Ethics Reporting in Publications About Research with Alzheimer's Disease Patients

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Persons with impaired decision-making capacity require special ethical protections during recruitment for and participation in research. To assess how fully basic protections for these persons were reported in the literature, the first structured review of a sample of reports of trials including Alzheimer's subjects was performed in 62 journals between January 1992 and December 1998. Neither institutional review board review nor informed consent was mentioned in 28% of the studies. In 48% of the studies, there was no mention of subject involvement in the consent process or that any potential subjects refused or withdrew. Protections may have been offered and simply not reported in the journal articles. The critical importance of these protections would be demonstrated if editors required that authors provide full documentation of ethical protections when submitting an article for review. These might be briefly reported in the articles but be made available electronically to interested readers. Authors could then specify in detail how they conducted their research involving persons with diminished decision-making capacity. **J Am Geriatr Soc 52:305–310, 2004.**

Key words: research ethics; informed consent; decision-making capacity; vulnerable subjects

Research with subjects who might have impaired decision-making capacity—persons with dementia or psychiatric illness or persons who are critically ill—has long been an area of concern and debate.[1,2] Such concern predates the current scrutiny of research with human subjects engendered by subject deaths,[3] by legal cases,[4] and by the temporary closure of research operations at some major universities for insufficiencies in the institutional review board (IRB) process.[5]

In December 1998, the National Bioethics Advisory Commission (NBAC) published a report entitled "Research Involving Persons with Mental Disorders That May Affect Decisionmaking Capacity."[1] The report included 21 recommendations regarding additional protections for "human subjects who suffer from mental disorders that may affect their decisionmaking capacity." Although NBAC has since disbanded, its carefully argued recommendations engendered wide debate and institutional reaction, even absent regulatory changes. Although researchers generally supported the protective spirit of NBAC's recommendations, some feared that more stringent regulations might slow or even curtail potentially important research.[6,7]

A multipart study of the potential effect of the regulations and guidelines proposed by NBAC was undertaken, including development of a compendium of relevant state laws, a survey of attorney generals' opinions, a survey of dementia researchers,[8] and a structured review of a subset of dementia research literature, which is reported here.

A structured literature review was conducted to understand how the process of human subjects review and informed consent had been documented in published reports of dementia research trials between 1992 and 1998. The time period was chosen to begin after the enactment of the Common Rule (Title 45, Code of Federal Regulations, Part 46),[9] which reconciled the human subject protection regulations of 17 federal departments and agencies, and to end with the publication of the NBAC report, which recommended augmenting those protections. Some research conducted under the Common Rule raised the concerns examined by NBAC and addressed in their recommendations. This review differs from others in the range of professional journals included and the specificity of the vulnerable population examined. Previous researchers[10–16] have conducted reviews of selected parts of the literature or journal instructions to authors,[17,18] sometimes combined with surveys of authors[10,19,20] or surveys of journal editors.[21,22] These analyses have provided insights into different aspects of the type and detail of human subjects reporting in published research, some of which have led to specific recommendations for change. Some of

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The research reported here was supported by a grant from the Alzheimer's Association.

A portion of data from this study was presented in a poster at the November 2002 meeting of the Gerontological Society of America, Boston, Massachusetts.

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0002-8614/04/$15.00

these studies have counted any mention of IRB/Ethics Committee review and any mention of informed consent in published research as appropriate indicators of ethics reporting. Others have employed more extensive criteria. Yet, many of these have focused on a small number of the most prestigious journals. None have focused on research in dementia.

Additional information was sought about human subjects protections beyond reports of IRB review and informed consent. Six focal criteria were identified reflecting continuing concerns in the research and ethics communities that might have been in place and reported during the study period. In addition to reflecting some of NBAC's recommendations, these are among the core concerns of other bodies as well.[23–27]

The six selected focal criteria are the appropriateness of persons with a mental disorder as subjects, evidence that objections to enrollment or continuing participation were heeded, assessment of the risk level of trial, the methods of assessment of potential subjects' capacity to consent, the prospect of direct medical benefit to subjects, and the identification and role of the proxy.

