Long-term clinical and cost-effectiveness of psychological intervention for family carers of people with dementia: a single-blind, randomised, controlled trial

Long-term clinical and cost-effectiveness of psychological intervention for family carers of people with dementia: a single-blind, randomised, controlled trial

Gill Livingston, Julie Barber, Penny Rapaport, Martin Knapp, Mark Griffin, Derek King, Renee Romeo, Debbie Livingston, Cath Mummery, Zuzana Walker, Juanita Hoe, Claudia Cooper

Summary

Background Two-thirds of people with dementia live at home supported mainly by family carers. These carers frequently develop clinical depression or anxiety, which predicts care breakdown. We aimed to assess the clinical effectiveness (long-term reduction of depression and anxiety symptoms in family carers) and cost-effectiveness of a psychological intervention called START (STrAtegies for RelaTives).

Methods We did a randomised, parallel-group trial with masked outcome assessments in three UK mental-health services and one neurological-outpatient dementia service. We included self-identified family carers of people with dementia who had been referred in the previous year and gave support at least once per week to the person with dementia. We randomly assigned these carers, via an online computer-generated randomisation system from an independent clinical trials unit, to either START, an 8-session, manual-based coping intervention delivered by supervised psychology graduates, or treatment as usual (TAU). The primary long-term outcomes were affective symptoms (Hospital Anxiety and Depression Scale total score [HADS-T]) 2 years after randomisation and cost-effectiveness (health and social care perspectives) over 24 months. Analysis was by intention to treat, excluding carers with data missing at both 12 and 24 months. This trial is registered ISCTRN70017938.

Findings From November 4, 2009, to June 8, 2011, we recruited 260 carers. 173 carers were randomly assigned to START and 87 to TAU. Of these 260 participants, 209 (80%) were included in the clinical efficacy analysis (140 START, 69 TAU). At 24 months, compared with TAU the START group was significantly better for HADS-T (mean difference −2·58 points, 95% CI −4·26 to −0·90; p=0·003). The intervention is cost effective for both carers and patients (67% probability of cost-effectiveness at the £20 000 per QALY willingness-to-pay threshold, and 70% at the £30 000 threshold).

Interpretation START is clinically effective, improving carer mood and anxiety levels for 2 years. Carers in the control TAU group were seven times more likely to have clinically significant depression than those receiving START. START is cost effective with respect to carer and patient outcomes, and National Institute for Health and Care Excellence (NICE) thresholds. The number of people with dementia is rapidly growing, and policy frameworks assume that their families will remain the frontline providers of (unpaid) support. This cost-neutral intervention, which substantially improves family-carers' mental health and quality of life, should therefore be widely available.

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Division of Psychiatry, University College London, London, UK (Prof G Livingston MD, P Rapaport DClinPsych, D Livingston MChS, Z Walker MD, J Hoe PhD, C Cooper PhD); **Statistical Science and PRIMENT Clinical Trials Unit, University College London, London, UK** (J Barber PhD, M Griffin MSc); **Personal Social Services Research Unit, London School of Economics and Political Science, London, UK** (Prof M Knapp PhD, D King PhD); **Institute of Psychiatry, King's College London, London, UK** (R Romeo PhD); **Institute of Neurology, University College London, London, UK** (C Mummery PhD); **North Essex Partnership University NHS Foundation Trust, Chelmsford, UK** (Z Walker); **and Camden and Islington NHS Foundation Trust, St Pancras Hospital, London, UK** (Prof G Livingston, C Cooper)

Correspondence to: Prof Gill Livingston, Division of Psychiatry, University College London, London W1W 7EJ, UK **g.livingston@ucl.ac.uk**

Introduction

Two-thirds of people with dementia live at home, with their family providing most of their care.[1] About 40% of family carers of people with dementia have clinical depression or anxiety; others have substantial psychological symptoms.[2,3] Carer psychological morbidity predicts care breakdown and care home admission.[4]

The STrAtegies for RelaTives (START) psychological intervention for family carers has been the first to show both clinical effectiveness (reduced anxiety and depressive symptoms, reduced depression caseness, and improved quality of life) and cost-effectiveness for family carers of people with dementia.[5,6] These were short-term results (8 months), and for how long these effects are sustained is unclear. Previous studies of family carers suggest that effects persist for 7–11 months.[7] A multicomponent intervention showed no effect at 4 months, but the effect at 1 year was sustained for another 2 years.[8]

We therefore tested START's long-term primary hypothesis that this intervention would show clinical and cost-effectiveness for family carers' affective psychological symptoms 2 years after randomisation. We also examined clinical and cost-effectiveness for people with dementia. We prespecified a primary short-term outcome at 8 months and a primary long-term outcome at 24 months.

Methods

Study design and participants

START is a parallel-group, superiority, single-blind, randomised controlled trial, which recruited participants 2:1 to START intervention or treatment as usual (TAU) to allow for therapist clustering, and was undertaken in the UK at four sites. The methods have been reported in detail elsewhere.[5,6]

See Online for appendix

Eligible participants were self-identified family carers providing support at least once per week to people with a clinical diagnosis of dementia, living in their own homes and referred in the previous year. Carers who were unable to give informed consent to the trial, or who were already in a trial of carer support or who lived more than 1·5 h from the researchers' base were excluded. We recruited participants through three mental health trusts and a tertiary neurology clinic. Ethics approval was obtained, and participants gave written, informed consent.

Randomisation and masking

Randomisation was stratified by centre with random permuted blocks of different sizes via an online computer-generated randomisation system from an independent clinical trials unit. Assessors were unaware of the randomisation status, but the trial participants knew their allocation.

