Participation in clinical trials and long-term outcomes in Alzheimer's disease

S.M. Albert, PhD; M. Sano, PhD; K. Marder, MD; D.M. Jacobs, PhD; J. Brandt, PhD; M. Albert, PhD; and Y. Stern, PhD

Article abstract—The objective of this study was to determine whether participation in clinical trials affects long-term outcomes in Alzheimer's disease (AD). Participation in clinical trials for persons with dementia is often justified on the grounds that patients benefit from the medical oversight typical of trials, even when experimental agents do not demonstrate short-term benefits. This claim has not been rigorously assessed. Of 215 community-resident subjects enrolled in a prospective study of outcomes in AD, 101 participated in randomized clinical trials (RCTs) during the first 2 years of follow-up. These subjects were compared with subjects who met eligibility requirements for RCTs but did not participate (N = 57) and with subjects who were ineligible (N = 57), over a total of 3.5 years of follow-up. Survival analyses assessed risk of death, nursing home placement, and incident functional deficit end points, adjusting for baseline differences. Subjects who participated in RCTs were younger and more highly educated. Mortality, risk of hospitalization, number of medical examinations conducted by study physicians, and onset of severe functional deficit did not differ between the groups, but risk of nursing home admission was significantly lower among RCT participants compared with eligible nonparticipants and ineligible subjects (16.8% versus 36.8% and 31.6%, respectively [$p = 0.01$]). The difference in risk of nursing home placement may represent a long-term, drug-related benefit to patients, a selection effect (caregivers of patients who participate in RCTs differ from caregivers of patients who do not), or a positive effect on caregivers (greater contact with a medical service may be associated with better care-giving outcomes). Further research is required to assess these effects.

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An argument advanced for participation in clinical trials is that patients benefit from more intensive medical care even in the absence of demonstrated treatment effects.[1] This claim is particularly relevant with Alzheimer's disease (AD), for which therapies have mostly shown small benefit, and in which comorbidities amenable to treatment (such as weight loss[2] and dysphagia[3]) may not be recognized or aggressively treated in routine medical settings. However, the claim of medical benefit in randomized clinical trials (RCTs) has not been rigorously assessed.

It would be valuable to know if participation in clinical trials had such indirect benefits for AD patients. First, such benefits would support more aggressive medical care for AD patients. Second, they may point to more generalized benefits associated with participation in clinical trials; for example, effects on caregivers that enable them to care for demented patients more effectively. In this sense, the clinical trial itself can be considered a "treatment"; it offers a package of services (medical care and physician contact with caregivers) that may affect the course of AD.

We had an opportunity to assess the effect of participation in clinical trials in a cohort of patients with AD. AD patients followed in a natural history study of disease course were offered an opportunity to participate in controlled RCTs in the first 2 years of follow-up. About half the patients participated in at least one of the RCTs for some period of time. At the same time, information was available for all subjects in the cohort, allowing us to determine retrospectively which patients may have been eligible for the study but did not participate and which patients were ineligible. We then compared outcomes over an additional 1.5 years, for a total maximal follow-up of 3.5 years, among patients who participated in the RCTs (i.e., the group of patients receiving drug or placebo), patients who were eligible for the trials but did not participate, and patients who were ineligible. The comparison of central interest is whether time to reach AD milestones differs between RCT participants and nonparticipants who were eligible to participate.

Methods. *Subjects.* Subjects in this research come from the Predictor's Study,[4,5] a multisite longitudinal study of patients with AD. Beginning in 1988, patients were re-

From the Gertrude H. Sergievsky Center and Department of Neurology (Drs. S.M. Albert, Sano, Marder, Jacobs, and Stern), Columbia University, New York, NY; the Department of Psychiatry and Behavioral Sciences (Dr. Brandt), Johns Hopkins University, Baltimore, MD; and the Department of Neurology (Dr. M. Albert), Massachusetts General Hospital, Boston, MA.

