Received: 16 July 2024 | Revised: 12 September 2024 | Accepted: 26 September 2024

DOI: 10.1002/trc2.70009

Alzheimer's & Dementia
Translational Research & Clinical Interventions

RESEARCH ARTICLE

Impacts of informant replacement in two industry-sponsored Alzheimer's disease clinical trials

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Funding information
National Institute of Aging, Grant/Award Numbers: P30-AG066519-03, RF1 AG059407

Abstract

INTRODUCTION: In Alzheimer's disease (AD) clinical trials, participants must enroll with a study partner informant who completes validated study instruments. We hypothesized that mid-trial informant replacement impacts study data in industry-sponsored trials.

METHODS: We conducted a retrospective analysis of two industry-sponsored AD clinical trials testing semagacestat in mild-to-moderate AD dementia. We assessed the relationships between informant replacement and Alzheimer's Disease Cooperative Study Activities of Daily Living (ADCS-ADL) scores. Using generalized estimating equations, we assessed bias and variability using mean (bias) and mean absolute (variance) change in ADCS-ADL between successive visits as outcomes. Both models adjusted for a priori–specified potential confounding variables including participant sex, age, informant type, trial, time, previous ADCS-ADL score, and region. To analyze the impact on end-of-study change-from-baseline results, we used an analysis of covariance model to estimate the association between replacement and end-of-study change-from-baseline in ADCS-ADL, in which we adjusted for participant sex, age, informant type, trial, baseline measurement, and region. We conducted an *F*-test to compare the variances of this change.

RESULTS: Among $N = 2637$ randomized participants, 69 participants (2.6%) experienced 78 occurrences of replacement. For visits standardized to be 3 months apart, the difference in mean between-visit change in ADCS-ADL was approximately −1.61 points (95% confidence interval [CI]: −3.79, 0.57; $P = 0.147$), comparing participants who experienced replacement to similar participants who had stable informants. The difference in the mean between-visit absolute change was approximately 2.02 points (95% CI: 0.34, 3.70; $P = 0.019$). We did not estimate a statistically significant difference in end-of-study change-from-baseline (Est. = −0.70 points; 95% CI: −5.88, 4.48; $P = 0.790$) or a significant ratio of variances (Est. = 1.13; 95% CI: 0.67, 2.28; $P = 0.600$) for participants with replacement compared to those with stable informants.

DISCUSSION: Informant replacement was associated with increased between-visit variability but had limited impact on overall trial outcomes.

KEYWORDS
Alzheimer's Disease Cooperative Study Activities of Daily Living, informant, informant replacement, study partner

Highlights

- Informant replacement occurred in 2.6% of participants in these industry trials.
- Informant replacement was associated with increased variance in acute Alzheimer's Disease Cooperative Study Activities of Daily Living reporting.
- Informant replacement had a limited impact on overall change-from-baseline outcomes.

1 | INTRODUCTION

Participants in Alzheimer's disease (AD) clinical trials must enroll with a study partner, or "informant."[1] The participant's primary caregiver generally serves in the informant role. Duties of the informant include attending study visits and completing interviews and questionnaires that provide essential data regarding the cognitive and functional performance of the participant.[2] These data frequently are used as primary endpoints in AD trials, including for registration studies. Informant replacement, or a change in the person completing these duties, can occur at any time throughout the study.

The impacts of informant replacement are relatively understudied. In 2015, an assessment of the National Alzheimer's Coordinating Center (NACC) Uniform Data Set found that replacement was common and had impacts on Functional Assessment Questionnaire (FAQ) outcomes in AD dementia participants.[3] In 2023, we explored replacement in AD dementia trials performed by an academic network of sites in the United States.[4] Replacement was associated with systematic bias toward greater reported functional worsening and increased variance for visit-to-visit informant-based reporting as well as systematic bias toward greater reported functional worsening for the end-of-study change-from-baseline outcomes.[4] These findings remain largely unreplicated while the role of study partners in AD trials remains critical.[1]

In this study, we examined the construct of informant replacement in two global, industry-sponsored AD dementia trials.[5] We quantified informant replacement and assessed the relationships between replacement and informant-reported Alzheimer's Disease Cooperative Study Activities of Daily Living (ADCS-ADL)[6] score. Based on our previous work in academic trials,[4] we hypothesized that informant replacement is associated with bias and variance for informant-reported measures. We analyzed the potential impacts of informant replacement on acute (i.e., visit-to-visit) and end-of-study change-from-baseline informant-reported outcomes. We also analyzed the trajectories of ADCS-ADL over time. Given that the available trials were conducted in multiple nations, we also conducted exploratory analyses of the region-specific impacts of replacement on acute ADCS-ADL reporting.

