

Informal Care Time and Cost in a Large Clinical Trial Sample of Patients with Mild to Moderate Alzheimer's Disease: Determinants and Level of Change Observed

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ABSTRACT

Introduction: We evaluate the association between caregiver (informal) time/cost and illness severity from two recently completed clinical trials of an investigational drug for Alzheimer's disease (AD).

Methods: Changes from baseline caregiver time were calculated and treatment effects analyzed using a restricted maximum likelihood-based mixed model for repeated measures. Four separate models were then estimated to examine the association between caregiver time costs and the clinical endpoints measured

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during the trials, including cognition (MMSE), function (DAD), behavior (NPI), global disability (CDR) and dependence (DS).

Results: Caregiver time cost was significantly associated with all clinical measures of illness severity with a 1-unit change in MMSE, DAD, NPI, CDR and DS associated with a 11.57%, 4.81–4.97%, 3.58–3.67%, 42.52% and 71.05% change, respectively, in primary caregiver time cost. The association between caregiver time cost and DS was the strongest of all the associations examined.

Conclusion: Caregiver time costs increase with increasing AD severity in all key domains of AD (cognition, function, behavior, global disability and dependence on others). Our analysis demonstrated that patient dependence is a particularly important predictor of caregiver time costs and should be considered as a potential outcome measure in intervention clinical trials in AD.

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Keywords: Alzheimer's disease; Informal caregiver; Time and costs

INTRODUCTION

Alzheimer's disease is a progressive dementia characterized by cognitive deficits, altered behavior and inability to care for oneself. Sixty to seventy percent of persons with AD live in the community, with much of the care provided by family or other unpaid persons [1]. These unpaid caregivers provide an estimated 17.4 billion hours of unpaid care per year, constituting an estimated value of \$210 billion [1]. The value placed on caregiver time, informal care cost, represents the largest component of the total cost of care for AD [2–7]. Estimates range from 37% of total care costs in community dwelling patients participating in a study in Scandinavia [3] to 86% of the total cost of care in a clinical trial sample of mild to moderate AD from multiple countries [4]. A study of cost of illness in dementia reported that 56% of total costs in the EU27 in 2008 were contributed by informal care costs [2]. In the US, Zhu et al. reported that when patients with AD are not institutionalized, informal care-giving cost represents 70% of the total cost of care [7].

Given the important role of care-giving time in the management of person with AD, informal care time/cost has been included as an outcome measure in evaluations of AD treatments [8–12]. Some of these studies reported significant reductions in caregiver time with galantamine [8] and donepezil treatment in patients with AD [8–11] and others did not [12]. More recently, care-giving time was included as an outcome measure in two RCTs examining the efficacy of bapineuzumab in mild to moderate AD, and is the focus of this analysis [13].

In the economic evaluation of interventions in AD, it is frequently necessary to model the economic implications of changes in clinical

progression (e.g., MMSE), in order to determine cost-effectiveness. Having robust estimates of the associations between clinical progression measures and economic outcomes, like informal caregiver time, is very important for such models. Many studies have reported a significant association between informal care-time (and -cost) and disease severity measures of cognition [3–5], function [4, 5, 14] and behavior [4, 5]. In Mauskopf et al.'s review of the literature, they concluded that functional and behavioral measures were consistently associated with caregiver time [15]. Two recent studies conducted comprehensive evaluations of associations in AD [4, 5]. Gustavsson et al. [4] examined the association between informal care and measures of cognition (MMSE, ADAS-COG), function (ADCS-AD), behavior (NPI-total and NPI distress) and global disability (CDR-SOB) using correlations. Whilst the authors provided estimates of the proportional change in total care cost with marginal change in clinical severity measures, no estimates were provided specifically for informal care cost. Rapp et al. [5] provided estimates of the proportional changes in informal care costs with marginal changes in MMSE, ADL, NPI and ZBI but did not examine associations with a global measure, like CDR-SOB and the dependence scale (DS). The large dataset from the two bapineuzumab randomized clinical trials (RCTs) provide a rich dataset to investigate associations between: (1) caregiver time and baseline severity and (2) informal care costs and baseline clinical severity measures, which are the aims of this current study.