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Address correspondence and reprint requests to Dr. Steven M. Albert, Gertrude H. Sergievsky Center, Columbia University, 630 West 168th Street, P&S Box 16, New York, NY 10032.

cruited into the cohort from Columbia University, Johns Hopkins University, and Massachusetts General Hospital. Patients were enrolled from memory disorders clinics and neurology practices, and received detailed clinical evaluations every 6 months. To be included in the cohort, patients had to meet DSM-III-R criteria for dementing disease along with National Institute of Neurological Disorders and Stroke (NINDS)–Alzheimer's Disease and Related Disorders Association (ADRDA) criteria for probable AD. In addition, subjects were recruited to be at a relatively mild stage of dementia, defined as a modified Mini-Mental State Examination (MMSE) score of ≥ 30,[6] corresponding to approximately 16 on the standard MMSE. The cohort enrolled 236 patients, who have been followed for as long as 6 years. Enrollment of the cohort and baseline features have been described.[4,5] Because nursing home placement is an outcome of interest for this research, we limited analyses to the 215 subjects who were living in the community at baseline.

In the first 2 years of follow-up, subjects in the cohort could have participated in a variety of clinical trials conducted at the different study sites. Agents included physostigmine, piracetram, and acetyl carnitine, although a small number of subjects was recruited for other RCTs as well. Patients spent varying amounts of time in clinical trials and may have participated in more than one trial.

Measures. Patients were considered to be participants in a clinical trial if they were enrolled in a clinical trial at any point in the first 2 years of follow-up, as indicated by clinical trial status at the first five study assessments (at baseline, and at 6, 12, 18, and 24 months). A score was calculated to indicate the proportion of time subjects were involved in trials, taking into account deaths and loss to follow-up. Because of the small numbers of subjects in any given trial, and because of our interest in examining the effect of RCT participation itself, we did not attempt analyses of particular RCTs. Site effects were assessed by introducing a term for recruitment site in multivariate models.

Nonparticipants in the RCTs were divided into two groups—an eligible, nonparticipant group and an ineligible group—based on inclusion-exclusion criteria for the RCTs, which were uniform across the different clinical trials. The ineligible group included subjects who met any of the following exclusion criteria: not living with an informant, currently taking a psychoactive medication, and presence of life-threatening condition (e.g., active cancer). Subjects who did not participate in any of the RCTs and who did not meet exclusion criteria were considered eligible nonparticipants.

Outcomes were assessed over 3.5 years of follow-up, including the initial 2-year period, because not all subjects have completed subsequent follow-up assessments. The following end points were examined: mortality (divided by primary cause into infectious and chronic disease categories), onset of severe functional deficit (defined as a need for help in two of three basic activities of daily living [ADLs]: dressing, grooming, toileting),[7] and nursing home placement. In addition, two indicators of medical utilization were noted: hospital admissions and physician examinations conducted as part of routine Predictor's Study follow-up that were triggered by caregiver reports of new medical conditions in cohort subjects. For the latter we calculated the proportion of subjects who had any hospitalization and the number of medical examinations linked to an incident medical condition over the follow-up period.

Covariates examined in this research include sociodemographic indicators (age at study entry, gender, years of schooling) as well as indicators of baseline functioning (instrumental activities of daily living [IADLs] and ADLs),[7,8] cognitive status,[6] agitation, and depression.[9]

Statistical Methods. Participants in the RCTs, eligible nonparticipants, and ineligible subjects were compared at baseline using ANOVA to determine comparability of the three groups. Post hoc pairwise comparisons were also conducted using the Scheffé test. Outcomes in the three groups were compared first using ANOVA and then using survival models to compare time to onset for each end point. For these analyses, Kaplan-Meier plots were generated for univariate analyses and Cox proportional hazards models were generated for multivariate models.[10,11] Attrition rates in the three groups were compared to ensure that loss to follow-up was not differential across the groups. The multivariate models estimate the risk associated with RCT status, adjusting for baseline differences between the groups. Differences in the proportion hospitalized and those receiving physician workups for incident medical conditions were compared using the Chi-square test. Differences in patient functional status at the time of nursing home placement were also examined.

Results. Of the 236 subjects enrolled in the cohort, 215 resided in the community at baseline. Ninety-five were enrolled at Columbia, 76 at Johns Hopkins, and 44 at Massachusetts General Hospital. At 6 months, 177 were seen; at 12 months, 173; at 18 months, 155; and at 24 months, 142. Following the 2-year clinical trial period, 131 subjects were followed at 30 months, 105 at 36 months, and 70 at 42 months.

Of the 215 subjects residing in the community at baseline, 101 participated in at least one RCT, 57 met eligibility requirements but did not participate, and 57 were ineligible to participate in the trials. The majority of subjects participating in the randomized trials were recruited for physostigmine or acetyl carnitine trials.