Procedures

We developed the 8-session START manual-based, individual coping intervention for dementia family carers from the US Coping with Caregiving intervention.[9] We trained and supervised non-clinically trained psychology graduates to deliver START, and monitored intervention fidelity by devising checklists that rated the most important components of every session. Therapists (the psychology graduates) recorded one therapy session per participant selected randomly by the trial manager. This session was completed by a therapist in the same team who was not associated with that participant's intervention. An overall fidelity score for every session was then given by the assessor, from 1 (not at all) to 5 (very focused).

Panel 1: **The START Manual: STrAtegies for RelaTives**

Session 1: Stress and wellbeing

Session 2: Reasons for behaviour

Session 3: Making a behaviour plan

Session 4: Behaviour strategies and unhelpful thoughts

Session 5: Communication styles

Session 6: Planning for the future

Session 7: Introduction to pleasant events and your mood

Session 8: Using your skills in the future

Therapists worked on a one-to-one basis with carers to identify individual difficulties and implement strategies.

Carers kept their own manual and filled it in. Every session finished with a relaxation session. Carers were asked to practice the strategies and relaxation between sessions.

The full START intervention manual is in the appendix and can be used after training. START is also summarised in panel 1. Therapists were trained and supervised as a group with additional time available for individual support. The graduate therapists were encouraged to be empathetic, adhere to the intervention, and to work with carers to find answers rather than give solutions or advice. Together they identified individual difficulties and implemented strategies including relaxation, behavioural management, communication strategies, identification and changing of unhelpful thoughts, positive reframing, accessing of emotional support, future planning, and increasing occurrence of pleasant events.

Every session finished with a relaxation session using a tailored CD. We asked carers to practise the strategies from the manual and listen to the relaxation CDs between sessions. The final session included the development of a maintenance plan of useful strategies. Sessions were usually in participants' homes, unless they preferred the team's office.

TAU within the health-care trusts connected with the trial was based on National Institute for Health and Care Excellence (NICE) guidelines,[10] with services based around the person with dementia. TAU is medical, psychological, and social, and is supposed to consist of assessment, diagnosis and information-giving, risk assessment and management (eg, assessments of risk of fire, driving standards, adequate nutrition and self-care, vulnerability, and management of money), drug treatment, cognitive-stimulation therapy, practical support, treatment of neuropsychiatric and cognitive symptoms, assessment of capacity to make long-term decisions and help given to make them, and carer support. We judged that the health trusts in our study had high TAU standards.

Outcomes

After the trial started, with funding body approval (while the database was locked), we agreed that the primary outcome should be Hospital Anxiety and Depression Scale total score (HADS-T) because this has better sensitivity and positive predictive value than the anxiety or depression score for identifying depression.[11] The primary outcomes were HADS-T 2 years after randomisation and cost-effectiveness (health and social care perspectives) over 24 months. The same primary outcomes were also assessed after 8 months for the short-term effects.

We obtained carer and patient sociodemographic details at baseline, and the following data at baseline, 4, 8, 12, and 24 months after randomisation.

For carers: Hospital Anxiety and Depression Scale (HADS),[11,12] a validated, self-complete scale[11] summarised as HADS-D (depression) and HADS-A (anxiety) with scores from 0 to 21, and a total HADS score (HADS-T) from 0 to 42 (high scores are suggestive of more symptoms). HADS-D and HADS-A are also validated as scores for caseness, classified as a case or non-case, with a cutoff point of 8–9;[11] Zarit Burden Interview[13] to adjust for baseline carer burden because carers with a high burden might be more stressed; Brief COPE,[14] a self-complete, coping strategies measure, validated in family dementia carers,[15] with subscales for difficulty-focused, emotion-focused, and dysfunctional coping; Health Status Questionnaire (HSQ)[16,17] that measures mental-health domain measures of quality of life; European quality of life five dimensions questionnaire (EQ-5D)[18] that measures health status, generating a usefulness score; Client Service Receipt Inventory (CSRI)[19] that measures carer health and social care service use over 4 months retrospectively; and the Modified Conflict Tactics Scale (MCTS) that measures potentially abusive behaviour by carers towards care recipients. Ten behaviours, ranging from shouting to slapping, over the previous 3 months are rated from never (0) to all the time (4). A score of at least 2 for any item is classified as abusive.[20]

Carer's information about the patient: Clinical Dementia Rating (CDR) of dementia severity from very mild (0·5) to severe (3);[21] Neuropsychiatric Inventory (NPI)[22] to adjust for baseline NPI. High patient neuropsychiatric symptoms increase carer psychological morbidity; Quality of life-Alzheimer's Disease[23] that measures the quality of life for a patient with Alzheimer's; and a CSRI that retrospectively measures patient health and social care service use over 4 months.

We did not obtain data for adverse events, because we judged that such events, in terms of carers being unwell, would not be due to the therapy. We did obtain adverse outcomes in terms of costs, which are reported later in the Article.

Statistical analysis

This study was originally powered for a primary outcome of HADS anxiety score[5] needing a sample size of 90 in the control TAU group and 168 in START (participant allocation was unequal to allow for therapist clustering in START). When the primary outcome was changed to HADS-T, the sample then available (87 TAU, 173 START) was sufficient to detect a mean difference in HADS-T of at least 2·4 points (with 80% power, 5% significance) assuming an SD of 7·4 (as for pilot data), allowing for analysis of covariance (assumed correlation 0·5) and two repeated follow-up measurements (assumed correlation 0·7). A drop-out of 10% was assumed, and a design effect of 1·4 was applied for the START group (with an intracluster correlation coefficient of 0·03)[24] and an average cluster size of 15 carers per therapist).

