

RESEARCH ARTICLE

Effects of informant replacement in Alzheimer's disease clinical trials

Mikaela K. Nishida¹  | Michelle M. Nuño² | Joshua D. Grill^{3,4,5,6} | Daniel L. Gillen^{1,3,4}

¹Department of Statistics, Donald Bren School of Information and Computer Sciences, University of California, Irvine, Irvine, California, USA

²Department of Population and Public Health Sciences, University of Southern California, Los Angeles, California, USA

³Institute for Memory Impairments and Neurological Disorders, University of California, Irvine, Irvine, California, USA

⁴Alzheimer's Disease Research Center, University of California, Irvine, Irvine, California, USA

⁵Department of Neurobiology and Behavior, University of California, Irvine, Irvine, California, USA

⁶Department of Psychiatry and Human Behavior, University of California, UCI Health, Irvine, California, USA

Correspondence

Mikaela K. Nishida, Department of Statistics, Donald Bren School of Information and Computer Sciences, University of California, Irvine, Bren Hall 2019, Irvine, CA 92697-1250, USA.

Email: mikaeln@uci.edu

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Abstract

INTRODUCTION: Alzheimer's disease (AD) trials require enrollment with an informant.

METHODS: We assessed relationships between informant replacement and Alzheimer's Disease Cooperative Study Activities of Daily Living (ADCS-ADL) scores across four AD trials. Using generalized estimating equations, we examined associations between replacement and change in ADCS-ADL between successive visits. We used analysis of covariance to estimate the association between replacement and 18-month change from baseline, and an *F*-test to compare the variance of this change.

RESULTS: Among 1336 participants, 63 (≈5%) experienced replacement. Between-visit mean change in ADCS-ADL was 2.44 points lower comparing replacement to stable informants (95% confidence interval [CI]: -3.91, -0.98). The difference in between-visit mean absolute change was 2.38 points (95% CI: 1.24, 3.52). Replacement was not significantly associated with an 18-month change from baseline. The ratio of variances (replacement/stable) was 1.80 (95% CI: 1.19, 2.99).

DISCUSSION: Informant replacement is associated with bias and increased variability between visits and increased variance for overall ADCS-ADL.

KEYWORDS

activities of daily living, Alzheimer's Disease Cooperative Study, informant, informant replacement, study partner

1 | INTRODUCTION

In Alzheimer's disease (AD) clinical trials, participants must enroll with another individual known as a study partner. Trial protocols often outline eligibility criteria for the study partner, such as a minimum amount of time spent with the participant. The study partner role is generally filled by the primary caregiver, who is usually the spouse or an adult child of the person with dementia.¹ Study partners play key

roles in trial conduct² including ensuring protocol compliance, such as visit attendance and treatment adherence between visits. Study partners also provide key data, including adverse event reporting and completing validated assessments regarding the participant's cognitive and functional performance, neuropsychiatric symptoms, quality of life, and other constructs.¹ In this capacity, study partners serve as informants and play a critical role in the success of AD clinical trials.

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Informant-based scales are frequently primary outcomes in AD trials.^{3,4} In fact, until recently, efficacy assessments in AD registration trials typically included a co-primary outcome measure that was exclusively informant-based.⁵ In more recent registration trials (i.e., a late-phase trial that could be used to support the approval by the Food and Drug Administration [FDA] for use of treatment in clinical practice), the single primary outcome is frequently a composite scale that includes informant-based assessments.⁶ A critical assumption in trials is that informant reporting is consistent and without bias. Randomization should minimize the impact of such bias, but understanding the integrity of informant reporting is key to planning, analyzing, and interpreting AD trials. One occurrence that may bring unwanted risk of such bias is a change in the individual filling the study partner role, or informant replacement. Informant replacement can occur for a variety of reasons, including the death of the informant or simple inability or unwillingness to continue the role due to other family obligations or inconvenience.

Informant replacement is understudied in AD clinical trials. In this study, we assessed the frequency and impact of informant replacement in a sample of four controlled AD trials performed by an academic network of sites. We hypothesized that informant replacement would impact bias and variance on informant-reported measures, and tested this hypothesis for informant-reported activities of daily living (ADL). We further analyzed the potential impact of informant replacement on acute (i.e., visit-to-visit) and end-of-study outcomes, including the trajectory of ADL measurements throughout the entire study period.