Table 1 compares the three groups using one-way ANOVA for continuous measures and the Chi-square test for proportions. Subjects participating in clinical trials were significantly more likely to be male, younger, and better educated. In post hoc tests of pairwise differences between the groups, subjects recruited for the clinical trials were significantly younger and better educated than eligible subjects who did not participate in the trials ($p < 0.01$, by Scheffé test for both comparisons). However, the three groups did not differ significantly on any measure of dementia severity, including measures of function (ADLs), cognition, presence of agitation, or depression. Although not shown in table 1, subjects in the three groups also did not differ significantly in composite measures of dementia severity. For example, at baseline, similar proportions of subjects were mildly and moderately demented using the Clinical Dementia Rating (CDR) scale.[12] In all groups, about 90% of subjects were mildly demented at baseline (CDR 1). The medical status of subjects was also similar except in the case of neoplastic disease. Ineligible subjects were significantly more likely to have had a history of cancer (13% versus 0% in both ineligible and eligible non-

Table 1 *Baseline features of randomized clinical trial participants, eligible nonparticipants, and ineligible subjects*

Baseline features	Ineligible (N = 57)	Eligible nonparticipant (N = 57)	On protocol (N = 101)	F/χ^2
Sociodemographics				
Female (%)	70.2	59.6	48.5	7.2*
Age (yr)	75.1 (± 6.3)	73.5 (± 6.9)	69.0 (± 8.2)	14.1†
Education (yr)	12.0 (± 3.2)	13.1 (± 3.7)	13.9 (± 3.9)	5.5‡
Functional status (μ ± SE)				
Blessed IADL§	3.0 ± 1.3	3.0 ± 1.3	2.8 ± 1.2	0.83
Blessed ADL§	0.58 ± 0.84	0.49 ± 1.0	0.47 ± 0.83	0.30
mMMS¶	37.6 ± 5.3	38.1 ± 6.3	37.9 ± 5.5	0.12
Depression#	3.5 ± 4.4	3.7 ± 3.8	3.2 ± 4.1	0.22
Agitation (%)**	39.3	36.8	43.6	0.37

* $p < 0.05$.
† $p < 0.001$.
‡ $p < 0.01$.
§ High scores indicate poorer function.
¶ Range, 0–57.
# Hamilton 21-item scale.
** Assessed with single dichotomous item.

IADL = instrumental activities of daily living; ADL = activities of daily living; mMMS = modified Mini-Mental State Examination.

participating groups). The groups did not differ in the prevalence of cardiac disease, hypertension, diabetes, psychiatric disorders, or other conditions elicited by physical examination or medical history.

Ineligible and eligible nonparticipating groups differed from RCT participants in the number of assessments completed. Over the 2-year clinical trial period, 42.1% and 47.4% of the ineligible and eligible nonparticipants were seen at all five assessments (baseline, and 6, 12, 18, and 24 months), compared with 63.4% among RCT participants ($p < 0.01$). Similarly, across the entire 3.5 years of follow-up, mean days of follow-up significantly differed between the groups: 815.4 days among the ineligibles, 919.7 days among eligible nonparticipants, and 1,067.0 days among participants in the trials ($p < 0.05$).

Assessment of outcomes. Table 2 compares the three groups on outcomes over the 3.5 years of follow-up. The mortality experience of the groups did not differ, with somewhat more than 25% of patients dying in all three groups. A further breakdown by cause of death also did not reveal differences. Using death certificate information and reports from institutional or family caregivers (when available), we divided deaths into infectious disease (e.g., pneumonia) and chronic disease (e.g., cancer) categories. The three groups did not differ on either outcome.

Incidence of severe functional disability, defined as dependence in two of three basic ADLs (dressing, grooming, toileting), also did not differ significantly between the groups.