In the primary analysis, we used regression methods to estimate group differences in long-term follow up (12 and 24 months) for HADS-T, treatment costs for carers, and quality-adjusted life-years (QALYs) calculated from European quality of life-5D measures with societal weights.[25] Random-effects models accounted for therapist clustering in the START group and measurements were repeated at 12 and 24 months. We adjusted results for baseline total score, centre (by which randomisation was stratified), and factors known to have an effect on affective symptoms (patient age, sex, and NPI, and carer burden). For cost-effectiveness analyses, we adjusted for the same characteristics, plus prerandomisation costs. Non-parametric bootstrapping was used to estimate 95% CIs for mean costs because of skewed data. All analyses were by intention-to-treat but excluded carers with data missing at both 12 and 24 months. Because QALY estimation needs data at every timepoint, we included only complete cases for this analysis.

Sensitivity analyses for both clinical and economic outcomes were tested for robustness, with adjustments made first for imbalances in baseline characteristics and second for predictors of missing outcomes. The effect of missing data was also addressed, for clinical outcomes, with a multiple-imputation method. By inclusion of interaction terms, we examined possible differential effects of treatment at 12 and 24 months and fitted models incorporating all repeated measurements, to explore differential treatment effects over both short-term (up to 8 months) and long-term (up to 24 months) periods.

Similar approaches were taken for cost-effectiveness and analysis of secondary outcomes. Random effects logistic regression was used for binary outcomes. START's effect on time until care home admission was examined with parametric, shared, frailty models, allowing for clustering in the START group and adjustment for baseline factors. Models had gamma distribution for shared frailty and Weibull distribution for time until care home admission.

Unit costs were set at 2009–10 prices.[26,27] Costs and outcomes in the second year were discounted at 3·5%.[28] START intervention cost was calculated from therapist time spent in training, supervision, and intervention delivery. The relaxation CDs were costed at market rates for copying and delivery.[6] Costs were calculated separately for carers' and patients' service use, from a health and social care perspective. Costs for months 13 to 21 were estimated by interpolation from data obtained at 12 and 24 months to generate costs for the full period.

We calculated incremental cost-effectiveness ratios (difference in cost between START and TAU divided by difference in outcome) for carer plus patient costs and, in turn, two carer outcomes (HADS-T, quality-adjusted life-years) and one patient outcome (quality of life-Alzheimer's Disease) over 24 months. We repeated these analyses for carer-only costs. In view of the uncertainty in estimation of costs and outcomes, we plotted

cost-effectiveness acceptability curves using a net-benefit approach across a range of willingness-to-pay values.

We used the STATA version 11 computer program to do the statistical analyses for the clinical outcomes, and STATA version 12 for the cost-effectiveness analyses. This trial is registered ISCTRN70017938.

Role of the funding source

The funder of the study had no role in study design, data collection, analysis, data interpretation, manuscript writing, or decision to submit for publication. GL, CC, JB, MK, RR, DK, DL, and MG had access to all the data. All authors had final responsibility for the decision to submit for publication.