METHODS

Study Design

Data from two 18 month, multi-center, randomized, double-blind, placebo

controlled, parallel group trials examining bapineuzumab in patients with mild to moderate AD were merged in order to study caregiver time patterns in AD. The two studies had the same design: study ELN115727-301 (301) enrolled subjects with mild to moderate Alzheimer's disease (AD) who were apolipoprotein E ϵ 4 (*APOE*E4*) non-carriers, and they were randomly assigned to receive bapineuzumab (0.5 and 1.0 mg/kg) or placebo every 13 weeks for a total of six infusions. Study ELN115727-302 (302) enrolled similar subjects who were *APOE*E4* carriers who were randomized to receive either bapineuzumab (0.5-mg/kg) or placebo by IV infusion. The studies recruited subjects in sites in the US. Informed consent was obtained from all participants, or, if not capable of providing informed consent, from their legally acceptable representative. The studies were conducted according to the Declaration of Helsinki and were approved by the Independent review board at each participating site.

Subjects were enrolled in the study if they were 50 to <89 years of age; had a diagnosis of probable AD according to the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria and a screening visit brain MRI scan consistent with a diagnosis of AD; an MMSE score of 16–26 inclusive; a Rosen Modified Hachinski Ischemic score ≤ 4 [16]; lived at home or independently in a community dwelling and had a caregiver who consented to participate in the study, could accompany the subject on all clinic visits, and was a reliable informant in the opinion of the Investigator. Subjects were excluded if they had clinically significant neurological disease other than AD; a major

psychiatric disorder; history of stroke or seizures; a brain MRI scan indicative of significant non-AD abnormality; or history or evidence of any clinically significant autoimmune disease or chronic illness, which was likely to result in deterioration affecting the subject's safety during the study.

The resource utilization of each patient was assessed using the RUD-Lite [17], which was administered at baseline, week 26, week 52, and week 78. A brief summary of total costs by cost category (direct medical, direct nonmedical and informal costs) is presented first. Since informal costs are the largest category of costs, this paper provides additional analysis on the caregiver time component of the RUD-Lite. Caregiver time was assessed for both primary and secondary caregivers over the past month and was calculated as the product of the average time spent caring per day by the number of days in a month spent caring. The primary caregiver total time was calculated as the sum of caregiver time allocated to instrumental activities of daily living (IADL), activities of daily living (ADL) and to supervision. The secondary caregiver total time was calculated in the same way. The total caregiver total time is the sum of the primary caregiver time and the secondary caregiver time, measured as hours per month. For the purposes of assigning costs, the number of caregiver hours was capped at 16 h per day to allow for 8 h of sleep per night, which is consistent with the approach taken by other researchers [18]. Caregiver time was costed by assigning 30% of the average hourly wage of \$23.54 (\$7.06) to account for lost leisure time and not full hourly wage. In the literature, others have assigned 25–35% of the average hourly wage to caregiver time to account for lost leisure time [19–21].

At each visit, cognitive function was assessed using the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog; range 0–70) [22] and Mini Mental State Examination (MMSE; 0–30) [23], functional ability with the disability assessment for dementia (DAD; range 0–100%) [24] and neuropsychiatric symptoms with the neuropsychiatric Inventory (NPI; range 0–144) [25]. Patient dependence on others was assessed using the dependence scale (DS; range 0–15) [26]. Global disability was assessed using the clinical dementia rating scale (CDR) [27]. In addition, the age and gender of patients and caregivers, their relationship, and marital status was recorded.

Analysis

Total Cost Analysis Using Merged 301 and 302 Dataset

The resource use and estimated costs at each visit corresponded to the 6-month period preceding the visit (i.e. –26 to 0, 1–26, 27–52, and 53–78 weeks). Unit costs (\$US inflated to 2012) were applied to the resource use data collected in the study. Table 1 provides details of the component costs contributing to total costs and the sources used.

Informal Caregiver Time Analysis Using Merged 301 and 302 Dataset

The mean changes in primary caregiver and secondary caregiver time at week 78 were determined for three sub-groups of patients with the following baseline severity: (1) very mild (MMSE \geq 24); (2) mild (MMSE \geq 21); (3) moderate (MMSE < 21).

To understand the relative distribution of time across different caring tasks, the mean times primary caregivers allocated to IADLs, ADLs and supervision at baseline and week 78 were estimated using the merged dataset.