METHODS

The Sample of Articles for the Structured Review

To locate articles, a MEDLINE (1966–2001) search was conducted starting with the key words "dementia" and "Alzheimer's disease" (AD) (N = 41,172) and then limited to studies with human subjects, published in English between January 1992 and December 1998, and to all the variants of clinical trials. The authors were interested in protections reported about trials conducted under U.S. regulation, so 464 trials conducted in 37 other countries were excluded. To be certain that the review included studies that clearly presented more than minimal risk, all studies in which the abstract explicitly mentioned maximum tolerated dose (n = 7), cerebrospinal fluid or lumbar puncture (n = 8), or drug administration intravenously or by catheter (n = 8) were selected. Half of the 204 articles remaining on the MEDLINE-generated list were chosen by selecting every other title. Thus, the final sample for review was 125 articles published in 62 journals (Figure 1).

Structured Data Collection Form

Information from the sample articles was abstracted and recorded on a structured data collection form developed for this project. The form included items describing the trial (sponsorship, number of subjects, procedures involved), IRB review, informed consent, and items designed to capture the six focal criteria. Reviewers assessed greater than minimal risk level using Common Rule standards, defined narrowly as maximum tolerated dose studies, other kinds of drug studies, research that required lumbar puncture, and studies in which agents were administered intravenously. NBAC recommended that certain kinds of imaging studies might be considered as presenting more than minimal risk when administered to persons with dementia, so this criterion was added to this study's Common Rule criteria for a second evaluation of risk level.

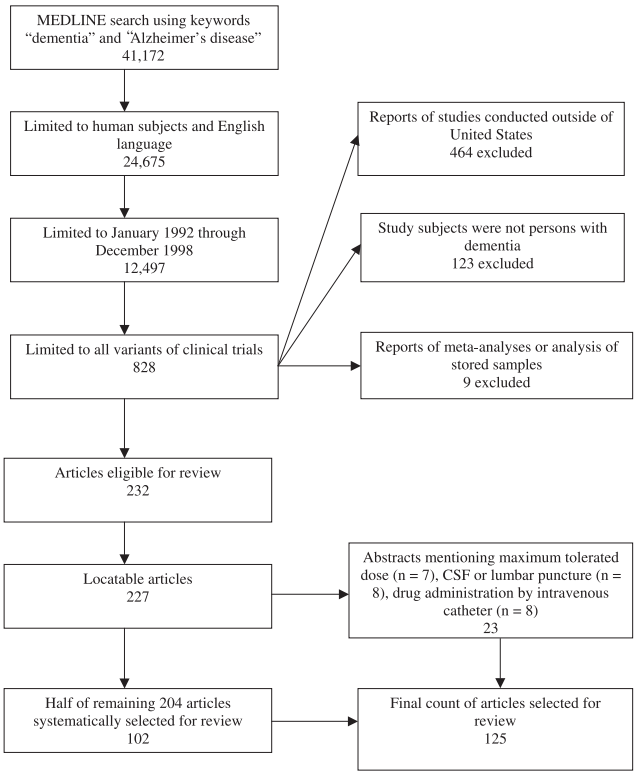

Figure 1. Article search protocol. CSF = cerebrospinal fluid.

Two trained research assistants independently read and coded each article. Ambiguities or disagreements about coding or categories were resolved by consensus with a third reader (CS or GS). Disagreements between coders resulted from differing interpretations of exactly what was done to trial subjects and the consequent assessment of risk level.

Frequency distributions and associations, including chi-square tests, were generated using SAS (SAS Institute, Inc., Cary, NC).

Ethical Considerations

The University of Chicago Medical Center's IRB reviewed and approved the study. Consent was not required for the literature review because no human subjects were involved.

RESULTS

Table 1 contains information about the types of studies, sources of support, and institutional origins of the papers in the sample. The number of subjects with AD in the studies ranged from 1 to 663 (median = 25). At least some subjects in 64 (51.2%) studies were described as community dwelling, 17 (13.6%) included some nursing home residents, and 14 (11.2%) included psychiatric or other inpatients. In 36 additional studies (28.8%), it was impossible to determine the source of the subjects.