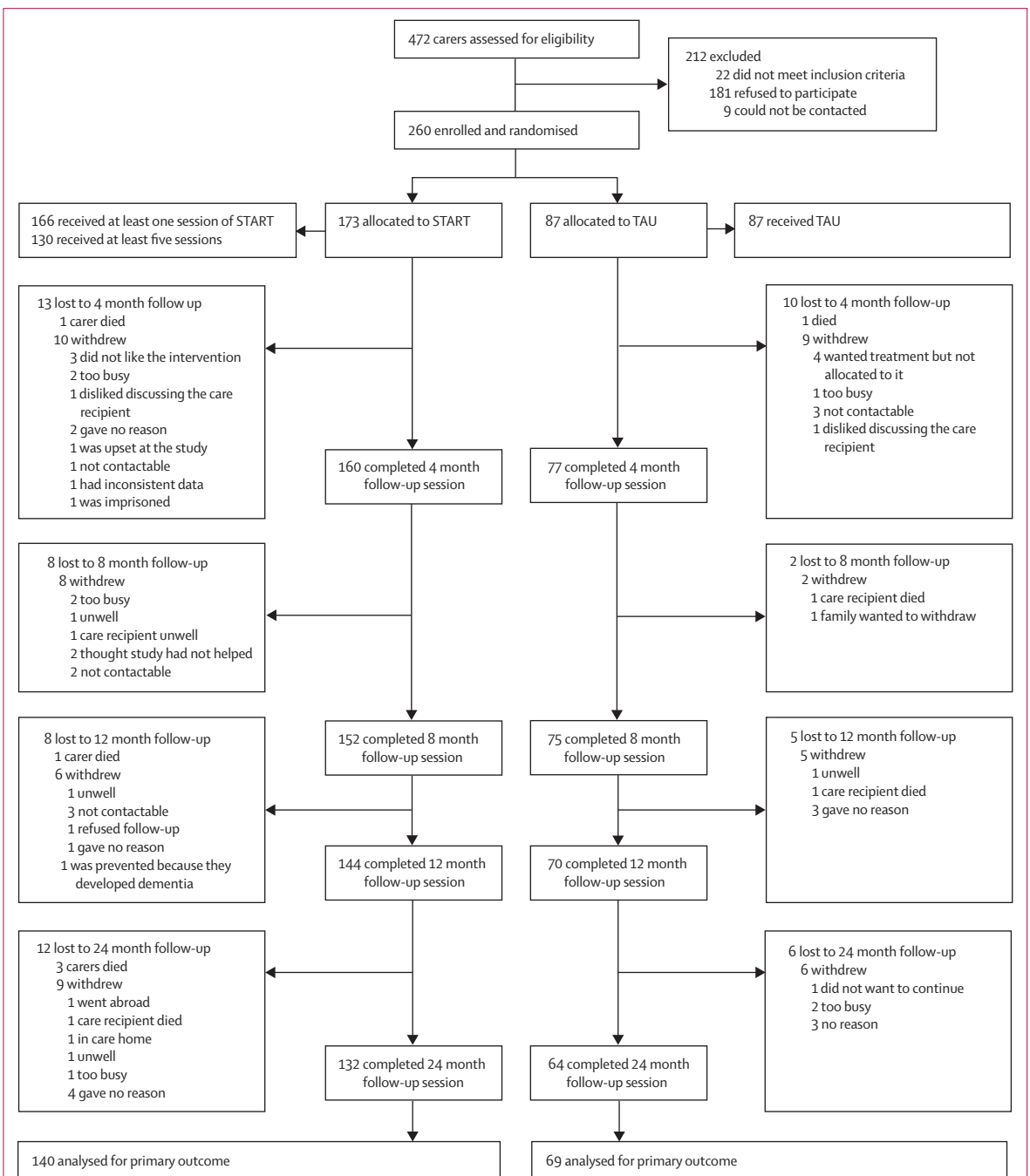

Figure 1: **Trial profile**
To be included in the primary long-term analysis, the individual should have had at least one Hospital Anxiety and Depression Scale (HADS) score at 12 or 24 months. START=STrAtegies for RelaTives (intervention). TAU=treatment as usual (control). People were included in the final analyses if they gave data about the HADS at 12 or 24 months.

Results

472 carers were referred to us for potential inclusion in our trial. Of these, 181 (38%) refused to take part, 22 (5%) did not meet inclusion criteria, and nine (2%) were not contactable. Those who consented were slightly more likely to be married to the patient than those who did not consent.[5] Therefore we randomly assigned 260 (55%) of 472 of the carers referred between Nov 4, 2009, to June 8, 2011 to one of the trial groups (figure 1). 173 (67%) participants were assigned to START intervention and 87 (33%) to TAU. Randomisation generally achieved good balance in terms of sociodemographic and clinical characteristics (table 1).

130 (75%) carers in the intervention group attended at least five therapy sessions, eight (5%) withdrew before any therapy sessions. Each of ten therapists (seven women) delivered the intervention to between 11 and 32 carers, with a mean fidelity score of 4·7/5 (SD 0·66). Primary clinical analyses included 209 (80·4%) participants with HADS-T data at 12 or 24 months. Table 2 shows the primary outcomes. Analysis of HADS-T at 24 months, adjusting for centre, baseline score, and factors related to outcome (carer age and sex, NPI, Zarit) showed a mean difference of –2·58 points (95% CI –4·26 to –0·90; p=0·003) in favour of START.

In the model not including outcome-related factors, mean HADS-T decrease was –1·84 (95% CI –3·50 to –0·17; p=0·03). Sensitivity analyses adjusting for relevant predictors of missing HADS-T scores (coresidence with carer and a high COPE dysfunction score) showed a mean difference of –2·69 (95% CI –4·39 to –0·98, p=0·002, n=200), and adjustment for baseline imbalances (carer work, carer education, patient education, relationship with carer, and living with carer) showed a mean difference of –2·37 (–4·11 to –0·63, p=0·008). Results were also similar after multiple imputation (–2·28; –3·94 to –0·63, n=260).

Models including interaction with time showed no evidence of differential effects at 12 or 24 months (p=0·76). Short (up to 8 months) and long-term effects (12 to 24 months) showed no differences (p=0·92).

Significantly fewer cases of HADS-depression occurred in START compared with TAU (odds ratio [OR] 0·14, 95% CI 0·04–0·53). The difference in HADS-anxiety caseness was not significant (OR 0·57, 0·26–1·24).

Adjusted models for HADS-anxiety and HADS-depression continuous scores showed significant beneficial intervention effects over 24 months with START, with mean decreases of –1·16 (95% CI –2·15 to –0·18, n=200) and –1·45 (–2·32 to –0·57), respectively. Models showed no evidence of differential intervention effects with time for HADS-anxiety or HADS-depression (p=0·99 and p=0·86, respectively).

START improved carer Health Status Questionnaire-Mental Health scale compared with TAU (mean difference 7·47 [95% CI 2·87–12·08], n=183). Patient quality-of-life-Alzheimer's Disease measurements did not differ between groups. Models including an interaction with time showed no evidence of differential effect for quality-of-life-Alzheimer's Disease measurements or Health Status Questionnaire-Mental Health scale (p=0·24 and p=0·14, respectively).

17 (20%) of 84 patients whose carers were receiving TAU and 32 (18%) of 171 whose carers were receiving START moved to a care home within the 24 month trial period. In regression models, no significant difference in