Informal Care Cost Analysis Using Merged 301 and 302 Dataset

Using generalized linear modelling (GLM), the association between caregiver time cost over the previous 6 months and baseline clinical measures of severity was estimated. Caregiver time costs were log transformed to improve normality. Four models were investigated: the first examined associations with cognition (MMSE), function (DAD) and behavior (NPI); the second with an alternative measure of cognition (ADAS-COG), as well as function (DAD) and behavior (NPI); the third with a global measure (CDR-SOB) and the fourth with an alternative global measure (DS). All models controlled for patient age and gender.

RESULTS

Caregiver and Patient Demography and Characteristics

Baseline patient demographics are presented in Table 2 and caregiver demographics in Table 3. A total of 2204 patients participated in the 301 and 302 studies and were randomized to receive either placebo (925) or bapineuzumab (1279). The two groups in each study were similar at baseline with respect to patient age, gender, duration of AD and severity of AD, as measured by the MMSE. The mean for the total population of 21.0 for MMSE is consistent with the Mild to Moderate AD entry criteria. The two groups in each study were similar with respect to caregiver characteristics. Approximately 90%, overall, lived with the patient (Table 3). Approximately 75% of primary caregivers reported that there were no other caregivers (Table 3).

In comparison with other recent survey data on caregivers of Alzheimer's patients

Table 1 \$US unit costs assigned to resource use components of Rud-lite

Accommodation	
Intermediate forms of accommodation (not dementia-specific) (per day) ^a	\$116.71
Dementia-specific residential accommodation (per day) ^a	\$158.04
Long-term institutional care/nursing home -private room (per day) ^a	\$261.00
Community services	
Registered nurse home visits (per visit) ^{b,h}	\$139.08
Home health aide/orderly (per hour) ^a	\$21.00
Food delivery/Meals on wheels (per meal) ^c	\$8.00
Day care (per day) ^a	\$70.00
Transportation (publicly/insurance paid) (round trip) ^a	\$20.00
Inpatient care	
Geriatric (per night) ^{d,h}	\$7220.37
Psychiatric (per night) ^{d,h}	\$7220.37
Internal Medicine (per night) ^{d,h}	\$7220.37
Surgery (per night) ^{d,h}	\$7220.37
Other (per night) ^{d,h}	\$7220.37
ER (per visit) ^{e,h}	\$1401.20
Outpatient care	
General practitioner (per visit) ^{f,h}	\$148.13
Geriatrician (per visit) ^{f,h}	\$148.13
Neurologist (per visit) ^{f,h}	\$148.13
Psychiatrist (per visit) ^{f,h}	\$148.13
Physiotherapist (per visit) ^{f,h}	\$148.13
Occupational therapist (per visit) ^{f,h}	\$148.13
Social worker (per visit) ^{f,h}	\$148.13
Psychologist (per visit) ^{f,h}	\$148.13
Other (specialist, please specify) (per visit) ^{f,h}	\$148.13
Caregiving time	
Caregiver informal care time (per hour) ^g	\$7.06

^a Metlife Mature Market Institute—Market Survey of Long-Term Care Costs (Nov 2012)

^b CPT code 99349, page 83 of 2008 PF&CG (inflated to 2012 dollars)

^c <http://www.sdslane.org/mow.html>

^d HCUP All cause hospitalization discharges, 2010 (inflated to 2012 dollars)

^e HCUP Emergency Department State Statistics, 2005 (inflated to 2012 dollars)

^f CPT code 99243, page 69 of 2008 PF&CG (inflated to 2012 dollars)

^g Employment, hours, and earnings from the current employment statistics survey (National)

^h Medical care inflation index

[1], caregivers in the 301 and 302 studies tended to be older on average (65 versus 52 years of age), less likely to be female (60%

versus 70% female), and more likely to be the spouse of the subject (70% versus 6–17%).