Seventy-nine articles did not mention IRB review (63.2%), and 38 (30.4%) did not mention informed consent. The type of consent (written, oral, or both) was not specified in 55.2% of the 87 articles that mentioned informed consent. Table 2 contains additional details on the

extent to which IRB review and informed consent were mentioned in the sampled papers.

Of the 70 studies that reported some support from the National Institutes of Health, 23 (32.8%) reported IRB review. Of the 24 studies with pharmaceutical company support, 16 (66.7%) reported IRB (or similar) review. Similar percentages of studies with some government (65.7%) or private foundation (65.3%) support reported that informed consent was obtained; 95.8% of studies supported by pharmaceutical companies reported informed consent. If studies with support from pharmaceutical companies are compared with all others, those with pharmaceutical company support were more likely to report IRB (or similar) review (66.6% vs 29.7%, $P = .001$) and to report informed consent (95.8% vs 63.3%, $P = .002$).

The two reviewers separately judged 64 articles (51.2%) to present greater than minimal risk according to this study's Common Rule standards. These included maximum tolerated dose (n = 13), other kinds of drug studies (n = 42), research that required lumbar puncture (n = 8), studies in which agents were administered intravenously (n = 10), and other (n = 2). Because raters could code two reasons for evaluating a study as presenting greater than minimal risk, there were 75 responses for the 64 trials. Studies that were rated as presenting more than minimal risk were more likely than less risky studies to include reports of IRB review ($P = .002$), informed consent ($P = .001$), or both ($P = .001$).

Table 1. Studies in the Sample

Variable	Studies n	Studies %
Type of study (N = 125)		
Drug	63	50.4
Psychological	25	20.0
Diagnostic	19	15.2
Imaging	9	7.2
Behavioral	6	4.8
Other	3	2.4
Main sources of support (N = 93 studies listing sources)*		
NIH	70	75.2
Foundation	26	27.9
Industry	24	25.8
Origin of study (based on location of corresponding author) (N = 125)		
Medical school/ university	82	65.6
Hospital	13	10.4
Industry	18	14.4
NIH intramural	9	7.2
Other	3	2.4

* More than one source of support could be coded, so percentages add to more than 100%.
NIH = National Institutes of Health.

The Six Focal Criteria

The use of demented subjects was clearly justified in all of the studies, and 50 (40.0%) of the trials offered the possibility of direct medical benefit to participants (Criteria 1 and 5).

The risk level involved in clinical trials is particularly important in determining the appropriate level of subject protection. NBAC drew attention to the likelihood that imaging studies such as magnetic resonance imaging or positron emission tomography, normally not thought of as invasive, could be frightening or confusing to persons with diminished mental capacity and thus present more than minimal risk. The 16 trials in our review that focused on imaging were added to the 64 identified as more than minimal risk by the study's Common Rule standard. Thus, by a more protective standard, 80 (64.0%) of the studies reviewed were judged to present greater than minimal risk. Thirty-eight studies presented greater than minimal risk and offered no prospect of medical benefit to the subject. Of these, three did not mention informed consent, five provided no information about who provided consent, 18 reported that subjects were involved in the consent/assent process, and seven reported that the subject or proxy consented (Criteria 3 and 5).

Many of the sampled reports were of studies conducted with large AD patient registries. Often it was not possible to tell whether evaluations described—including assessment of decision-making capacity—were done for the study being reported or had been done when subjects presented for initial diagnosis. As shown in Table 2, 103 reports (82.4%) indicated that something about the capacity of subjects was known. For example, in 37 articles, mental capacity was one of the eligibility criteria, but when that information was obtained was not specified. Only 10 reports stated that decision-making capacity was assessed specifically for the reported study and that it was completed before recruitment. Similarly, it was difficult to discern how many of the 87 articles that reported consent used a blanket consent obtained at clinic or registry entry. Twenty studies made explicit that a separate consent was obtained for participation in the study being reported (Criterion 4).