2 | METHODS

2.1 | Data source

We conducted a retrospective analysis of data from four AD dementia clinical trials conducted by the Alzheimer's Disease Cooperative Study (ADCS). We received these datasets through the University of California, San Diego ADCS Legacy database. These trials were selected based on their similarities in design and conduct and because of their collection of informant data such as informant demographics and timing of informant replacement. The trials tested vitamin B supplementation,⁷ the Chinese herb-derived huperzine,⁸ the cholesterol-lowering drug simvastatin,⁹ and the psychotropic agent valproate.¹⁰ In each trial, the intervention of interest was not found to be efficacious for the treatment of AD. In general, the four trials shared common inclusion/exclusion criteria such as a minimum age of 50 or 55 years and the requirement that participants met the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable AD.¹¹ The valproate trial also permitted possible AD. There were slight differences in exclusion criteria across the trials, particularly with respect to concomitant medications. For example, the simvastatin trial did not enroll participants otherwise requiring lipid-lowering treatments. Trial duration also varied across the four studies (Table 1). The vitamin B and simvastatin trials both used 18-month protocols while

RESEARCH IN CONTEXT

1. **Systematic review:** We examined the literature using PubMed and other common scientific databases. We searched for papers examining informant or study partner replacement and other relevant titles. To our knowledge, this is the first assessment of informant replacement in Alzheimer's disease (AD) trials.
2. **Interpretation:** Informant replacement has negative impact on AD trial data, particularly at early visits after replacement.
3. **Future directions:** These results emphasize the need for investigators to develop strategies to reduce the bias and variance associated with informant replacement in AD clinical trials. Examples may include methods to retain informants through trial completion and methods to acclimate new informants with previous study ratings.

the huperzine and valproate trials used 6-month and 24-month protocols, respectively. Time between visits varied for each trial, ranging from 2 weeks to 3 months between protocol-specified visits. The valproate trial required informants to have at least 2 days of contact with the participant per week. The remaining three protocols did not specify informant-specific criteria other than requiring the ability to accompany the participant to scheduled study visits.

2.2 | Participant- and informant-based outcomes

Participant and informant demographic data were collected at screening. Data regarding informant replacement were systematically collected in the trials. Specifically, informant demographics were assessed at the first visit and in cases in which replacement occurred, an indicator of a new informant was recorded per protocol. The pre-specified categories for informant type included husband, wife, son, daughter, son-in-law, daughter-in-law, paid caregiver, friend, and other. Although replacement occasionally occurred before baseline and after the primary endpoint (at wash-out visits), only cases of replacement that occurred between baseline and the specified primary endpoint for the respective trials were considered in this study. Cognitive and functional measures were collected at protocol-specified visits. In this study, we used data for the ADCS Activities of Daily Living (ADCS-ADL) since it is a common informant-reported measure in AD trials and was available for each of the included trials. The ADCS-ADL is a 24-item structured interview administered to the informant to assess the functional performance of the participant (i.e., basic and instrumental ADLs).¹² ADCS-ADL scores range from 0 to 78 with higher scores indicating better functional performance. ADCS-ADL was not collected at every protocol-specified visit. The time between visits at which ADCS-ADL was collected ranged from 3 months to 6 months for the four trials.

TABLE 1 Summary of key aspects of included trials.

	Vitamin B	Huperzine	Simvastatin	Valproate
Trial period	March 2003 – February 2007	June 2004 – December 2007	December 2002 – January 2006	November 2005 – March 2009
Trial length (months)	18	4	18	24
Trial phase	3	2	3	3
Population	- Mild to moderate AD - Older than 55 years	- Mild to moderate AD - Older than 55 years	- Mild to moderate AD - Older than 50 years	- Moderate AD - Older than 55 years and 90 years at most
Primary outcome measure	Change in ADAS-Cog	Change in ADAS-Cog	Rate of change in ADAS-Cog	NPI and physician's judgement
Number of sites	39	32	45	43

Abbreviations: ADAS-Cog, Alzheimer's Disease Assessment Scale Cognitive subscale; AD, Alzheimer's disease; NPI, Neuropsychiatric Inventory.