	Carer		Patient	
	TAU (n=87)	START (n=172)	TAU (n=87)	START (n=173)
Age (years)	56·1 (12·3)	62·0 (14·6)	78·0 (9·9)	79·9 (8·3)
Women	62 (71%)	116 (67%)	50 (58%)	102 (59%)
Ethnicity				
White UK	65 (75%)	131 (76%)	61 (70%)	126 (73%)
White other	5 (6%)	10 (6%)	6 (7%)	14 (8%)
Black and minority	17 (20%)	31 (18%)	20 (23%)	33 (19%)
Not currently married	25 (29%)	61 (35%)	47 (54%)	92 (53%)
Education				
No qualifications	18 (21%)	45 (26%)	44 (51%)	73 (45%)
School level	33 (38%)	51 (30%)	16 (19%)	28 (17%)
Further education	36 (41%)	77 (45%)	26 (30%)	63 (38%)
Work				
Full time	28 (32%)	36 (20%)	NA	NA
Part time	20 (23%)	27 (16%)	NA	NA
Retired	23 (26%)	80 (46%)	NA	NA
Not working	16 (18%)	30 (17%)	NA	NA
Living with carer	NA	NA	50 (58%)	113 (65%)
Relationship to patient				
Partner	31 (36%)	78 (45%)	NA	NA
Child	42 (48%)	71 (41%)	NA	NA
Other	14 (16%)	24 (14%)	NA	NA
NPI Total	NA	NA	26·6 (20·1; n=86)	24·0 (19·0; n=171)
CDR overall score	NA	NA	1·3 (0·6; n=87)	1·2 (0·6; n=171)
Zarit	38·1 (17·0; n=84)	35·3 (18·4; n=165)	NA	NA
HADS-T score	14·8 (7·4)	13·5 (7·3)	NA	NA
HADS-A score	9·3 (4·3)	8·1 (4·4)	NA	NA
HADS-D	5·5 (3·9)	5·4 (3·8)	NA	NA
EQ5D	0·79 (0·18)	0·74 (0·24)	NA	NA
QOL-AD	NA	NA	29·9 (6·9)	30·2 (6·9)
HSQ mental health	58·2 (21·7)	58·3 (22·4)	NA	NA
HADS Anxiety Case (score ≥9)	48 (55%)	85 (49%)	NA	NA
HADS Depression Case (score ≥9)	17 (20%)	36 (21%)	NA	NA
MCTS (at least one item score ≥2)	38 (44%)	82 (48%)	NA	NA
Cost (£, during a 4 month period prebaseline)	315	218	3205	2446

Data are n (%) or mean (SD). If some participants did not complete the measure, the changed n is given.NA=not applicable. TAU=treatment as usual. START=STrAtegies for RelaTives. HADS=Hospital Anxiety and Depression Scale. CDR =Clinical Dementia Scale. MCTS=Modified Conflict Tactics Scale. Zarit=Zarit Burden Interview. EQ5D=European quality of life five dimensions questionnaire. NPI=Neuropsychiatric Inventory. QOL-AD=Quality of Life-Alzheimer's Disease. HSQ=Health Status Questionnaire

Table 1: **Baseline characteristics of the intention-to-treat population**

	TAU at 12 months (n=67)	TAU at 24 months (n=64)	START at 12 months (n=138)	START at 24 months (n=132)	Differences adjusted for baseline and centre (n=209)	Differences in scores at 24 months adjusted for baseline, centre, carers' age, sex, NPI and Zarit (n=200)
HADS Total	14·6 (8·9)	15·5 (9·5)	12·5 (7·9)	13·6 (8·3)	–1·84* (–3·50 to –0·17)	–2·58* (–4·26 to –0·90)
HADS Depression Case (score ≥9)	18 (27%)	19 (30%)	24 (17%)	30 (23%)	0·22† (0·05–0·96)	0·14† (0·04–0·53); (n=192)
HADS Anxiety Case (score ≥9)	33 (49%)	32 (50%)	54 (39%)	57 (43%)	0·53† (0·24–1·16)	0·57† (0·26–1·24)
HADS Anxiety	8·8 (5·1)	9·2 (5·3)	7·5 (4·4)	8·1 (4·9)	–0·75* (–1·75 to 0·25)	–1·16* (–2·15 to –0·18)
HADS Depression	5·9 (4·3)	6·3 (4·9)	5·0 (4·2)	5·5 (4·2)	–1·14 (–2·00 to –0·28)	–1·45* (–2·32 to –0·57)
HSQ–Mental Health	56·2 (22·5); (n=61)	55·0 (21·3); (n=55)	61·9 (20·6); (n=121)	60·2 (19·8); (n=113)	7·16* (2·72–11·60); (n=189)	7·47* (2·87–12·08); (n=183)
QOL-AD	30·0 (6·4); (n=53)	29·4 (7·0); (n=49)	30·5 (6·7); (n=114)	29·9 (6·7); (n=95)	0·16* (–1·30 to 1·63); (n=174)	0·17* (–1·37 to 1·70); (n=168)
MCTS (at least one item with a score ≥2)	21 (38%); (n=55)	11 (23%); (n=47)	41 (36%); (n=114)	28 (30%); (n=95)	0·96† (0·42–2·19); (n=176)	0·83† (0·36–1·93); (n=171)

Data are mean (SD), n (%), or difference (95% CI), unless otherwise indicated. Treatment effect estimates (differences and odds ratios) are from models taking into account repeated measurements, therapist clustering in the intervention arm and which are adjusted for baseline characteristics. TAU=treatment as usual. START=STrAtegies for RelaTives. HADS=Hospital Anxiety and Depression Scale. Zarit=Zarit Burden Interview. NPI=Neuropsychiatric Inventory. MCTS=Modified Conflict Tactics Scale. QOL-AD=Quality of Life-Alzheimer's Disease. HSQ=Health Status Questionnaire. One person with dementia was noted to have two carers (spouse and daughter) in the intervention group. This person was represented only once in the analysis of patient outcomes. Therapist intracluster correlation at 12 months was 0·0 (95% CI 0–0·07) and at 24 months was 0·0 (0–0·07). *Data are treatment-effect differences between START and TAU; 95% CI), †data are odds ratios (95% CI).

Table 2: **Primary and secondary outcomes at 12 and 24 months**

time until care home admission by randomised group was noted (hazard ratio [HR] 0.83, 95% CI 0·44–1·56, p=0·56; n=242) adjusted for centre, carer age, carer sex, and baseline NPI and Zarit score. Sensitivity analyses adjusted for baseline imbalances (carer work, carer education, patient education, relationship with carer, and living with carer) gave HR 0·62 (0·31–1·23, p=0·17; n=232). The appendix shows a Kaplan-Meier plot for times to care home admission.