The importance of the proxy of a person with impaired decision making capacity has been the subject of continuing discussion,[26,27] and NBAC made specific recommendations about the selection and role of the proxy in making decisions about research participation. Table 2 contains the breakdown of the role of subject and proxy as far as could be determined for the 87 studies in which the person (or persons) consenting was described. Proxies were certainly involved in 48 of these enrollment decisions and were possibly involved in 21 more (subject or proxy category). Thus, proxies may have been involved in providing consent for as many as 79% of those studies in which informed consent was mentioned.

Proxies were identified using different criteria: family role (e.g., spouse, next of kin, empowered family member, or even family member named durable power of attorney for this study by subject); caregiving role (e.g., caregiver, an identified caregiver), legal status (e.g., legal guardian, legally authorized caregiver, conservator), or less clearly, advocate or responsible agent. Many of these are mentioned in combinations, such as family member or guardian, or legal representative or next of kin (Criterion 6).

Table 2. Ethics Reporting in the Sample Articles

Variable	Studies n	Studies %
Mention of IRB review or informed consent* (N = 125)		
IRB mentioned	46	36.8
Informed consent	87	69.6
Both mentioned	43	34.4
Neither mentioned	35	28.0
Informed consent mentioned (N = 87)		
Written	26	29.9
Oral	2	2.3
Written and oral	11	12.6
Type not specified	48	55.2
Person giving consent (N = 87 in which consent was mentioned)		
Subject and proxy	31	35.6
Subject or proxy	21	24.1
Subject alone	11	12.6
Proxy alone	11	12.6
Proxy consent plus subject assent	6	6.8
Not specified	7	8.0
Decision-making capacity determination described (N = 125)		
Not at all	22	17.6
Described*	103	82.4
As eligibility criterion	37	29.6
Method of assessment	76	60.8
Assessor qualifications	15	12.0
Study-specific capacity	10	8.0
Subjects' wishes heeded (N = 125)		
Some subjects refused	11	8.8
Some subjects withdrew	34	27.2
Subject consent or assent required (with or without proxy consent)	48	38.4
No evidence of patient's role in consent process	61	48.8

*More than one response could be coded, so percentages add to more than 100%.
IRB = institutional review board.

Even if a potential subject (or subject already enrolled in a study) lacks decision-making capacity, NBAC and others have stressed that a subject must be allowed to refuse participation or to withdraw. As shown in Table 2, any of the following were considered to be indicators that subjects' objections were heeded: reports that some potential subjects refused to participate, reports that some subjects withdrew, reports that the subject alone consented, that the subject and proxy consented, or that the subject assented and the proxy consented. Reports that the "subject or the proxy" consented were not included. Despite this inclusive definition, 61 studies (48.8%) provided none of these clues to the patient's role in the consent procedure (Criterion 2).

DISCUSSION

In this sample of dementia research, there was a paucity of information about subject protections. This deficit is all the more striking because of the vulnerable population enrolled in these studies and the variety of journals contained in the sample. Because it is impossible to tell from published articles what subject protections might actually have been provided during the conduct of the research yet not reported, more complete reporting of the ethical protections of decisionally incapacitated subjects is urged.

Including a broader range of journals than similar reviews gives a fuller and somewhat bleaker picture of the standard of ethics reporting. An approximate comparison of the 28% of articles in 62 journals that mentioned neither informed consent nor IRB review can be made with the 14% of articles in five journals that mentioned neither.[15] A review of pediatric research published in 2000[19] found that only 35% reported both IRB review and informed consent, thus confirming that underreporting remains a significant problem.

In nearly half of the studies reviewed, no documentation was found that the subject was involved in the consent process, and descriptions of the consent process itself varied widely.

Only 10 articles (8%) made clear that the competence of the prospective participant was evaluated before recruitment for the study being described. In other studies, the eligibility rules for the study included information about competence, but the source of that information or the way it may have been used in the consent process was not made clear. The independence of the assessment was not addressed in any article.