Table 2 Patient demographics and baseline characteristics

	301		302		Merged 301 + 302
	Placebo (<i>N</i> = 493)	Bapineuzumab (pooled) (<i>N</i> = 621)	Placebo (<i>N</i> = 432)	Bapineuzumab (0.5 mg/kg) (<i>N</i> = 658)	Total (<i>N</i> = 2204)
Age (years)					
<i>N</i>	493	621	432	658	2204
Mean (SD)	71.9 (10.10)	73.1 (9.35)	72.3 (8.40)	72.0 (8.03)	72.4 (8.94)
Gender, <i>n</i> (%)					
Male	245 (49.7)	281 (45.2)	190 (44.0)	300 (45.6)	1016 (46.1)
Female	248 (50.3)	340 (54.8)	242 (56.0)	358 (54.4)	1188 (53.9)
Duration of AD (years)					
<i>N</i>	493	621	432	658	2204
Mean (SD)	3.1 (2.32)	3.1 (2.43)	3.5 (2.48)	3.4 (2.37)	3.2 (2.40)
MMSE					
<i>N</i>	493	621	452	658	2204
Mean (SD)	21.2 (3.21)	21.2 (3.31)	20.7 (3.17)	20.8 (3.15)	21.0 (3.22)
ADAS-COG					
<i>N</i>	493	621	432	658	2204
Mean (SD)	22.2 (10.08)	22.3 (9.85)	23.9 (9.52)	23.5 (9.44)	22.9 (9.74)
DAD					
<i>N</i>	493	621	432	658	2204
Mean (SD)	80.5 (19.5)	80.2 (18.46)	79.4 (18.85)	80.9 (17.32)	80.3 (18.36)
NPI					
<i>N</i>	479	603	423	642	2147
Mean (SD)	11.2 (12.42)	11.0 (12.60)	10.1 (11.75)	10.0 (11.85)	10.6 (12.18)
DS					
<i>N</i>	493	619	431	658	
Mean (SD)	4.6 (2.23)	4.6 (2.29)	4.8 (2.0)	4.7 (2.07)	4.7 (2.16)

Total Cost Analysis Using Merged 301 and 302 Dataset

Based on the merged dataset, the mean total and component costs of care are presented for each visit in Fig. 1. The mean total cost of care

for the previous 6 months was estimated to be US \$9144 at baseline and US\$ 17,066 at week 78. The total cost of care includes informal care costs (based on caregiver time) and the cost of healthcare (direct medical cost) and social care services used (direct nonmedical costs). Direct

Table 3 Caregiver demographics and characteristics at baseline

	301		302	
	Placebo (<i>N</i> = 493)	Bapineuzumab (pooled) ^a (<i>N</i> = 621)	Placebo (<i>N</i> = 432)	Bapineuzumab (0.5 mg/kg) (<i>N</i> = 658)
Age (years)				
<i>N</i>	491	617	429	655
Mean (SD)	64.9 (13.28)	64.0 (13.75)	65.4 (12.30)	65.5 (12.07)
Gender, <i>n</i> (%)				
Male	181 (36.7)	243 (39.2)	185 (42.9)	281 (42.8)
Female	312 (63.3)	377 (60.8)	246 (57.1)	375 (57.2)
Missing	0	1	1	2
Relationship to subject, <i>n</i> (%)				
Husband	141 (28.6)	182 (29.4)	152 (35.3)	236 (36.0)
Wife	213 (43.2)	229 (36.9)	170 (39.4)	261 (39.8)
Child	94 (19.1)	143 (23.1)	74 (17.2)	114 (17.4)
Friend	13 (2.6)	19 (3.1)	10 (2.3)	19 (2.9)
Healthcare professional	3 (0.6)	7 (1.1)	6 (1.4)	3 (0.5)
Other	29 (5.9)	40 (6.5)	19 (4.4)	22 (3.4)
Missing	0	1	1	3
Marital status, <i>n</i> (%)				
Married/cohabitating	430 (87.6)	533 (86.5)	380 (89.2)	588 (89.8)
Never married	25 (5.1)	37 (6.0)	12 (2.8)	27 (4.1)
Divorced/separated	27 (5.5)	28 (4.5)	29 (6.8)	29 (4.4)
Widowed	9 (1.8)	18 (2.9)	5 (1.2)	11 (1.7)
Missing	2	5	6	3
Do you live with the subject? <i>n</i> (%)				
Yes	406 (88.8)	235 (82.7)	359 (93.5)	544 (94.9)
No	51 (11.2)	49 (17.3)	25 (6.5)	29 (5.1)
Missing	36	23	48	85
How many additional caregivers? <i>n</i> (%)				
0	367 (74.9)	442 (71.4)	325 (75.6)	476 (72.7)
1	73 (14.9)	111 (17.9)	56 (13.0)	101 (15.4)
2	28 (5.7)	38 (6.1)	27 (6.3)	38 (5.4)
3	10 (2.0)	14 (2.3)	10 (2.3)	23 (3.5)
≥4	12 (2.4)	14 (2.3)	12 (2.8)	17 (2.6)
Missing	3	2	2	3