2 | METHODS

2.1 | Data source

We conducted a retrospective analysis of two global, industry-sponsored, Phase III, AD clinical trials that tested semagacestat, an oral gamma-secretase inhibitor, in mild-to-moderate AD dementia (ClinicalTrials.gov numbers: LFAN—NCT00594568 and LFBC—NCT00762411). LFAN ran from March 2008 to May 2011, and LFBC ran from September 2008 to April 2011. Both trials were similar in design and conduct and included participants who were ≥ 55 years and had a Mini-Mental State Examination (MMSE) score between 16 and 26. An informant was defined in the protocol as a reliable caregiver who had frequent contact (at least 10 hours per week) with the participant. The protocol specified that the same individual should serve as the informant at all study visits. Collected informant-related data included some informant demographics and the timing of replacement. Both trials were stopped early for futility as advised by the data safety monitoring board; the drug was found to be associated with weight loss, skin cancers and infections, treatment discontinuations due to adverse events, and serious adverse events.[5] We received access to these datasets through the University of California, San Diego ADCS Legacy database.

2.2 | Participant- and informant-based outcomes

Demographic information for informants was collected via the Resource Utilization in Dementia (RUD) questionnaire.[7] Longitudinal RUD questionnaires also assessed for change in informant since the last visit. In most cases, the new informant completed the RUD. Including the primary endpoint visit, there were 16 scheduled visits. The co-primary outcomes of the two trials were the change from baseline at week 76 in Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-Cog11) and ADCS-ADL scores. Both were scheduled to be collected at weeks 0, 12, 28, 40, 52, 64, and 76. Additional visits scheduled after treatment cessation were not considered in our analyses.

The outcome of interest for our analyses was the ADCS-ADL score. The ADCS-ADL is a 23-item, interview-structured questionnaire that is answered by the informant and measures the functional performance of the participant.[8] ADCS-ADL scores range from 0 to 78, with higher scores indicating better functional performance on daily tasks.

2.3 | Statistical methods

The main objective of this study was to assess the potential impacts of informant replacement on ADCS-ADL measurements. We used generalized estimating equations (GEE)[9] to evaluate the acute impacts of informant replacement on systematic bias. When estimating the association between informant replacement and mean rate of change in ADCS-ADL between successive visits, the predictor of interest was an indicator for whether replacement occurred since the previous visit, and the response was the rate of change in ADCS-ADL. To account for missing visits and varying lengths of time between visits, we standardized differences in ADCS-ADL measurements by dividing by the number of days between visits. We restandardized model estimates for mean change in ADCS-ADL to reflect the change for visits spaced 3 months apart. In this model, we also included a priori–specified potential confounding and precision variables including participant age, sex, informant type at previous visit (spousal vs. non-spousal), time since baseline ADCS-ADL measurement, trial (LFAN vs. LFBC), previous ADCS-ADL score, and global region of the site where the participant was enrolled. We repeated this model with the absolute rate of change in ADCS-ADL as the response variable to evaluate the potential acute impacts of replacement on variability. For both models, we used an autoregressive (Lag 1) correlation structure, which assumes a stronger correlation between observations that are closer together in time, as well as a robust variance estimator to account for any potential misspecification of the covariance structure.[10] We reported model estimates along with corresponding 95% confidence intervals and Wald-based *P*-values. We evaluated associations between informant replacement and systematic bias and variance using Wald tests of the main effects at the 0.05-significance level.

We used GEE to estimate the trajectories of ADCS-ADL before and after replacement. This model used ADCS-ADL as the response and included the main effects of time, an indicator for after replacement, and the interaction between time after replacement and the indicator for after replacement. Potential confounding variables including participant age, sex, baseline informant type, and trial were specified a priori and were also included in this model. We reported the estimated mean change in ADCS-ADL for each included covariate (or linear contrast of covariates) with corresponding 95% confidence intervals and Wald-based *P*-values and evaluated whether the trajectories were significantly different before and after replacement using a Wald test on the interaction term at the 0.05-level.