Ninety-four articles (75.2%) included information about a detailed diagnostic evaluation, often including various measures of the mental status of participants, but whether that information was obtained previously during enrollment in a clinic or collected as part of the study being described was unclear.

Studies that present more than minimal risk and offer no prospect of medical benefit to the subject constitute the segment of research that is the most controversial. Of the 38 such studies in this review, 13 provided little or no information about consent. Research in this area is much in need of clear explication of the consent process and other protections involved.

NBAC provides a useful definition of an appropriate proxy as "an individual authorized by law (statutory or judicial) or previously published institutional rules to make medical decisions on behalf of another individual." Proxies involved in the trials reviewed were variously described, and in most cases, it was not clear what standards were used to select them.

LIMITATIONS

A number of the limitations of this study are obvious from the search strategy (e.g., trials conducted in the United States, publications in English, before 1999). Some of the subjects in all of the trials reviewed were persons with AD, yet there are other categories of persons with impaired decision-making capacity who require similar protections. Finally, the brevity and ambiguity of the descriptions of subject protections in many of the articles may have limited the understanding that could be derived from them.

Toward a Proposal for Greater Transparency

The actual conduct of research and the respectful protection of subjects who participate in it are the phenomena of import; reporting those procedures is epiphenomenal. But how better to emphasize the importance of care in the conduct of research with this vulnerable population than to require a detailed description of recruitment and consent procedures in published accounts? The critical importance of these protections would be demonstrated if authors documented them in published accounts of research, just as researchers assume the responsibility of implementing them in the conduct of research. However, it is clear that this documentation is not commonly done.

Since the publication of the NBAC report, there has been ongoing controversy and debate about the adequacy of protection of human subjects. The Office for Human Research Protections has provided detailed and specific guidance to IRBs about what they must require and document.[28] Such guidance may lead to more complete and uniform IRB submissions across institutions. Journal editors might then require that a copy of the IRB submission be provided with manuscripts sent in for review.

Alternatively, a form might be provided for authors to complete indicating what ethical protections were provided for subjects in the study being reported. Several consensus statements (for example, by Consolidated Standards of Reporting Trials[29] or Quality of Reports of Meta-Analysis[30]) have been promulgated in an effort to standardize and improve the reporting of clinical trials and other types of research. An analogous form might be used to improve the quality of reports of the ethical conduct of research with decisionally incapacitated adults.

One starting point for such a form might be questions derived from the six focal criteria identified for this review. They are among the core concerns expressed by NBAC and other concerned groups such as the American Geriatrics Society and the Alzheimer's Association.

1. Could the trial have been done with subjects who did not have impaired decision-making capacity?
2. Were subjects' objections to entering or continuing in the trial heeded?
3. Did the investigator's IRB feel that the trial presented greater than minimal risk?
4. Was the capacity of potential subjects to consent assessed before enrollment in the trial? When? How? By whom? Was consent sought specifically for the trial being reported? From whom was consent/assent/permission obtained?
5. Did the trial present the prospect of direct medical benefit to the subject? What special protections were offered for subjects being recruited to trials that presented greater than minimal risk and did not offer the prospect of direct medical benefit to the subject?
6. How were subjects' proxies (legally authorized representatives) selected?

In 1980, two researchers pointed out that, "editorial policy no longer encourages sufficient detail to allow experimental replication, much less a detailed account of the conditions under which human beings agree to become subjects."[21]

In an attempt to resolve the tension between wishing to allow readers to assess the ethical quality of a study and understandable editorial requests for word count limitations, journal editors might require full documentation as part of article submission and make it available to reviewers. It is even possible that such an editorial requirement would improve the protection of vulnerable subjects without any changes in the law. The protections could be briefly described in the published article but made fully available electronically to interested readers.

This kind of transparency and accountability is essential if the research community is to maintain the trust of the public and to continue to be allowed to conduct important research with decisionally impaired subjects and other vulnerable populations.

ACKNOWLEDGMENTS

The authors wish to acknowledge the assistance of Elizabeth F. Davis in this project.

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