2.3 | Statistical methods

The main goal of this study was to analyze the acute and overall effects of informant replacement in AD dementia trials using ADCS-ADL as a primary outcome. To assess the acute impact of informant replacement on systematic bias, we used generalized estimating equations (GEEs) to quantify the association between informant replacement and rate of change in ADCS-ADL measurements at successive visits.¹³ Differences in ADCS-ADL measurements were standardized by time due to missed visits and the varying length of time between visits for each protocol. We re-standardized estimates of mean change in ADCS-ADL measurements for successive visits spaced 3 months apart. The predictor of interest was an indicator of whether informant replacement occurred since the previous visit. Potential confounding variables were identified a priori and included participant age, sex, informant type at previous visit (spousal vs. non-spousal), time since baseline ADCS-ADL measurement in the trial, and trial. We also adjusted for previous ADCS-ADL measurements for added precision in coefficient estimates. We repeated this model with absolute successive rate of change in ADCS-ADL to examine the potential acute impact of informant replacement on variability in ADCS-ADL reporting. We used an autoregressive (Lag 1) correlation structure, which indicates lower correlation between measurements spaced further apart in time for both GEE models and then used a robust variance estimator to account for any potential misspecification of the covariance structure.¹⁴ For both models, we reported the estimated mean change and mean absolute change in ADCS-ADL for a 3-month period for each included covariate with corresponding 95% confidence intervals (CIs) and Wald-based *P*-values. We evaluated the significance of the association between informant replacement and systematic bias and variance using a Wald-based test of the main effects at a significance level of 0.05.

To analyze the potential impacts of informant replacement on the trajectory of ADCS-ADL over time, we used a GEE framework to estimate the trajectory of ADCS-ADL measurements before and after replacement occurred. We included a main effect of time, an indicator of first replacement, and the interaction between the two, along with confounding adjustment for participant age, sex, informant type

at baseline, and trial. For both models, we reported the estimated mean change in ADCS-ADL for each included covariate with corresponding 95% CIs and Wald-based *P*-values. We evaluated whether the trajectories of ADCS-ADL were significantly different before and after informant replacement using a Wald-based test of the interaction term at the 0.05-level.

Lastly, to examine the effect of informant replacement on a trial primary outcome, we analyzed the association between replacement and change from baseline ADCS-ADL measurements taken at month 18. We chose the 18-month visit as a proxy for the primary endpoint of these trials, as it was the furthest, most common endpoint among three of the four ADCS trials. Due to the absence of an 18-month ADCS-ADL measurement, the huperzine trial was excluded from this analysis. We used an analysis of covariance (ANCOVA) model to estimate the association between informant replacement and the overall change from baseline. We adjusted for participant age, sex, informant type, baseline ADCS-ADL, and trial as potential confounding or precision variables in this model. Additionally, we conducted an *F*-test comparing the variance of the overall change from baseline ADCS-ADL between participants who experienced replacement and participants who had stable informants for 18 months.

For all analyses, we performed appropriate diagnostics to validate model assumptions and fit. For all multivariate analyses, we adjusted for trial as a fixed effect to control for any potential confounding with respect to the trial. Two participants were omitted from the analyses due to apparent input errors with regard to date and ADCS-ADL measurement records. The removal of these observations had minimal influence on study outcomes and these analyses.

3 | RESULTS

3.1 | Descriptive statistics

Baseline participant characteristics stratified by informant replacement status are summarized in Table 2. Among the *N* = 1336 participants, there were 76 occurrences of informant replacement with 63 (≈5%) unique participants experiencing replacement at least once.

TABLE 2 Baseline participant characteristics summarized by informant replacement status. Mean (standard deviation) is given for continuous variables, and count (%) is given for discrete variables.

	All N = 1336	Stable informant N = 1273	Informant replacement N = 63
Baseline ADCS-ADL	59.3 (12.5)	59.4 (12.5)	57.3 (13.3)
Age	76.2 (8.5)	76.2 (8.5)	76.3 (8.1)
Sex			
Male	548 (41)	527 (41)	21 (33)
Female	788 (59)	746 (59)	42 (67)
Race			
American Indian/Alaska Native	4 (0)	4 (0)	0 (0)
Asian	19 (1)	19 (1)	0 (0)
Black	95 (7)	86 (7)	9 (14)
Multiracial	10 (1)	9 (1)	1 (2)
Native Hawaiian or Pacific Islander	3 (0)	3 (0)	0 (0)
White	1203 (90)	1151 (90)	52 (83)
Missing	2 (0)	1 (0)	1 (2)
Ethnicity			
Hispanic	67 (5)	60 (5)	7 (11)
Non-Hispanic	1259 (94)	1203 (95)	56 (89)
Missing	10 (1)	10 (1)	0 (0)
Years of education	13.9 (3.2)	14 (3.1)	12.5 (4.2)
Baseline informant type			
Non-spousal	466 (35)	437 (34)	29 (46)
Spousal	870 (65)	836 (66)	34 (54)
Trial			
Vitamin B	409 (31)	388 (30)	21 (33)
Huperzine	210 (16)	201 (16)	9 (14)
Simvastatin	405 (30)	389 (31)	16 (25)
Valproate	312 (23)	295 (23)	17 (27)