^a Bapineuzumab 0.5 and 1.0 mg/kg pooled

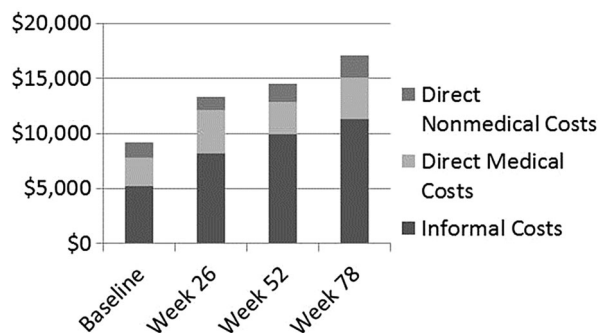


Fig. 1 Mean costs for previous 6 months from baseline to week 78

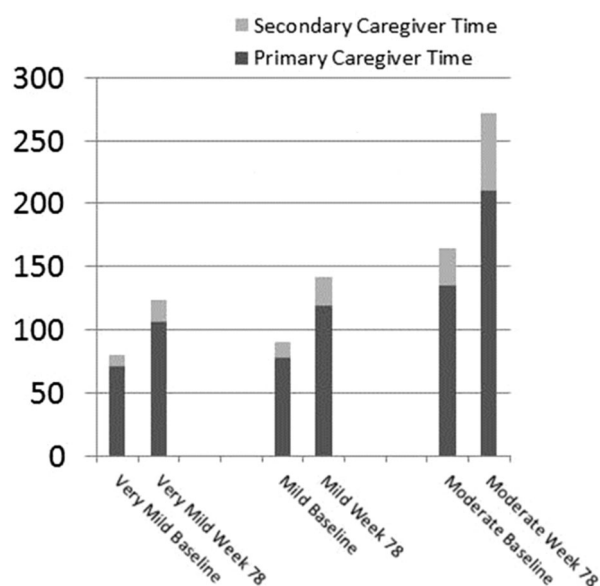


Fig. 2 Mean caregiver time (hours per month) by baseline severity, as measured by the MMSE

medical costs increased 45% over the 78 week period, from \$2591 at baseline to \$3746 at week 78. Direct nonmedical costs increased 54%, from \$1323 at baseline to \$2038 at week 78. Caregiver time increased 116%, from \$5230 at baseline to \$11,282 at week 78. Caregiver time represented the largest percentage of total care costs, at 57.2% at baseline and 66.1% at week 78. Other than caregiver time, the only component of total care costs to increase its percentage contribution to total care cost from

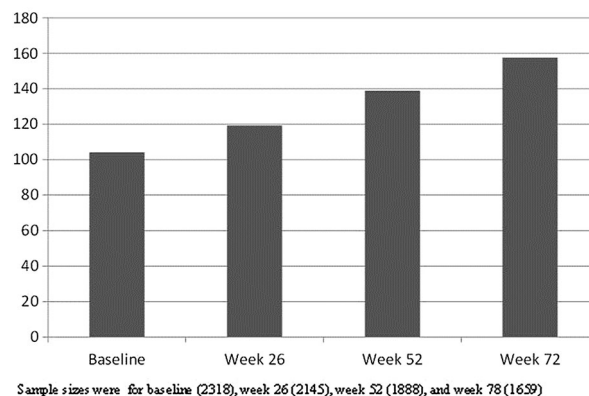


Fig. 3 Mean primary caregiver time (hours per month) over time using pooled dataset

baseline (4.5%) to week 78 (7.1%) was community care cost.