196 (75%) carers had 24 month follow-up service use data (64 TAU, 132 START). Service use patterns are in the appendix. Health-care costs for carers in the START group were not higher than those in the TAU group, suggesting that START did not cause substantial adverse health events.

Mean therapy cost was £232 per carer. When adjusted for baseline characteristics, carer-service costs were slightly higher in the START group than in the TAU group, but not significantly different between groups from 1 to 24 months (£170; 95% CI –132 to 472), and patient-service costs were lower in START than in TAU, but were also not significantly different between the groups over the same period (–£1368; 95% CI –5027 to 2291; table 3).

Cost-effectiveness analyses included carer-only costs and carer-and-patient costs combined. Sample sizes in cost-effectiveness analyses are smaller because of missing values.

In the main analyses with combined costs (table 4), START dominates TAU when looking at carer outcomes (HADS-T and quality-adjusted life-years), because outcomes are better and costs not significantly different. For the second primary outcome of cost-effectiveness (with quality-adjusted life-years as an outcome [figure 2]), START is cost effective with respect to NICE thresholds (67% probability of cost-effectiveness at £20 000 per quality-adjusted lifeyear willingness-to-pay threshold; 70% at £30 000 threshold).[28]

For patient quality of life-Alzheimer's Disease measures, neither cost nor outcome was significantly different between the groups. In view of uncertainty in the analyses, cost-effectiveness acceptability curves were plotted. For quality of life-Alzheimer's Disease measures, the curve suggests a high probability of cost-effectiveness (figure 2) at all willingness-to-pay values. For HADS-T, the curve again shows a high probability of cost-effectiveness for the intervention (appendix) across all willingness-to-pay values, although there is no externally recommended threshold.

When looking only at carer-only costs, the pattern of cost-effectiveness is little changed (table 4). Cost per QALY is now £12 400, again less than the NICE threshold. From a health and social care perspective, cost-effectiveness analyses using combined costs are more relevant.

To assess the robustness of these findings, we adjusted the results for relevant predictors of missing data, which gave similar results–the intervention having a 67% likelihood of cost-effectiveness at the NICE £20 000 per quality-adjusted life-year threshold (75% at £30 000 threshold). For the second sensitivity analysis with adjustments for baseline characteristics imbalances, mean incremental cost-effectiveness ratios (ICERs) change (table 4), as does the pattern of probability of cost-effectiveness across the willingness-to-pay range (see

	TAU*		START*		START versus TAU from 1 to 24 months	
	1–12 months	13–24 months	1–12 months	13–24 months	Difference adjusted for score at baseline and centre	Difference adjusted for score at baseline, centre, and baseline variables†
Costs for carers (£, 2009–10)						
Hospital	370 (963)	291 (679)	275 (436)	435 (1530)	51 (–182 to 284) (n=208)	49 (–190 to 287) (n=199)
Community health	349 (554)	313 (623)	324 (458)	330 (425)	–1 (–116 to 113) (n=208)	–28 (–147 to 90) (n=199)
Community social care	11 (29)	0 (0)	57 (538)	28 (209)	36 (–54 to 126) (n=208)	15 (–80 to 110) (n=199)
Intervention	0 (0)	0 (0)	232 (98)	0 (0)	116 (96 to 136) (n=260)	115 (94 to 136) (n=247)
Total	730 (1155)	598 (907)	912 (1012)	783 (1626)	240 (–61 to 542) (n=208)	170 (–132 to 472) (n=199)
Costs for patients (£, 2009–10)						
Hospital	3660 (6411)	3909 (6460)	2375 (5582)	3642 (7826)	–683 (–2109 to 744) (n=206)	–735 (–2210 to 740) (n=197)
Community health	1002 (1895)	924 (1885)	64 (968)	72 (1236)	–205 (–591 to 181) (n=206)	–220 (–622 to 182) (n=197)
Community social care	3054 (5226)	4388 (15 338)	4017 (12 024)	4875 (17 050)	1352 (–1900 to 4603) (n=206)	1144 (–2207 to 4496) (n=197)
Care home	1755 (7176)	4682 (11 610)	1000 (4762)	2922 (8071)	–1281 (–3277 to 715) (n=213)	–1536 (–3535 to 463) (n=204)
Total	9577 (13 524)	13 904 (19 051)	7922 (14 410)	12 358 (19 976)	–649 (–4263 to 2965 (n=206)	-1368 (–5027 to 2291) (n=197)
Outcomes used in economic evaluation						
Carer: EQ5D	0·81 (0·19)	0·80 (0·19)	0·79 (0·23)	0·77 (0·26)	0·04 (–0·04 to 0·12) (n=190)	0·05 (–0·03 to 0·13) (n=184)
Carer: QALY	0·79 (0·15)	0·75 (0·16)	0·80 (0·18)	0·73 (0·21)	0·02 (–0·02 to 0·06) (n=179)	0·03 (–0·01 to 0·07) (n=174)
Carer: HADS-T	14·6 (8·9)	14·4 (8·9)	12·5 (7·9)	12·7 (7·7)	–1·75 (–3·31 to –0·19) (n=209)	–2·47 (–4·03 to-0·91) (n=200)
Patient: QOL-AD	30·0 (6·4)	27·4 (6·5)	30·5 (6·7)	27·9 (6·3)	0·28 (–1·09 to 1·66) (n=174)	0·26 (–1·16 to 1·68) (n=168)

Data are mean (SD), n (%), or difference (95% CI) (sample size). TAU=treatment as usual.START=STrAtegies for RelaTives. EQ5D=European quality of life five dimensions questionnaire. QALY=quality-adjusted life-year. HADS-T=Hospital Anxiety and Depression Scale-Total score. QOL-AD=Quality of Life-Alzheimer's Disease. *Not adjusted for any baseline scores or centre.†For carers, differences adjusted for baseline score, centre, age, sex, Neuropsychiatric Inventory, and the Zarit Burden Interview. Outcomes also adjusted for baseline total carer cost. For patients, differences adjusted for baseline score, centre, patient's age, sex, NPI, and carer's Zarit. Outcomes are also adjusted for baseline total patient costs.

