)
Yes, slightly more	18 (47.4)
Yes, much more	8 (21.1)
Don't know	8 (21.1)
B. Does the IRB at your institution provide greater protection for decisionally incapacitated subjects than it did when you conducted the Reference Study?	
No, the same	7 (18.9)
Yes, slightly more	15 (40.5)
Yes, much more	6 (16.2)
Don't know	9 (24.3)
C. Overall, would you say that it is harder now to conduct research with decisionally impaired persons than it was when you conducted the Reference Study, or is it the same, or has it become easier?	
Much harder	8 (21.1)
Slightly harder	15 (39.5)
Same	8 (21.1)
Easier	0
Don't know	7 (18.4)

IRB = institutional review board.

In assessing the potential effect of the proposed recommendations on future studies similar to the RS, most respondents considered that most of the recommended procedures would provide at least a slight increase in protection for decisionally incapacitated candidates for research participation. At the same time, most respondents considered that most of these protections would make research less feasible (table 2).

Twenty-six respondents (68%) reported that IRB requirements at their institutions are more exacting now, 21 (57%) considered that their IRB provide greater protection now, and 23 (61%) considered it harder to conduct research with decisionally impaired persons now than it was at the time when the RS was conducted (table 3).

Discussion. NBAC and others have suggested how more effective protection of this potentially vulnerable population may be achieved. There are no data available about how effective any of these proposed additional protections might be in the actual conduct of research. This study provides systematic data on the opinions of experienced researchers about the possible effects of some of the proposed changes, complementing previous studies documenting existing methods of recruitment and consent for research in Alzheimer's centers[8,9] and views of potential subjects toward proposed regulations.[10]

Respondents provided scant detail about capacity assessment prior to recruitment to the RS, and most reported no changes in the process. Descriptions of proxy selection were also minimal, and the process appears to be unsystematic in most settings. It is imperative that decisionally incapacitated persons have an appropriately designated proxy when being recruited for research. However, half of the respondents did not consider that standardized proxy selection would add anything to subject protection. This may be because proxies are already selected in a systematic way, or perhaps subjects have few options and the proxy choice is pragmatic.

Although the experienced researchers in our study gave somewhat mixed reviews of the proposed protections, they mainly saw them as providing greater protection while recognizing that they may make the conduct of research harder.

New protections involve this tradeoff, which much of the debate until now has not adequately confronted. This is not a theoretical issue. In considering greater protections and monitoring, we as a society are making concrete choices about where we will balance the risk of harm to vulnerable populations against the pace of research on devastating illnesses.

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