Abbreviations: Alzheimer's Disease Cooperative Study Activities of Daily Living.

There was a higher proportion of female participants and participants with non-spousal informants among those who experienced informant replacement at least once compared to participants with stable informants. Figure 1 illustrates the patterns of informant replacement. Most replacements were from a spouse to another informant type. The frequency of replacement was roughly consistent across the included trials (Figure 2).

3.2 | Impact of informant replacement on acute bias and variance

We estimated that the difference in the mean between-visit change in ADCS-ADL was approximately -2.44 points (95% CI: $-3.91, -0.98$, $P = 0.001$) comparing participants who experienced informant replacement to participants of similar age, sex, previous ADCS-ADL, informant type, and trial who had stable informants (Table 3). This indicates

greater reported functional worsening at a successive visit for participants who experienced replacement. We also estimated that the mean between-visit absolute change in ADCS-ADL was approximately 2.38 points higher (95% CI: 1.24, 3.52; $P < 0.001$) for participants who experienced informant replacement, compared to participants with stable informants, indicating that replacement was associated with higher variance in successive ADCS-ADL measurements.

3.3 | Impact of informant replacement on longitudinal ADCS-ADL measurement

We estimated that the average change in ADCS-ADL was approximately -0.68 points (95% CI: $-0.73, -0.64$) per month for all participants prior to informant replacement (Table 4). After informant replacement, we estimated that the average change in ADCS-ADL was approximately -0.76 points (95% CI: $-1.11, -0.41$) per month for

TABLE 3 Estimated acute changes in ADCS-ADL between visits spaced 3 months apart from GEE models.

	Mean change in ADCS-ADL (95% CI)	P-value	Absolute change in ADCS-ADL (95% CI)	P-value
Informant replacement since last visit	-2.44 (-3.91, -0.98)	0.001	2.38 (1.24, 3.52)	<0.001
Age (5 years)	-0.02 (-0.13, 0.09)	0.708	0.06 (-0.05, 0.16)	0.279
Female (vs. male)	-0.16 (-0.52, 0.20)	0.383	0.05 (-0.30, 0.41)	0.763
Time since first ADL (3 months)	0.03 (-0.06, 0.12)	0.486	-0.24 (-0.32, -0.16)	<0.001
Previous ADL (5 points)	0.03 (-0.04, 0.09)	0.396	-0.16 (-0.22, -0.10)	<0.001
Spousal informant at last visit	-0.13 (-0.54, 0.29)	0.539	-0.11 (-0.49, 0.27)	0.579
Trial				
Vitamin B	Referent		Referent	
Huperzine	0.32 (-0.80, 1.45)	0.571	1.31 (0.44, 2.18)	0.003
Simvastatin	-0.32 (-0.71, 0.08)	0.117	1.22 (0.83, 1.61)	<0.001
Valproate	-1.31 (-1.76, -0.86)	<0.001	1.38 (0.94, 1.81)	<0.001

Abbreviations: ADCS-ADL, Alzheimer's Disease Cooperative Study Activities of Daily Living; CI, confidence interval; GEE, generalized estimating equation.

TABLE 4 Estimated mean change in ADCS-ADL from longitudinal GEE model.

