Clinical effectiveness of START (STrAtegies for RelaTives) psychological intervention for family carers and the effects on cost of care for people with dementia: six year follow-up of a randomised controlled trial

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Clinical effectiveness of START (STrAtegies for RelaTives) psychological intervention for family carers and the effects on cost of care for people with dementia: six year follow-up of a randomised controlled trial

Short title START: Six year clinical and dementia cost outcome

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Abstract

Background

START (STrAtegies for RelaTives) intervention reduced depressive and anxiety symptoms of family carers of relatives with dementia at home over two years and was cost-effective.

Aims

To assess clinical-effectiveness over six years and impact on costs and care home admission.

Methods

We conducted a randomised, parallel group, superiority trial recruiting from 04/11/2009 to 08/06/2011 with six year follow-up. 260 self-identified family carers of people with dementia were randomised 2:1 to START, an eight-session manual-based coping intervention delivered by supervised psychology graduates or Treatment as Usual (TAU). The primary outcome was affective symptoms (hospital anxiety and depression total score; HADS-T). Secondary outcomes included patient and carer service costs, and care home admission.

Results

222 (85.8%) of 173 carers randomised to START and 87 to TAU were included in the 6-year clinical efficacy analysis. Over 72-months, the intervention group compared to TAU was better on HADS-T (adjusted mean difference -2.00 points; 95% confidence interval [CI]: -3.38 to -0.63). Patient-related (START versus TAU respectively: median £5759 versus £16964 in the final year; p =0.07) and carer-related costs (median £377 versus £274 in the final year) were not significantly different between groups nor were group differences in time until care home [Intensity ratio START:TAU = 0.88 (CI: 0.58 to 1.35)].

Conclusions

START is clinically effective and this effect lasts for six years without increasing costs. This is the first intervention with such a long-term clinical and possible economic benefit and has potential to make a difference to individual carers.

Declarations of interest

None

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Introduction

Families provide most of the care to people with dementia living at home. Family carers have worse physical health, more absences from work, lower quality of life and are more likely to be anxious or depressed than non-carers (1-4). Currently around 50 million people globally have dementia, projected to nearly triple by 2050, while the present annual global cost is US$818 billion(5). Nearly 85% of costs are family and social rather than medical costs (6).

The START (STrAtegies for RelaTives) multicomponent intervention for family carers, individually delivered by supervised psychology graduates (with a first degree in psychology and no clinical training), was tested by our research team in a randomised controlled trial and was the first to show both clinical-effectiveness (reduced anxiety and depressive symptoms, decreased depression caseness, improved quality of life) and cost-effectiveness for family carers of people with dementia(7, 8). Methods and results up to two years follow-up have been reported in detail elsewhere (7-11). We found that START carers had a decrease in symptom score which was greater than the minimum clinically important difference and at 8 months were one fifth as likely to have case-level depression. These benefits persisted for two years(9), when the intervention was also cost-neutral when considering health and care services used by both family carers and patients(9). To the best of our knowledge, there are no clinically and cost-effective interventions that have demonstrated effects beyond five years(12) (13, 14), and none are manualised; so the intervention can be delivered consistently to participants; by graduates without clinical training, with potential to implement at scale.

Objectives

Our aim is to determine the long-term (up to 6 years from baseline) clinical effectiveness of START for family carers' affective symptoms and costs compared to Treatment as Usual (TAU) in terms of:

1) Our primary outcome-Total HADS score (hospital anxiety and depression total score; HADS-T) in carers of people with dementia
2) Secondary outcomes
    - Anxiety and depression caseness and scores
    - Time until care home admission and death of the person with dementia
    - Time spent at home
    - Cost of care for both people with dementia and carers

Methods

We registered a trial protocol before recruitment began https://doi.org/10.1186/ISRCTN70017938. After registration we requested and received a 5-year no-cost extension to the trial and that our primary outcome would be repeated measures of the HADS-T and registered this prior to analyses. A standard reporting protocol was used.

Intervention and delivery

We recruited 260 participants to the study. We developed the eight-session START manual-based individual coping intervention for dementia family carers from the American "Coping with Caregiving"(15). We trained and supervised non-clinically trained psychology graduates to deliver the intervention (see supplementary figure 1), and PR supervised them clinically as a group with additional time available for individual support. There was a strong

practical focus in the training programme on how to deliver the therapy, potential clinical dilemmas, empathic listening, effective use of supervision, safe working practise and when to ask for help. They were trained to adhere to the manual and we used role-play with senior members of the team completing a competency checklist to ensure they could deliver each session competently. We monitored intervention fidelity using a checklist out of a possible five points, and it was satisfactory. . Therapists worked with carers to identify individual difficulties and to find workable solutions rather than give answers or recommendations, and implement strategies including: behavioural management, communication strategies, identifying and changing unhelpful thoughts, positive reframing, accessing support, future planning and increasing pleasant events. Each session included a relaxation exercise and we asked carers to put into practise the individualised strategies and relaxation between sessions. The final session was used to agree a plan of what to do in future based upon what that carer had felt worked. The carer kept their own manual and relaxation CDs.