We considered the change from baseline at week 76 (primary endpoint for both trials) to evaluate the impacts of informant replacement on end-of-study change-from-baseline outcomes. Using an analysis of covariance (ANCOVA) model, we estimated the association between informant replacement and change from baseline at week 76. This model also adjusted for potential confounding and precision variables including participant age, sex, baseline informant type, baseline ADCS-ADL measurement, trial, and region. We reported coefficient estimates with corresponding 95% confidence intervals and Wald-based *P*-values, and we evaluated the significance of the association between informant replacement and the change-from-baseline using a Wald test at the 0.05-level. We also conducted an *F*-test using a significance level of 0.05 to compare the variances of this change for participants who experienced replacement and participants who had stable informants for the duration of the trial. We reported the ratio of the variances with a corresponding 95% confidence interval and *P*-value.

Due to the global nature of these trials and the potential heterogeneity of trial conduct and results by region,[3,11] we conducted an exploratory analysis on the region-specific impacts of replacement on acute bias and variance. We repeated the first two models for seven mutually exclusive subpopulations defined by global region. For each region, we recorded estimates from both models along with the corresponding 95% confidence intervals. We displayed these findings in a forest plot.

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. There were two other papers examining the impacts of informant replacement on Alzheimer's disease (AD) trial results in various trials, which are cited in our manuscript.
2. **Interpretation**: Informant replacement was associated with increased variance for informant-reported measures immediately after replacement but did not have significant impacts on overall change-from-baseline outcomes.
3. **Future Directions**: Our findings replicate those observed in academic AD dementia trials and further emphasize the need for trialists to consider replacement in trial design and analyses.

3 | RESULTS

3.1 | Descriptive statistics

Between the two studies, there were 2648 participants randomized; however, a small number of participants were omitted from our analyses for specific reasons. Five participants were not considered due to completely missing informant information, and six participants did

TABLE 1 Baseline participant characteristics by informant status. Values are reported as mean (standard deviation) for continuous variables and count (%) for discrete variables.

Participant characteristics	All $N = 2637$	Stable informant $N = 2568$	Informant replacement $N = 69$
Baseline ADCS-ADL	59.8 (13.2)	59.8 (13.2)	60.2 (14.1)
Age (years)	73.1 (8.1)	73.1 (8.1)	74.6 (8.7)
Sex			
Female	1460 (55)	1404 (55)	56 (81)
Male	1177 (45)	1164 (45)	13 (19)
Region			
Asia	204 (8)	199 (8)	5 (7)
Australia/South Africa	153 (6)	146 (6)	7 (10)
Eastern Europe/Russia	289 (11)	282 (11)	7 (10)
Japan	254 (10)	250 (10)	4 (6)
North America	984 (37)	952 (37)	32 (46)
South America/Mexico	204 (8)	196 (8)	8 (12)
Western Europe/Israel	549 (21)	543 (21)	6 (9)
Race/Ethnicity			
Black	31 (1)	28 (1)	3 (4)
Asian	474 (18)	465 (18)	9 (13)
White	1990 (75)	1937 (75)	53 (77)
Hispanic	140 (5)	137 (5)	3 (4)
Native American	2 (0)	1 (0)	1 (1)
Years of education	12.3 (4.1)	12.3 (4.1)	12.3 (4.4)
Baseline informant type			
Non-spousal	908 (34)	861 (34)	47 (68)
Spousal	1729 (66)	1707 (66)	22 (32)
Trial			
LFAN	1532 (58)	1488 (58)	44 (64)
LFBC	1105 (42)	1080 (42)	25 (36)

Abbreviation: ADCS-ADL, Alzheimer's Disease Cooperative Study Activities of Daily Living.

not have any recorded scheduled visits. We conducted sensitivity analyses (results not presented) and found that the removal of these participants did not significantly affect results. Baseline characteristics for participants in this analysis are reported in Table 1. Out of the $N = 2637$ participants, 69 participants (≈ 2.6%) experienced informant replacement at least once (78 total occurrences). There was a higher proportion of female participants and participants with non-spousal informants at baseline among those who experienced informant replacement. The types of replacement that occurred are presented in Figure 1A. The most frequent occurrence was an adult child replacing another adult child, followed by an adult child replacing a spouse. The patterns of replacement were similar across regions, and the timing of replacement is outlined in Figure 1B. Among participants with non-spousal informants at baseline, the proportion of female participants was much higher than the proportion of females overall (Table S1 in supporting information).