	Mean difference in ADCS-ADL (95% CI)	P-value
After informant replacement	-4.78 (-7.51, -2.05)	0.001
Age (5 years)	-1.42 (-1.88, -0.96)	<0.001
Female (vs. male)	-0.67 (-2.27, 0.93)	0.409
Spousal informant at baseline	-0.01 (-1.74, 1.72)	0.989
Time before informant replacement (per month)	-0.68 (-0.73, -0.64)	<0.001
Time after informant replacement (per month)	-0.76 (-1.11, -0.41)	<0.001
Trial		
Vitamin B	Referent	
Huperzine	-2.65 (-4.90, -0.39)	0.021
Simvastatin	-0.37 (-2.20, 1.47)	0.695
Valproate	-8.28 (-10.28, -6.29)	<0.001

Abbreviations: ADCS-ADL, Alzheimer's Disease Cooperative Study Activities of Daily Living; CI, confidence interval; GEE, generalized estimating equation.

participants who experienced replacement. These trajectories were not significantly different ($P = 0.677$); however, informant replacement was associated with a -4.78 -point (95% CI: $-7.51, -2.05$; $P = 0.001$) difference in ADCS-ADL at the time of replacement (Figure 3).

3.4 | Impact of informant replacement on the trial primary outcome

We estimated that informant replacement was associated with a -2.73 -point (95% CI: $-6.83, 1.37$; $P = 0.192$) difference in a primary outcome, which we defined as the change from baseline ADCS-ADL at month 18, compared to participants of similar age, sex, baseline ADCS-ADL, informant type, and trial with stable informants (Table 5). The estimated ratio of variances of the primary outcome measurements comparing participants who experienced informant replacement to those who had stable informants was approximately 1.80 (95% CI: 1.19, 2.99; $P = 0.005$).

4 | DISCUSSION

In this study, we analyzed the acute and end-of-study effects of informant replacement on ADCS-ADL measurements in AD dementia clinical trials. We observed that informant replacement occurred in $\approx 5\%$ of participants and that this frequency was relatively consistent across the trials included in our analyses. We also observed that replacement occurred in a greater proportion of participants with initial non-spousal informants, compared to those with initial spousal informants. Replacement was associated with a bias toward worse performance and higher variance in ADCS-ADL measurements at successive visits. Although informant replacement did not significantly affect measures of change from baseline in ADCS-ADL at the end of the study, we did find that it was associated with significantly higher variance in these measures. The consistency of replacement across studies and the frequency with which it occurred suggest that these results should be considered by investigators designing and

TABLE 5 Estimated mean difference in primary outcome (baseline to month-18 change in ADCS-ADL) from linear model.

	Mean difference in primary outcome (95% CI)	P-value
Informant replacement	-2.73 (-6.83, 1.37)	0.192
Age (5 years)	0.24 (-0.31, 0.79)	0.389
Female	-1.38 (-3.32, 0.55)	0.161
Baseline ADL	0.14 (-0.26, 0.53)	0.503
Spousal informant at baseline	-0.85 (-2.97, 1.27)	0.431
Trial		
Vitamin B	Referent	
Simvastatin	-0.46 (-2.46, 1.55)	0.653
Valproate	-6.32 (-8.65, -4.00)	<0.001

Abbreviations: ADCS-ADL, Alzheimer's Disease Cooperative Study Activities of Daily Living; CI, confidence interval.

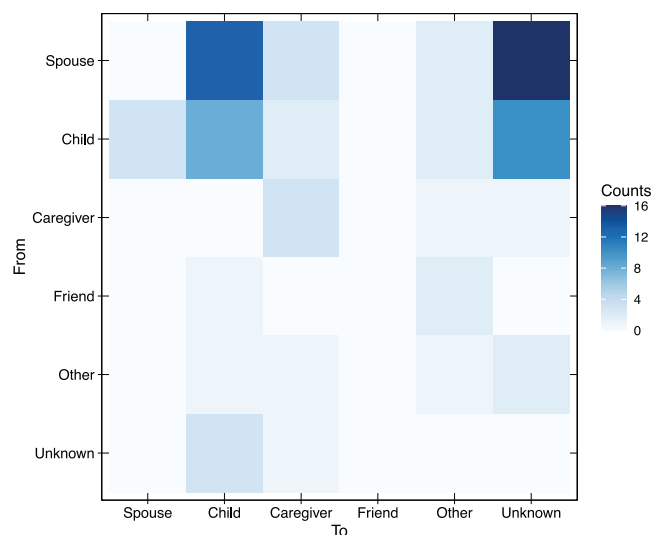


FIGURE 1 Counts of occurrences (76) of informant replacement by replacement type. Informants were classified as “unknown” if informant type was not recorded.