Among the medical utilization outcomes, neither risk of hospitalization (which ranged from 2% to 7%) nor the proportion receiving more than two physician examinations in

Table 2 *Outcomes by clinical trial status (unadjusted)*

Outcome	Ineligible (N = 57)	Eligible nonparticipant (N = 57)	On protocol (N = 101)	F/χ^2
Mortality				
All causes (%)	28.1	24.6	26.7	0.18
Infectious cause (%)	8.8	5.3	16.8	5.4
Chronic condition (%)	12.3	10.5	5.9	2.1
Function				
Onset of severe ADL deficit (%)*	28.3	48.9	36.5	4.3
Medical utilization				
Hospitalization (%)†	5.3	7.0	2.0	2.5
Medical examinations (%)‡	52.6	50.8	45.5	0.86
Nursing home admission (%)	31.6	36.8	16.8	8.8§

* Deficit in at least two of three activities of daily living (ADLs): dressing, grooming, toileting.
† Percent greater than or equal to one hospitalization in follow-up period.
‡ Percent greater than or equal to two examinations in follow-up period.
§ $p < 0.01$.

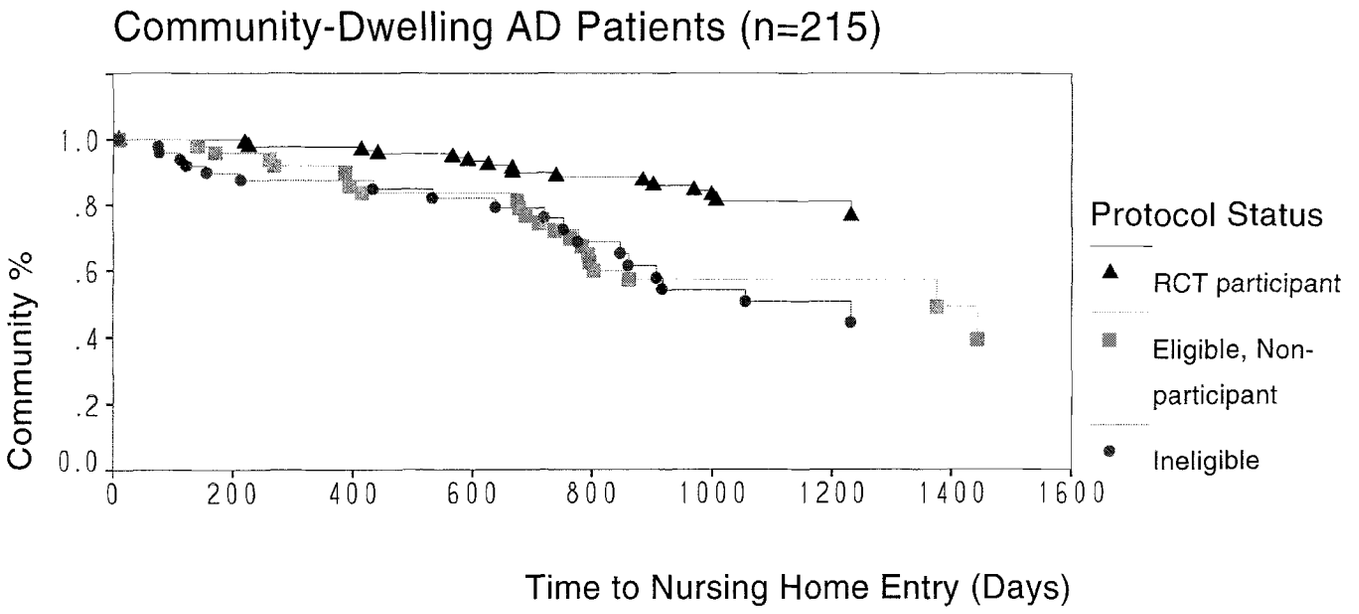

Figure 1. Proportion of patients entering a nursing home, by RCT status.

the follow-up period (which ranged from 46% to 53%) differed significantly by participation status. Risk of nursing home placement, however, was significantly lower among RCT participants. Among RCT participants, 16.8% entered nursing homes in the 3.5 years of follow-up compared with 36.8% among eligible nonparticipants and 31.6% among ineligible subjects. Risk of nursing home placement among the three groups is presented in figure 1, which shows time to nursing home admission, using Kaplan-Meier plots, for the three groups. The figure shows that the distribution of time to nursing home placement does not differ between ineligible and eligible nonparticipants, and that both differ significantly from the nursing home placement experience of subjects participating in clinical trials ($p < 0.01$). In Cox proportional hazards models, in which the baseline covariates of age, gender, education, and functional status were introduced (Blessed ADL and IADL scores), participants in clinical trials had a significantly lower risk of nursing home entry compared with eligible nonparticipants (relative risk, 0.39; 95% CI, 0.19 to 0.79).