Informant characteristics were collected via the RUD; however, many variables such as informant years of education and informant race were not collected for all subjects. Among the 2711 unique informants, 34 did not report their age. The average age of the remaining informants was 63.4 years. Among all informants, there were 1662 (≈ 61%) females, 1024 (≈ 38%) males, and 25 informants who did not report their sex. Among all non-spousal informants, a higher proportion were female (Table S2 in supporting information). Figure 2 illustrates the level of contribution to caregiving reported by each informant. A higher proportion of initial informants reported the highest level of contribution as a caregiver, compared to informants after replacement.

3.2 | Impact of informant replacement on acute bias and variance

We estimated that the difference in the mean change in ADCS-ADL between successive visits spaced 3 months apart was approximately −1.61 points (95% confidence interval [CI]: −3.79, 0.57; $P = 0.147$), comparing participants who experienced informant replacement since the last visit to participants of a similar age, sex, informant type, time since baseline measurement, trial, and previous ADCS-ADL measurement who had the same informant. This negative difference, though not statistically significant, indicated greater reported functional worsening for those who experienced replacement. The estimated mean absolute change in ADCS-ADL was approximately 2.02 points larger (95% CI: 0.34, 3.70; $P = 0.019$), indicating greater variability in reported ADCS-ADL, for participants who experienced replacement compared to similar participants with stable informants since the last visit. Estimates from both models are presented in Table 2.

3.3 | Impact of informant replacement on overall trial ADCS-ADL measurements

The mean change in ADCS-ADL measurement was approximately −0.52 points (95% CI: −0.55, −0.48) per month for all participants before replacement. For participants who experienced replacement, this change was approximately −0.61 points (95% CI: −0.99, −0.22) per month after replacement. These two trajectories were not significantly different ($P = 0.649$). We estimated a −0.54-point (95% CI: −2.63, 1.54; $P = 0.609$) difference in ADCS-ADL at the time of replacement.

The difference in the change from baseline at week 76 was approximately −0.70 points (95% CI: −5.88, 4.48; $P = 0.790$), comparing participants who experienced informant replacement to similar participants with stable informants. Other model estimates are presented in Table 3. Similarly, we estimated that the ratio of the variances of this change was approximately 1.13 (95% CI: 0.67, 2.28; $P = 0.600$) comparing participants who experienced replacement to those who did not. Only 608 participants (23 of whom experienced replacement) were included in these analyses due to the early stopping for futility.

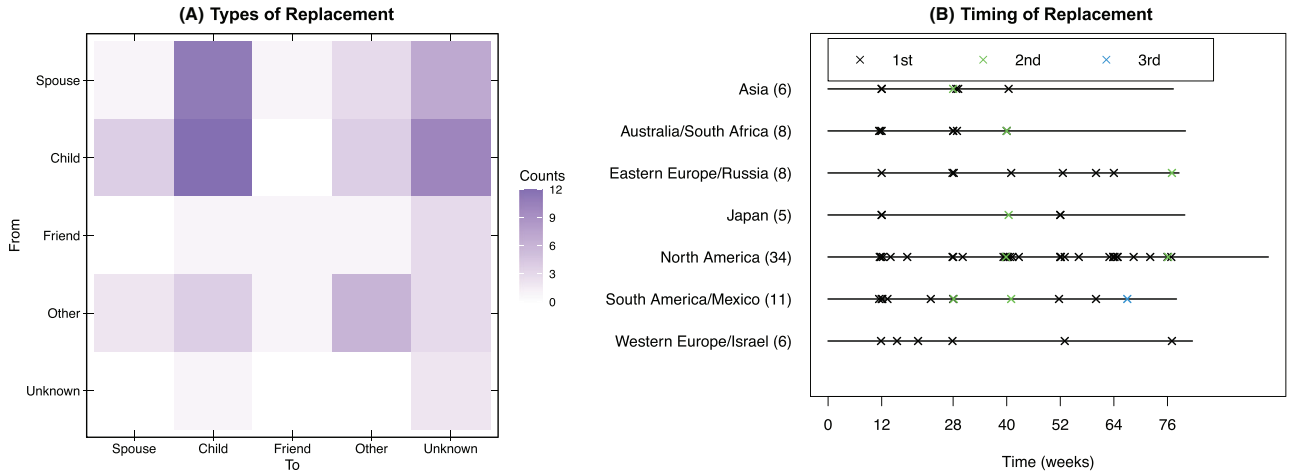

FIGURE 1 (A) Number of occurrences of informant replacement (78 total) by replacement type. Informants were classified as "Unknown" if the informant type was not recorded. (B) Swim plot illustrating the timing of replacement by region. Total number of occurrences is indicated next to the region name