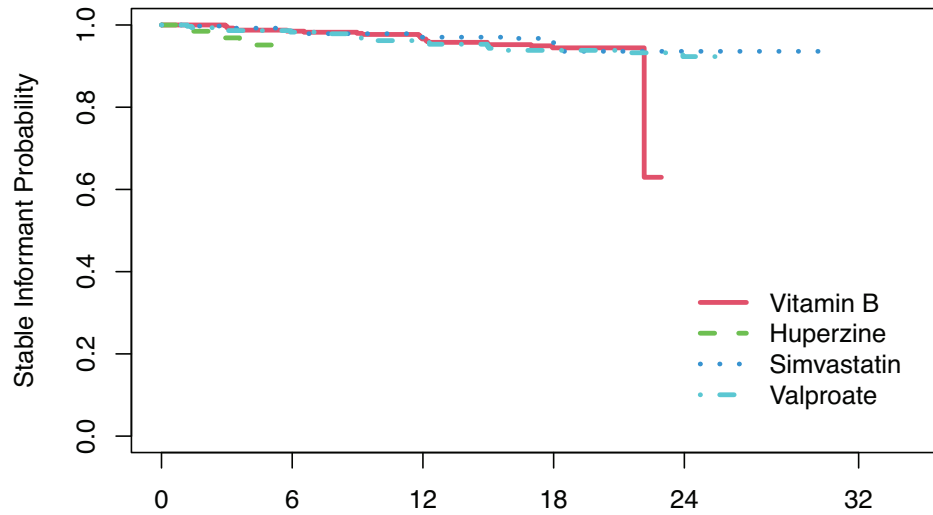
conducting AD trials. Specifically, the results may warrant efforts to minimize the occurrence of replacement and to develop interventions to reduce its impact.

Our data do not provide information about the cause of informant replacement. Approximately half of the occurrences of replacement, however, were from a spousal informant to a non-spousal informant. Because spouse informants are typically older than non-spouses,¹⁵ this may suggest that the health of these informants could have produced the need for replacement and could make prevention of replacement challenging in these cases. In the other half of cases of replacement, it cannot be ruled out that replacement was due to informant convenience or other factors. This may suggest that education of informants or strategies to ensure that consistent individuals perform outcome assessments when challenges arise with other roles, such as ensuring visit compliance, could function to minimize replacement and its impact on trial data.

In analyses of acute changes in ADCS-ADL, informant replacement was associated with bias toward worse performance and increased variance. While we cannot definitively determine the source of negative bias for ADCS-ADL measurements immediately after replacement, a few possibilities exist. One is that the new informant may have perceived the participant's function as worse than the initial informant did. This may be based on differences in informant relationships or the amount of time spent with the participant. This hypothesis may be supported by the observation that the most common occurrence of replacement was from an initial spouse informant to an adult child or another non-spouse relationship.¹⁶ Alternatively, it is possible that the event that produced the need for replacement, particularly if it were a stressful event such as the death of the participant's spouse, could have resulted in an actual decline in function for the participant and the observed bias is simply an accurate representation of functional decline.

Despite the acute effects on ADCS-ADL, we did not find that the trajectory of ADCS-ADL was significantly different for those who experienced informant replacement compared to those with stable informants when examining the trajectories before and after replacement. This result suggests that although there is initial bias at the time of replacement, the functional performance of the participant is likely declining at a similar rate to before replacement occurred, and new informants appear to assess change over time in a similar way compared to the previous and stable informant counterparts. This may suggest that replacement carries the greatest risk to trial data integrity when occurring late in the trial, particularly at the end-of-study visit. It may also suggest that interventions to align the new informant with the old informant's assessments could alleviate the initial bias. This could be as simple as asking the new informant to review the previous ratings as a form of orienting them to their new role. To our knowledge, such interventions have not been systematized in trial protocols or tested for their utility.

Although not statistically significant, the estimated difference in change from baseline ADCS-ADL at month 18 between those who experienced informant replacement and those who did not was highly concordant with the acute findings. This may be particularly problematic if replacement occurs disproportionately across trial arms,



	0	6	12	18	24	32
Vitamin B	409 (0)	384 (6)	352 (13)	140 (20)	0 (21)	0 (21)
Huperzine	210 (0)	0 (9)	0 (9)	0 (9)	0 (9)	0 (9)
Simvastatin	405 (0)	366 (6)	339 (11)	143 (14)	10 (16)	0 (16)
Valproate	312 (0)	259 (5)	215 (11)	178 (15)	54 (17)	0 (17)
Total	1336 (0)	1009 (26)	906 (44)	461 (58)	64 (63)	0 (63)

FIGURE 2 Kaplan–Meier plot of first occurrences of informant replacement for each trial in which participants were censored upon completion of the primary endpoint and participants lost to dropout were censored at the time of the last completed primary endpoint.