Table 3: **Carer and patient costs and outcomes**

	Incremental difference (START minus TAU) and cost-effectiveness ratio over 1–24 months (main analyses)		Incremental difference (START minus TAU) and cost-effectiveness ratio over 1–24 months (sensitivity analysis)*	
	With carer-only costs	With carer-plus-patient costs	With carer-only costs	With carer-plus-patient costs
Carer HADS-T	n=168	n=163	n=161	n=157
Incremental costs (mean £ [95% CI])	287 (–207 to 782)	–1324 (–9987 to 7339)	262 (–226 to 750)	–118 (–8873 to 8636)
Incremental HADS-T change: mean (95% CI)	–1·60 (–3·69 to 0·49)	–1·49 (–3·47 to –0·50)	–1·47 (–3·69 to 0·74)	–1·36 (–365 to –0·92)
Incremental cost-effectiveness ratio (£ per 1-point difference for HADS-T)†	179	–889	178	–87
Carer QALY	n=147	n=145	n=141	n=140
Incremental costs (mean £ [95% CI])	372 (–189 to 933)	–1471 (–10 909 to 7968)	321 (–286 to 927)	698 (–9459 to 10 855)
Incremental QALY gain: mean (95% CI)	0·03 (0·00 to 0·06)	0·03 (0·00 to 0·07)	0·03 (0·00 to 0·06)	0·03 (0·00 to 0·06)
Incremental cost-effectiveness ratio (£ per QALY gain)	12 400	–49033	10 700	23 267
Patient QOL-AD	n=134	n=131	n=129	n=127
Incremental costs (mean £ [95% CI])	266 (–328 to 859)	–3412 (–12 483 to 5659)	233 (–398 to 864)	1791 (–7595 to 11 176)
Incremental QOL-AD change: mean (95% CI)	1·09 (–0·75 to 2·92)	0·55 (–1·38 to 2·48)	0·88 (–1·14 to 2·90)	0·54 (–1·53 to 2·61)
Incremental cost-effectiveness ratio (£ per 1-point difference for QOL-AD)	244	–6204	265	3317

Data are given by outcome. HADS-T=Hospital Anxiety and Depression Scale-Total score. QALY=quality-adjusted life-year. QOL-AD=Quality of Life-Alzheimer's Disease. Sample sizes were based on complete data for each outcome and combined cost measures. *Additional covariates were added to the model to adjust for imbalances in baseline characteristics. †Sign reversed in line with convention for cost-effectiveness ratios.

Table 4: **Carer-only costs and carer-plus-patient costs combined**

appendix). The change in the ICER for the quality-adjusted life-year outcome is exaggerated by the very small between-group difference, but the effect on the cost-effectiveness acceptability curve is slight—eg, at £20 000 willingness-to-pay threshold, START has a 50% likelihood of being cost effective. With respect to HADS-T, START has more than a 50% likelihood of cost-effectiveness at all willingness-to-pay values. With respect to patient quality-of-life measures for Alzheimer's Disease, the case for START's cost-effectiveness is weaker in the sensitivity analysis; when

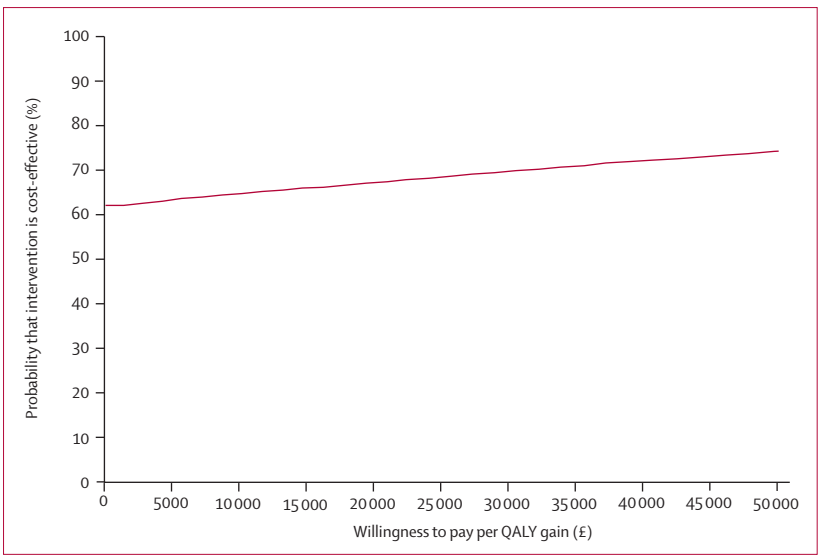

Figure 2: **Cost-effectiveness analysis for carer QALY gain**
Cost-effectiveness acceptability curve analysis done over 24 months. QALY=quality-adjusted life-year.