An alternative approach to examining the protective effect of clinical trial participation for risk of nursing home placement can be seen in figure 2, in which level of participation in the clinical trials is stratified according to the proportion of time subjects participated in the trials. Subjects could have participated in the trials for more than half their assessments in the first 2 years of follow-up (N = 59), for less than half their assessments (N = 40), or not at all (the combined group of eligible nonparticipants and ineligible subjects). Kaplan-Meier plots for comparison of

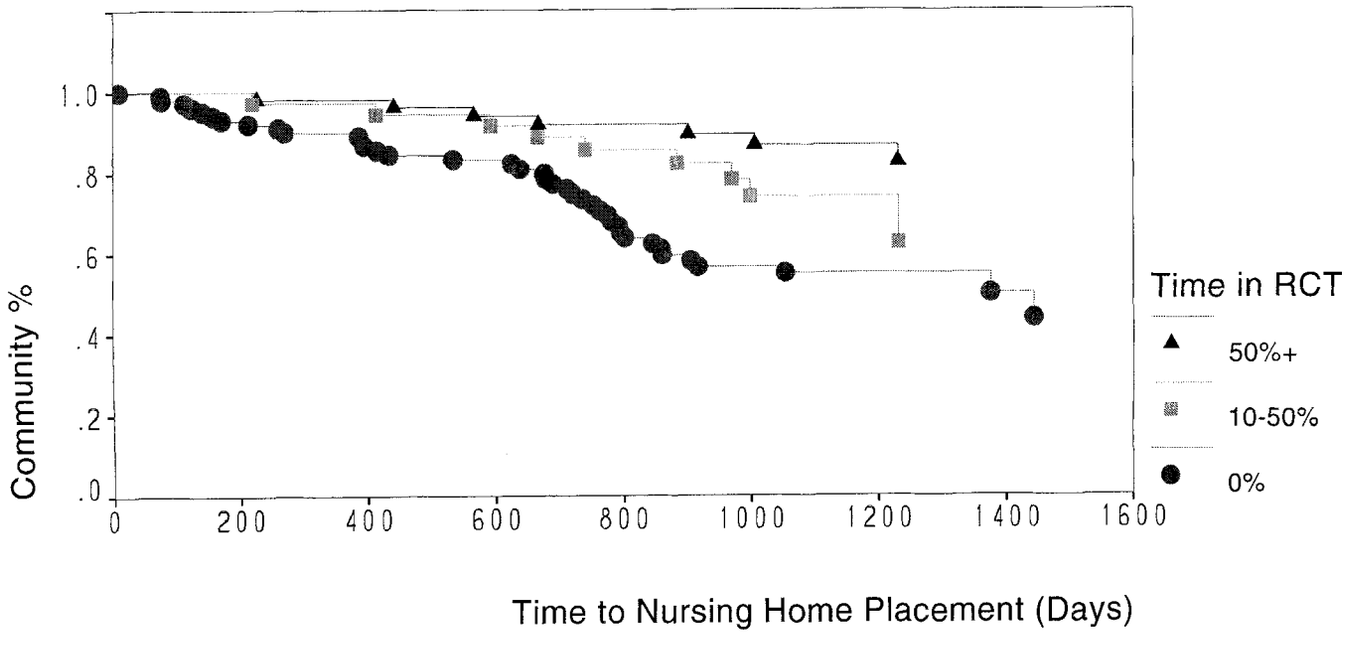

Figure 2. Proportion of patients entering a nursing home, by length of RCT participation.

time to nursing home placement show a dose-response relationship, with longer time in the clinical trials associated with lower risk of nursing home placement ($p < 0.001$ overall). Subjects participating in trials for more than 50% of their assessments had a lower risk of nursing home placement than other RCT participants; this difference approached statistical significance ($p = 0.06$).

Relation between nursing home placement and patient functional deficit among RCT participants and eligible nonparticipants. To examine differences in nursing home placement in more detail, we compared rates of nursing home placement among RCT participants and eligible nonparticipants when subjects reached two well-defined levels of incident functional deficit: (1) need for constant supervision and (2) severe ADL deficit (defined as the need for help in at least two of three ADLs).[7] Patients in the eligible nonparticipant group were more likely to be placed in nursing homes at early levels of functional dependency. For example, of subjects who began to need constant supervision over the course of the study (an early dependency milestone), risk of nursing home placement was significantly higher among eligible nonparticipants compared with RCT participants (50% versus 21%, $p < 0.01$). A similar risk difference was seen for subjects reaching the more severe dependency end point (65% versus 37%, $p < 0.05$).