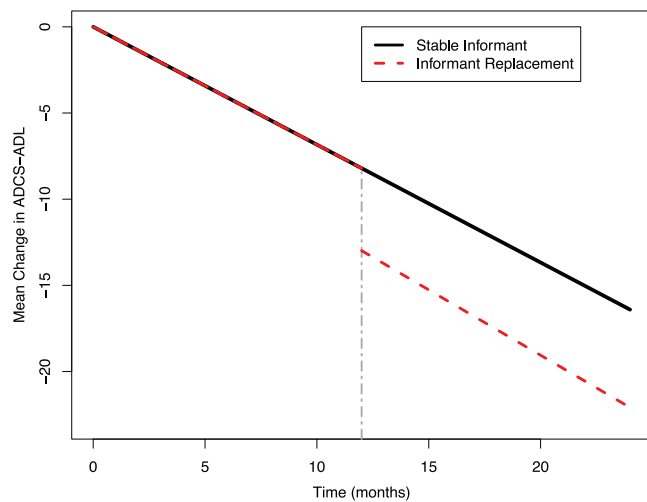


FIGURE 3 A theoretical example of estimated trajectories of Alzheimer's Disease Cooperative Study Activities of Daily Living (ADCS-ADL) over time for participants with stable informants and participants who experienced informant replacement at 12 months.

increasing risk for type I or type II errors. Investigators may therefore wish to assess replacement for its frequency, timing, and balance by arms before finalizing trial statistical analysis plans. We also observed a significant association between informant replacement and higher variance in change from baseline to month-18 outcomes. This unanticipated variance could reduce power to demonstrate treatment effects if they are present, resulting in higher type II error

rates. Investigators may wish to incorporate expectations for informant replacement and the associated increase in variance to sample size estimates. For example, in planning for a trial in which 5% of participants experience informant replacement, the targeted sample size may need to increase by $\approx 4\%$ to retain the same power as planning for a trial in which replacement does not occur. In cases in which there is greater than expected occurrences of informant replacement, investigators may need to consider adjusting sample sizes accordingly.

There are several limitations to these analyses that should be noted. Informant replacement is not universally tracked in AD trials, and among a larger collection of ADCS dementia studies,¹⁷ many lacked data to permit analyses of informant replacement. Even in the included studies, there was missing information on some informants such as informant type, age, and sex. The included trials had some key differences, notably including their durations, which complicated combining datasets to explore the implications of replacement. Several limitations to the generalizability of these results exist. The included trials were performed several years ago, before the advent of modern enrollment criteria, which include biomarker criteria as well as inclusion of samples that enroll both mild dementia and mild cognitive impairment (MCI). Many modern trials are sponsored by industry and include larger numbers of sites, including commercial and private practice sites.¹⁸ It is unknown whether the current results would generalize to these trials. Similarly, informant-based ADL measures are often used in MCI trials. We are investigating informant replacement in a separate analysis of these trials.

In conclusion, our analyses demonstrated that informant replacement occurred consistently in AD trials and was associated with negative bias in acute ADCS-ADL reporting and increased variance in acute and overall ADCS-ADL change scores. These results highlight ways that current data collection can improve to account for this source of potential bias and variance in AD clinical trials. In addition to routinely recording all informant demographics, it would be useful to collect information regarding if or when informant replacement occurs during trials, as well as time the informant spends with the participant to consider in future analyses. These results emphasize the need for investigators to consider informant replacement when planning trials, retaining participants and their informants, addressing replacement during trials, and performing post hoc analyses of trial data that consider the impact of informant replacement to ensure efficient and valid inference from trial results.

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CONFLICT OF INTEREST STATEMENT

Ms. Nishida, Dr. Nuño, Dr. Grill, and Dr. Gillen have no conflicts of interest to report. Author disclosures are available in the [supporting information](#).

CONSENT STATEMENT

All data used in these analyses were non-identifiable. Additionally, participants from each included trial were approved by local or central institutional review boards and signed consent for participation in the trial as well as for the use of these data in secondary analyses.

ORCID

Mikaela K. Nishida  <https://orcid.org/0009-0007-8676-9361>

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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