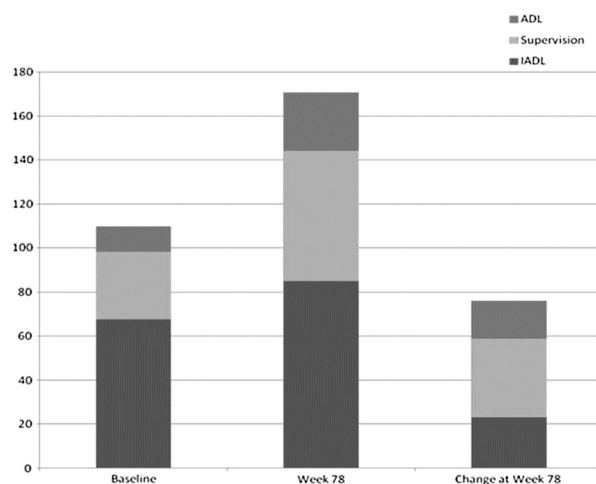
Informal Caregiver Time Analysis Using Merged 301 and 302 Dataset

The mean primary caregiver time and secondary caregiver time at baseline and week 78 are presented for three sub-groups of patients defined by their baseline MMSE into very mild, mild and moderate AD and for the total sample in Fig. 2. In general, both the baseline and week 78 mean caregiver time tended to increase with increasing severity of the sub-groups. In addition, the mean change in caregiver time at week 78 tended to increase with increasing severity.

The mean primary caregiver time over each time point is presented in Fig. 3. Primary caregiver time increased by approximately 15–20 h every 6 months.

The mean primary caregiver time allocated to IADLs, ADLs and supervision at baseline and week 78 is presented in Fig. 4. At baseline and week 78, primary caregiver time allocated to IADLs tended to be greater than time allocated to supervision, which tended to be greater than the time allocated to ADLs. An examination of

Fig. 4 Mean primary caregiver time (hours per month) allocated to different tasks at baseline, week 78 and change at week 78 using pooled dataset



changes at week 78 suggests that total primary caregiver time increased considerably, particularly for supervision and ADLs.

Associations Between Caregiver Time Costs and Clinical Severity

The results of model estimates are presented in Table 4. The beta coefficient estimates the proportional change in the cost outcome for a unit change in the explanatory variable (e.g., MMSE). That is, for a 1-unit increase in the explanatory variable, cost increases by 100% beta. The models demonstrated significant associations between both log primary caregiver time and log total caregiver time cost over 6 months and clinical severity measures. Based on the beta coefficients for model 1, a 1-unit change in MMSE is associated with an 11.57% change in primary caregiver time cost and a 12.06% change in total caregiver time costs. Based on models 1 and 2, a 1-unit change in DAD is associated with a 4.81–4.97% change in primary caregiver time cost and 4.98–5.25% change in total caregiver time cost. Similarly, a 1 unit change in NPI is associated with a 3.58–3.67% increase in primary caregiver time cost and 3.85–3.97% increase in total caregiver

time cost. Model 3 suggests that a 1-unit change in CDR-SOB is associated with a 42.52% increase in primary caregiver time cost and 45.16% increase in total caregiver time cost. The higher R^2 for Model 4 suggests that association between DS and caregiver time cost is the strongest of all of the associations tested in Models 1–4. A 1-unit change in DS was associated with a 71.05% change in primary caregiver time cost and 73.67% increase in total caregiver time cost.

Patient age and gender were not significantly associated with either primary caregiver time costs or total caregiver time costs.

DISCUSSION

The lack of significant treatment differences in change in caregiver time at week 78 in the 301 and 302 study is consistent with the previously reported lack of clinical efficacy of bapineuzumab [17]. However, the large sample size (2000+ patients), longitudinal data (18 months), and data on a wide spectrum of clinical measures provided an opportunity to thoroughly investigate how caregiver time changes with patient severity and to quantify

Table 4 Association between baseline log primary caregiver total time and total caregiver total time costs and clinical measures using GLM

Explanatory variables	Dependent variable	Log primary caregiver total time cost				Log Total caregiver total time cost ^a			
		Type III SS	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 4
MMSE	β Coefficient	-0.11571				-0.12063			
	Significance	<0.0001				<0.0001			
ADAS-Cog	β Coefficient		0.04312				0.04515		
	Significance		<0.0001				<0.0001		
DAD	β Coefficient	-0.04976	-0.04813			-0.05154	-0.0498		
	Significance	<0.0001	<0.0001			<0.0001	<0.0001		
NPI	β Coefficient	0.03671	0.03581			0.03948	0.03854		
	Significance	<0.0001	<0.0001			<0.0001	<0.0001		
CDR-SOB	β Coefficient			0.42527				0.45158	
	Significance			<0.0001				<0.0001	
DS	β Coefficient				0.71057				0.73674
	Significance				<0.0001				<0.0001
Age	β Coefficient								
	Significance								
Gender	β Coefficient	NS	NS	NS	NS	NS	NS	NS	NS
	Significance								
Intercept	β Coefficient	NS	NS	NS	NS	NS	NS	NS	NS
	Significance								
Obs used	β Coefficient	12.35856	8.99641	4.55159	3.83049	12.26967	8.75535	4.17445	3.46384
	Significance	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
<i>R</i> ²	β Coefficient	2274	2274	2333	2331	2274	2274	2333	2331
	Significance								
Overall	β Coefficient	0.15938	0.161954	0.131921	0.219322	0.179429	0.182397	0.153181	0.241145
	Significance	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