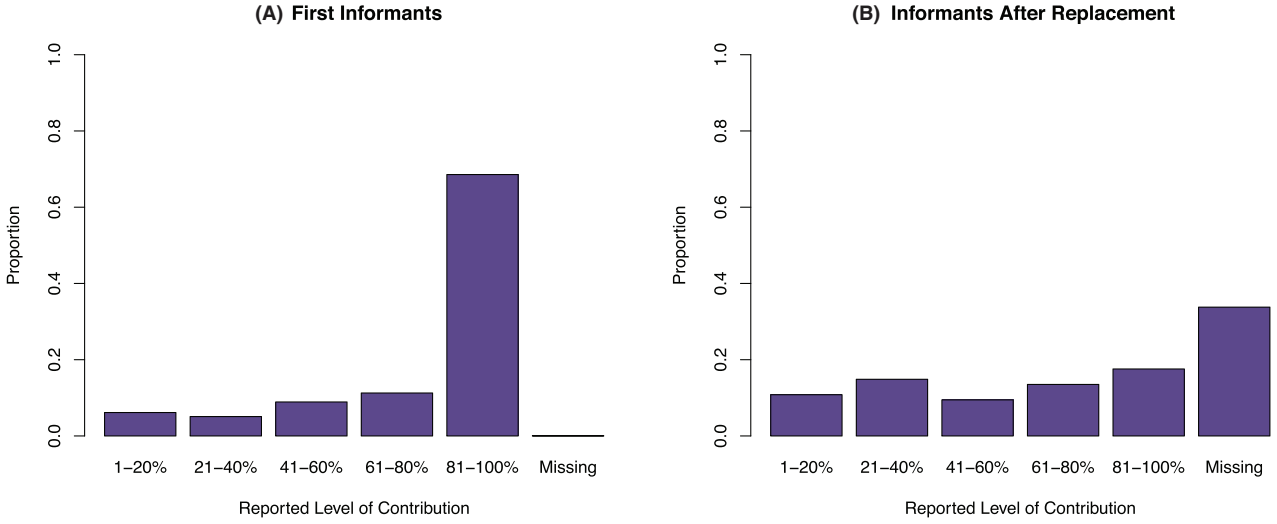

FIGURE 2 Proportions of responses to the Resource Utilization in Dementia question: "Among all caregivers, what is your level of contribution?" stratified by first informants versus informants after replacement for all unique informants (2711)

3.4 | Region-specific impacts on acute measures

The proportion of participants who experienced replacement was similar across global regions (Figure 3). For the North American region, we estimated that the difference in the mean change in ADCS-ADL between successive visits spaced 3 months apart was approximately −0.36 points (95% CI: −2.48, 1.76; $P = 0.738$) comparing participants who experienced informant replacement since the last visit to similar participants who had the same informant. Although not statistically significant, the estimated negative difference coincided with the result from the global analysis. Similarly, the mean absolute change in ADCS-ADL was approximately 1.36 points more (95% CI: −0.09, 2.80; $P = 0.066$), indicating greater variability in reported ADCS-ADL, for participants who experienced replacement compared to similar participants who had stable informants since the last visit. Estimates for other regions were largely similar and are presented in Figure 3.

4 | DISCUSSION

In this analysis of two global, industry-sponsored AD dementia clinical trials, we investigated the frequency and potential impact of informant replacement on acute reporting, trajectories, and overall outcomes of ADCS-ADL. We observed that approximately 2.6% of participants experienced replacement and that replacement was relatively evenly distributed across the duration of the trials. Replacement was associated with increased variability but not bias for acute ADCS-ADL reporting. We did not find evidence suggesting that replacement was associated with bias or variability for end-of-study change-from-baseline outcomes.

Our results add to the literature on informant replacement in different settings. We previously explored replacement in an analysis of AD dementia trials performed by an academic network of sites in North America, where replacement was associated with a systematic bias toward greater reported functional worsening and increased variance

TABLE 2 Estimated acute changes in ADCS-ADL for visits spaced 3 months apart.