Discussion. In this cohort of patients with AD, clinical trial participation was associated with only one difference in outcome over 3.5 years—a significantly lower risk of nursing home placement. The association between clinical trial participation and reduced risk of nursing home placement was evident in multivariate models that adjusted for differences in baseline covariates. Notably, RCT participants had a lower risk of nursing home placement compared with a group that was determined to be eligible for the trials but did not participate. Thus, it is reasonable to attribute the difference in nursing home placement to some feature linked to participation in the trials.

A number of explanations for this finding are possible. One is a true long-term benefit of the therapeutic agents themselves. Knopman et al.[13] recently reported such a benefit for tacrine treatment in AD. In 2 years of follow-up, they found that AD patients who received doses of tacrine >80 mg per day and remained on the medication had a lower risk of nursing home placement than patients who discontinued the drug or continued on lower doses. The lower relative risk of nursing home placement they report is comparable with that seen here. However, the tacrine study reported significantly reduced mortality as well, which we did not find. Recent randomized placebo-controlled trials involving acetyl-L-carnitine (ALCAR) and physostigmine salicylate have also shown benefits to AD patients—to early-onset patients in the case of ALCAR and to patients who responded to the initial-dose titration study period in the case of physostigmine.[14,15] Thus there is evidence for the efficacy of the therapies used by the RCT assessed in this research. However, the RCT group in this research included subjects on drug and placebo, because our primary goal was to assess the effect of RCT participation itself. The RCT group also included patients on a variety of medications, in some cases more than one, taken for variable lengths of time. Given the design of this research, we cannot rule out the favorable effect of long-term use of medications in a subset of patients. It is notable, however, that subjects who participated in the RCTs for longer lengths of time (>50% of study visits) had a reduced risk of nursing home placement when compared with subjects who participated in the RCTs for a shorter length of time (see figure 2). Since patients in the RCTs were offered long-term, open-label use of medications, this may point to a drug effect on reduced nursing home placement.

A second explanation that might account for the difference in outcome is a selection effect. Subjects in the eligible nonparticipant group were more likely to be placed in nursing homes than subjects in the RCT group, even when patients had equivalent levels of ADL dependency. Here again a number of explanations are possible. These patients may have had additional, unmeasured comorbidities that increased their risk for placement, although the groups did not show such differences at baseline. While we do not know if caregivers actually declined participation, decisions to decline participation in a clinical trial may indicate lower caregiver motivation (or different family constellations) and greater likelihood to place demented elders in nursing homes. Data on caregiving burden and satisfaction,[16] necessary to clarify this issue, are unavailable for the cohort.

Finally, a third explanation is the beneficial effect of RCT participation itself. Contact with a medical service in RCTs may have a beneficial effect of caregivers, perhaps enabling them to care for elders at home more effectively and in this way to delay nursing home placement until later stages of disease. An effect of this type might be examined with a study of caregiver coping strategies and patterns of service use. One would hypothesize that caregivers to RCT participants are better able to cope with the stress of caregiving and that they develop such skills through contact with service providers. A recent randomized trial reported by Mittelman et al.[17] showed that contact with a comprehensive support and counseling service significantly reduced the risk of nursing home placement for both mildly and moderately demented AD patients.

We conclude that RCT participation in a cohort of AD patients may be associated with a reduced risk of nursing home placement. Whether this effect is linked to long-term drug benefits to patients, selection factors, or a beneficial effect on caregivers remains unclear. To understand better the benefits of RCT participation to AD patients, especially in trials that specify nursing home placement as an end point, a more systematic evaluation of caregivers would seem appropriate, including information on caregiver burden, the distribution of caregiving tasks among family members (with close attention to type

of caregiver), attitudes toward nursing home placement, and the nature of contact with clinical trial medical staff. Also, these results suggest that historical or other kinds of unrandomized controls may not be appropriate as a comparison group in clinical trials involving AD. Finally, these results favor further research to examine how patients participating in RCTs may differ from those who do not, both in caregiving arrangements and in the clinical course of disease.

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