Panel 2: Research in context

Systematic Review

Before this study, we systematically reviewed evidence for family carer interventions for anxiety and depression using quality guidelines to prioritise high-quality evidence and combining it according to the type of intervention.[2,30] We searched the electronic databases Allied and Complementary Medicine, British Nursing Index, CINAHL(R), Embase, Medline, the Cochrane systematic review database, and reference lists from articles, until June, 2005. We noted that interventions up to now had been delivered by highly trained clinicians, usually psychologists. The most effective therapies were multicomponent, needed active participation of the carer, were tailored to individual carers, and delivered individually. They sometimes, over many years, delayed admission of people with dementia to a care home.

Interpretation

On the basis of our trial results we suggest that STrAtegies for RelaTives (START) is a clinical and cost-effective intervention to treat and prevent depression and anxiety in family carers of people with dementia. This is the first time that these results have been shown to continue long-term (2 years). START is also cost-effective for people with dementia, and these effects also continue over 2 years. There is no other rigorous study of an intervention delivered by psychology graduates without previous clinical training, and no other extensive studies of cost-effectiveness. Previous studies of similar interventions in the USA have shown results consistent with ours, but our intervention might be more practical for many carers, because they did not need to all attend a group at the same time. Trials of psychosocial interventions in Europe (UK, Denmark, and Norway) using different models have been ineffective in terms of carers' psychological symptoms and quality of life, thus showing that our results were not attributable solely to a therapist offering time and attention. Future studies should assess the effects of carer interventions on people with dementia in terms of clinical outcomes (ie, cognition and neuropsychiatric symptoms), and in the longer-term, care-home admission—we have extended our study for this latter aim. Additionally, we wish to further analyse the effect of carer interventions on abuse, especially the interaction between abuse and care-home admissions—abuse can lead to admission, and interventions for carers such as START could prevent further abuse and admissions.

including carer-only costs, the cost per quality-adjusted life-year becomes £23 267 (table 4).

Discussion

START, a structured psychological intervention for family carers of people with dementia, improved carers' depression and anxiety symptoms and quality of life not only in the short term, but also up to 24 months later. This is the first trial to show such results (panel 2).[29] The magnitude of difference in the total HADS symptoms is in the range that is important to patients and is clinically significant compared with other clinically meaningful changes.[30] Similarly, the quality of life difference between the START and TAU groups is the same magnitude as that between depressed and non-depressed community residents.[17] At 2 year follow-up, carers in the control TAU group were seven times more likely to have clinically significant depression than in the START intervention group–this result is by definition clinically significant. START is also cost effective over both short and long term. Both community social care and care-home costs rose over time for the patients with dementia in both groups, as a result of worsening dementia. Care-home costs increased in both groups, with a greater increase in TAU than START, although this result was not significantly different. We are monitoring care-home admissions for another 5 years.

Previous successful interventions for affective disorders in family carers show that coping strategies and individual (rather than group) therapy could be effective for depressive symptoms, but little evidence exists for their effect on anxiety. Previous studies have neither included prevention as an outcome, nor fully measured cost-effectiveness; a review showed some evidence that interventions could generate savings,[31] and a similar intervention to START showed a significant difference in carer-time inputs over 6 months.[32] Family carers become more anxious and depressed over time without an intervention; thus we did not exclude carers who were not depressed at the beginning of the study.[33,34] START's preventive effect underlines the fact that carers can benefit from early intervention.

A strength of our study was that carers were heterogeneous in sociodemographic and clinical characteristics, and recruited from varied services. Most patients had mild dementia at baseline, making the intervention generally acceptable to and applicable to family carers around the time UK patients present to secondary care with dementia. Limitations include the possibility of response bias in those who agreed to the study; because carer and patient morbidity levels were slightly higher than another cohort of newly referred people with dementia,[35] those with more difficulties might have been more likely to consent to participate this trial. However, because the interventions in this study both prevented and treated depression, this therapy is likely to be applicable to those not in the investigation.[36]

The trial was not powered for the economic evaluation, which could account for the non-significance of those differences. Follow-up showed a slight bias; adjustment for the bias suggested that START was slightly more cost effective and clinically effective than the primary analysis.

We minimised bias with standard measures validated for this population, independent randomisation, and follow-up assessors who were unaware of the allocation, although family carer participants inevitably knew the group allocation. At 2 years, the follow-up rate was 80% and sensitivity analyses showed similar results.

High fidelity ratings and very low intercluster correlations indicate that the results do not differ between therapists, suggesting that START can be delivered consistently. START is multifaceted because these interventions are more likely to work in complex situations; qualitative follow-up substantiated our idea that carers used different components of the intervention.[37] However, therapists saw most people at their homes (153 of 173) and were more flexible in timing than most NHS non-emergency services—eg, seeing 19 of 173 participants in the evenings. Our evidence for costs and cost-effectiveness for this method of delivery at home suggests that it should be feasible to provide in this format.

In conclusion, the START intervention is clinically effective in the long term, improving carer mood and quality of life for 2 years. It does not raise costs, and it is cost effective in terms of both carer and patient outcomes, with respect to NICE cost thresholds.

Many countries face rapidly growing numbers of people with dementia, including single people, over the coming decades, and policy frameworks assume their families will remain frontline providers of (unpaid) support. Most people with dementia also prefer to receive support from family members. In these circumstances, a cost-neutral intervention such as START, which substantially improves family carer mental health and quality of life whether or not they live with the person with dementia, should be made widely available.

Contributors

All authors contributed to data interpretation and writing. GL, CC, ZW, DL, CM, and JH obtained the data. GL, CC, ZW, DL, and MK contributed to the study design. JB and MG analysed the clinical data. MK, RR, and DK analysed the economic data.

Declaration of interests

During the study, ZW received personal fees, grants, and other payments from GE Healthcare, and grants from Lundbeck, outside the submitted work. All other authors declare no competing interests.

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For more on the **START project** see http://www.nets.nihr.ac.uk/projects/hta/081406

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