	Mean change in ADCS-ADL (95% CI)	*P*-value	Mean absolute change in ADCS-ADL (95% CI)	*P*-value
Informant replacement since last visit	−1.61 (−3.79, 0.57)	0.147	2.02 (0.34, 3.70)	0.019
Age (5 years)	0.01 (−0.07, 0.09)	0.796	0.07 (−0.01, 0.15)	0.068
Female (vs. male)	−0.21 (−0.46, 0.04)	0.098	−0.07 (−0.32, 0.18)	0.601
Time since first ADCS-ADL (3 months)	−0.21 (−0.29, -0.13)	<0.001	0.06 (−0.01, 0.13)	0.103
Previous ADCS-ADL	−0.03 (−0.07, 0.02)	0.299	−0.32 (−0.36, −0.27)	<0.001
Spousal informant at last visit	−0.11 (−0.40, 0.17)	0.426	−0.02 (−0.31, 0.27)	0.906
LFBC (vs. LFAN)	−0.22 (−0.50, 0.06)	0.127	0.10 (−0.18, 0.39)	0.489
Region				
Asia	0.54 (0.02, 1.07)	0.042	−0.60 (−1.13, −0.07)	0.027
Australia/South Africa	0.01 (−0.52, 0.54)	0.974	0.30 (−0.20, 0.80)	0.241
Eastern Europe/Russia	0.23 (−0.29, 0.74)	0.393	−0.31 (−0.90, 0.27)	0.296
Japan	0.36 (−0.03, 0.75)	0.070	−0.37 (−0.76, 0.02)	0.065
North America	Referent		Referent	
South America/Mexico	0.47 (−0.01, 0.94)	0.053	0.08 (−0.43, 0.58)	0.761
Western Europe/Israel	−0.13 (−0.46, 0.20)	0.448	0.29 (−0.04, 0.63)	0.085

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

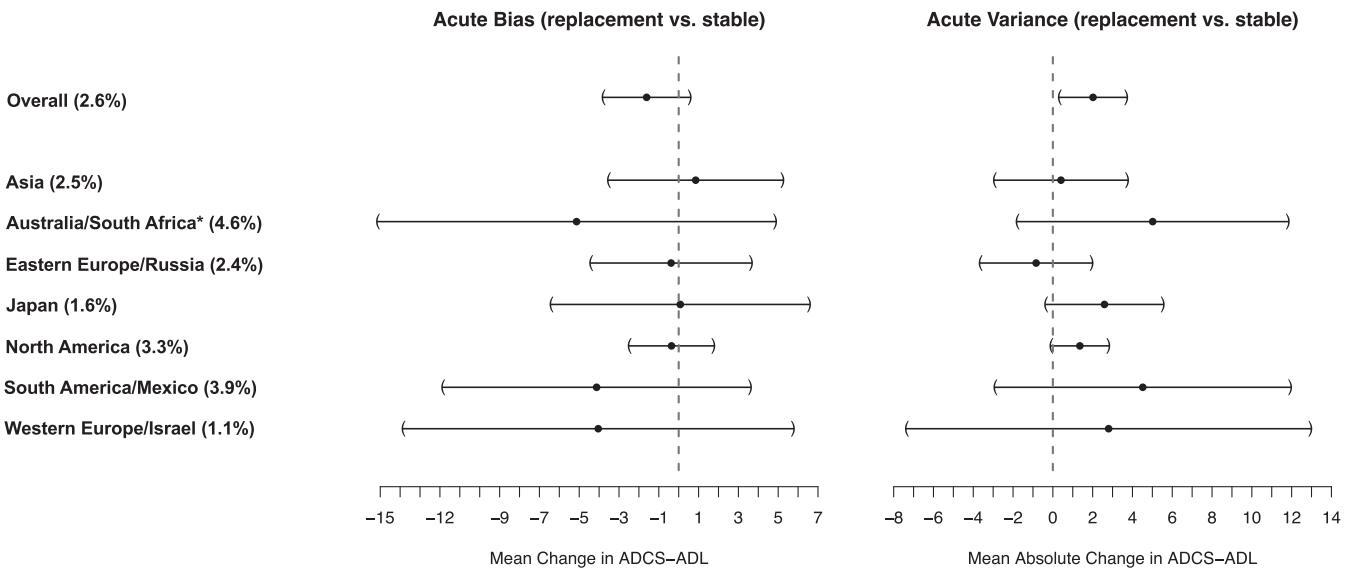

FIGURE 3 Estimated region-specific associations from exploratory analyses. Region (% replacement) is indicated on the left-hand side. *This model did not adjust for trial because all participants from this region were from the LFAN trial. ADCS-ADL, Alzheimer's Disease Cooperative Study Activities of Daily Living