^a Total caregiver time includes primary plus secondary caregiver time

associations with a comprehensive set of clinical severity measures.

The trend towards increasing caregiver time with increasing cognitive decline, as measured by the MMSE, observed in our cross-sectional analysis, was consistent with previous reports [4]. The trend towards greater changes in caregiver time for the more severe sub-groups, was a new observation but still consistent with the above trend. The larger proportion of care-giving time dedicated to IADLs than supervision and ADLs at baseline in our sample is consistent with the functional and behavioral deficits experienced by patients with mild to moderate AD. Interestingly, the greatest changes over the 78 week period were related to supervision. Typically, in AD, supervision is required to prevent wandering, falls, and other accidents.

The significant associations between clinical severity measures and informal care time are consistent with other reports [3–5, 15, 16]. The proportional change in primary caregiver (11%) and total caregiver time cost (12%) with a unit change in MMSE is higher than the 4.7 estimate reported by Rapp et al. [5]. The authors are unaware of any previous publications presenting the proportional change in informal care cost with unit change in DAD; it is not possible to compare our estimate of 4.97–5.15% change in informal care cost with marginal change in DAD. A comparison of *R*-squared for Models 1–4, suggests that the DS was the best predictor of informal care costs with the beta coefficient suggesting a 71–73% change in informal care cost with a one unit change in DS. Earlier studies have estimated that the DS worsens by 1 point per year [28].

The levels of change were much higher than that reported by Zhu et al. in their analysis of Predictor study dataset [29]. They reported that a one point increase in DS was associated with a

\$1690 increase in informal cost. As the baseline mean informal cost was \$12,808 in their study, the proportional change is considerably lower than our analysis showed. Our model differs from the Zhu model in that we did not include a functional measure as an additional explanatory variable in Model 4. Preliminary analysis suggested a strong correlation ($r = -0.630$) between the DS and DAD, so we were concerned about multicollinearity effects.

There are a number of limitations associated with our analysis. Firstly, the sample is a clinical trial population, who must meet stringent inclusion and exclusion criteria, and so may not be representative of the general AD population.

Secondly, the RUD-Lite utilizes self-reported data by caregivers. Hence, the resource use data collection relies on accurate and consistent recall from caregivers estimating the health care resources used by the patient as well as the time that they spent, on a daily basis, caring for the patient. This element of the study may be subject to an element of bias, both from under- and over-estimations of resource use and time spent in caregiving.

Thirdly, there is considerable debate about how to assign costs to caregiver time. The approach taken can influence greatly the contribution of total cost of care attributed to care giving time [3]. We assigned 30% of the average hourly working rate.

Another limitation, highlighted by others [4] is the possible overestimation of time per day. For this reason we capped the daily care-giving time at 16 h for the purposes of costing informal care costs.

Whilst all of our four models were significant, the levels of variation in informal care cost explained ranged from 13% to 24% so there was a considerable amount of variation left unexplained. Other possible sources of variation could be co-morbidities, or

ethnic/cultural differences, but these were not examined in this study.

CONCLUSION

Caregiver time costs increase with increasing AD severity in all key domains of AD (cognition, function, behavior, global disability, and dependence on others). Our analysis demonstrated that patient dependence is a particularly important predictor of caregiver time costs and should be considered as a potential outcome measure in intervention clinical trials in AD.

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Compliance with Ethics Guidelines. Informed consent was obtained from all participants, or, if not capable of providing informed consent, from their legally acceptable representative. The studies were conducted according to the Declaration of Helsinki and were approved by the Independent review board at each participating site.

Data Availability. The datasets analyzed during the current study are not publicly available because they were collected under a partnership but the datasets may be available from the corresponding author on reasonable request pending review and approval from the Alliance.

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