for acute reporting, as well as increased variance for an end-of-study change-from-baseline outcome of ADCS-ADL.[4] In the setting of the NACC Uniform Data Set, a longitudinal observational study, replacement was associated with a systematic bias toward greater functional worsening for annual reporting on the FAQ and increased variance for FAQ, Clinical Dementia Rating Sum of Boxes, and Neuropsychiatric Inventory scores.[12]

In our current analysis, the two industry-sponsored trials were 76 weeks in length (to the primary outcome). In contrast, the previously analyzed academic trials had durations ranging from 4 to 24 months, and the observational NACC study included data over 8 years of follow-up. In the current analysis, the frequency of replacement was lower than previously observed for academic AD trials[4] (≈ 2.6% vs. ≈ 5%), though both are much lower than that observed in NACC

TABLE 3 Estimated mean difference in the change from baseline at week 76 in ADCS-ADL from linear model.

	Mean difference in week-76 change in ADCS-ADL (95% CI)	*P*-value
Informant replacement	−0.70 (−5.88, 4.48)	0.790
Age (5 years)	0.48 (−0.14, 1.09)	0.130
Female (vs. male)	−3.64 (−5.72, −1.55)	0.001
Baseline ADCS-ADL	−0.12 (−0.59, 0.36)	0.631
Spousal informant at baseline	−2.29 (−4.82, 0.25)	0.077
LFBC (vs. LFAN)	−1.24 (−4.25, 1.78)	0.421
Region		
Asia	10.80 (−13.29, 34.90)	0.379
Australia/South Africa	1.40 (−2.68, 5.48)	0.501
Eastern Europe/Russia	−0.43 (−6.07, 5.22)	0.881
Japan	2.55 (−1.22, 6.32)	0.184
North America	Referent	
South America/Mexico	−2.17 (−8.37, 4.03)	0.492
Western Europe/Israel	0.55 (−1.86, 2.97)	0.654

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

(15.5%).[12] It is not possible to evaluate reasons for the observed differences in replacement frequency with the available data, though longer studies may inherently have a higher frequency of replacement. Trials also offer participants the opportunity to complete a study, while observational research may aim to retain participants as long as possible, even to death. Besides study duration, the study types differ in their purposes (test interventions vs. characterize natural history), visit frequency (monthly to quarterly vs. once a year), and could also differ in their use of retention strategies and tactics.[13] Further investigations will be needed to understand these observations.

When investigating acute ADCS-ADL reporting in these trials, informant replacement was associated with increased variance at the first visit with a new informant. This result replicates previous observations and suggests that replacement, regardless of its frequency, can have a non-ignorable impact on trial results, especially if replacement were to occur immediately before a study's primary endpoint. An unexpected increase in variance could result in lower power and a higher risk of type II error. The estimated association between replacement and acute variance in ADCS-ADL was approximately 1 point lower (1.36 vs. 2.38) for the North American region in the industry-sponsored trials compared to the academic trials (at sites in North America). To provide context for the scientific and clinical significance of this difference, we computed the design alternative for which each study's planned sample size ($N_{planned}$ = 1500 for LFAN, $N_{planned}$ = 1100 for LFBC) would yield 80% power to detect a treatment difference concerning ADCS-ADL (one of the two co-primary endpoints for the trials). Using the observed variance of the pooled end-of-study change-from-baseline measures, an 80% power design alternative for differences in ADCS-ADL between treatment arms is computed to be 1.37 and 1.60 points for LFAN and LFBC, respectively, suggesting that the 1 point difference we observed between our previous and current analyses could be meaningful. The replicability of this result demonstrating increased variability furthermore suggests that researchers should plan for the increased variability associated with cases of replacement in trials. Some strategies may include incorporating added variance for expected cases of replacement during the trial design phase and emphasizing the importance of trial completion to participants and informants throughout the trial, particularly at later visits.

Although some analyses in this study did not result in statistically significant conclusions, their point estimates were consistent with previous findings. For example, we estimated a negative association between replacement and systematic bias, which suggests greater reported functional worsening for participants who experienced replacement since the last visit. This analysis had high variability, but the point estimate was consistent with the conclusions in academic trials. A potential explanation for why participants with replaced informants might experience greater reported functional worsening includes the loss of a primary caregiver resulting in an actual decline in functional performance. It is not possible to examine whether this is the case, since reasons for replacement are not routinely documented. Furthermore, the difference in the trajectories of ADCS-ADL before and after informant replacement was not significant in our analyses. We observed a decline in ADCS-ADL of < 1 point per month before and after replacement, suggesting that the functional performance of the participant declines at a similar rate overall despite the increased variance that is associated with replacement. Similar patterns were observed in the academic ADCS trials. Lastly, we did not observe a significant association between replacement and end-of-study change from baseline or between replacement and variance of this change. The point estimates of these associations, however, were consistent with that of the academic trials with less precision.

There are differences between academic and industry-sponsored clinical trials. Perhaps the largest difference stems from the funding and resources available for industry-sponsored trials. These resources typically provide greater infrastructure for recruitment and retention efforts, study monitoring, and data management. The result of this difference in resources often translates into shorter trial timelines for industry-sponsored trials compared to academic trials. These differences may limit the ability to compare the current results to those from studies of academic trials. One additional difference between industry-sponsored and academic trials that may lead to differences in informant replacement and retention includes the geographic location of the participants. Recruitment sites in academic trials are generally limited to areas around participating academic institutions, which can be associated with differential participant demographics such as race/ethnicity, years of education, and access to care.

Informant replacement may occur for many reasons including unwillingness and inability to attend study visits or death of an informant. As mentioned, the reasons for replacement are not routinely recorded, limiting opportunity to conjecture about strategies to mit-

igate replacement and its impact. Additional limitations to our study should be noted. Early stopping for futility of the analyzed trials resulted in a large proportion of the participants not completing the study primary endpoint. In addition to potentially influencing the frequency of replacement, this directly affected the analysis of the impacts of replacement on the end-of-study change-from-baseline outcomes because only a subset of participants were included in these models. The lack of a full cohort analysis would affect the precision of these model estimates, and if cohort effects were present, then the results from these models may not generalize to fully completed trials. This may be particularly important for the end-of-study analyses, given the premature termination of the analyzed trials. Many of our analyses lacked precision, likely due to the small proportion of participants who experienced replacement. There were five participants for whom we could not conclude whether replacement occurred due to missing informant data, and some information such as informant race and years of education were not collected. The two trials were conducted without the use of biomarker enrollment criteria. All were limitations to the generalizability of these results. Finally, beyond the informants, the individuals performing data collection (raters) may also be replaced during a trial. We lacked data on trial raters to incorporate in our analyses.

In conclusion, we observed that replacement was less common in industry-sponsored AD dementia trials compared to academic AD dementia trials. We also demonstrated that the association between informant replacement and increased variance in acute ADCS-ADL reporting was replicated in industry-sponsored clinical trials. The impacts of replacement may be most pronounced when replacement occurs near the end of the trial, specifically at the final visit. These results further emphasize the need for trial investigators to routinely collect and report informant-related data, including reasons for replacement, as well as to account for replacement in trial design and the analysis of trial results. Moreover, these data emphasize the need for trialists to assess and enact potential solutions to alleviate the burden on participants and their informants.

ACKNOWLEDGMENTS

We would like to thank the study participants and study partners from each of the original trials along with the ADCS (U19 AG010483) for making this analysis possible. This project was based upon work funded by the National Institute of Aging Diversity Supplement to the UCI ADRC grant number P30-AG066519-03 and by RF1 AG059407.

CONFLICT OF INTEREST STATEMENT

Nishida, Nuño, and Gillen have no conflicts of interest to report. Grill received research support from NIA, the Alzheimer's Association, BrightFocus Foundation, Eli Lilly, Biogen, Genentech, and Eisai, and has consulted for SiteRx. 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.

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SUPPORTING INFORMATION

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

How to cite this article: Nishida MK, Nuño MM, Grill JD, Gillen DL. Impacts of informant replacement in two industry-sponsored Alzheimer's disease clinical trials. *Alzheimer's Dement*. 2024;10:e70009. https://doi.org/10.1002/trc2.70009