In summary START is a parallel-group, superiority, single-blind, randomised controlled trial (RCT) conducted in the UK (four sites). Participants were selected to represent varied clinical services, so we could see if the intervention was generalisable- a mental health trust based in a large city; a trust in a semi-rural area, a tertiary neurological clinic for rare and young-onset dementia; and a mental health trust where patients were allocated to a specialist nurse (Admiral Nurse. We recruited self-identified family carers providing at least weekly support to people with a clinical diagnosis of dementia, living in their own homes and referred to the service we recruited from during the previous year. We excluded those who were unable to give informed consent or who lived more than 1.5 hours travelling time from the researchers' base. We recruited from 04/11/2009 to 08/06/2011 through three mental health trusts and a tertiary neurology clinic. Last follow up was 28/04/2017. Standard treatment includes medical, psychological and social interventions, consisting of assessment, diagnosis and information-giving, risk assessment and management (e.g. fire, driving, adequate nutrition and self-care, vulnerability, managing money), drug treatment, cognitive stimulation therapy, practical support, treatment of neuropsychiatric and cognitive symptoms, assessment of capacity, help in making long-term decisions, and carer support. Patients in both groups received TAU and the use of services in both groups has been described in detail(16).

Randomisation and masking

Participants were randomised 2:1 to intervention: TAU in order to maintain study power given the potential for clustering of outcomes by therapist in the intervention arm Randomisation was stratified by centre using random permuted blocks via an online computer-generated randomisation system from an independent Clinical Trials Unit. Assessors were blinded to randomisation status, but study participants knew their allocation.

Outcome measures

We collected carer and patient socio-demographic details at baseline and measured dementia severity using the clinical dementia rating (CDR) (17). We also administered the Neuropsychiatric Inventory (NPI)(18), as neuropsychiatric symptoms have been shown to be associated with carer psychological morbidity, and the Zarit burden interview(19). Each NPI item is scored as the product of severity and frequency giving a potential score of 0-12 and scores are summed giving a possible total from 0-144. Higher scores indicate more neuropsychiatric symptoms and more burden, respectively. We also measured carers' anxiety and depressive symptoms, using the Hospital Anxiety and Depression

Scale HADS(20, 21) at baseline, 4, 8, 12 and 24 months. In an agreed extension with our funders and ethics committees we continued to collect carer HADS scores and place of residence for patients six-monthly from 24 until 72 months. We recorded the date that a patient was admitted to a care home or had died, and stopped measuring the HADS at that point. HADS is a scale, validated for all age groups and settings, in people who are physically well or ill, and in Asian and African ethnic groups(19); summarised as HADS-D (depression) HADS-A (anxiety) with scores from 0 to 21 and a total HADS score (HADS-T) from 0 to 42 (higher scores indicating more symptoms). The total score (HADS-T) is our chosen primary outcome as it has better sensitivity and positive predictive value than either of the individual scales in identifying depression, when compared to International Classification of Diseases (ICD) depression diagnosis criteria(21). HADS-D and HADS-A are also validated as scores for "caseness" and were dichotomised as "case" and "non-case", with a cut-point of ≥9 (19).

The Client Service Receipt Inventory (CSRI)(22) measured health and social care service use retrospectively until 24 months, but not beyond that point. Each carer reported their own and the patient's service use over the previous 4 months, covering the full range of services (8). Service contacts were multiplied by their unit costs (2009-10 prices) obtained from publicly available sources: NHS reference costs(23) for inpatient and outpatient attendances, and the PSSRU volume(24) for other services. Costs were discounted to present values at an annual rate of 3.5% (25).

Beyond the 24-month point, we estimated costs of services used by patients and carers up to the earliest of either withdrawal from the study, death of either patient or carer, or end of follow-up period (72 months). For patients who continued living in the community, we assumed that weekly costs remained the same as at 24 months. For patients moving to a care home, we attached a unit cost equal to the weekly charge for a private nursing home for older people (24), the most likely type of admission for someone with dementia, for the duration of stay, and we assumed that carer service use costs continued. Costs were carried forward as long as the patient/carer remained alive.

Statistical analysis

Analyses were conducted as intention-to- treat based on a predefined statistical analysis plan. Most analyses were carried out in STATA (version 14), but some models (as detailed) were fitted using R.

HADS scores

HADS data included in the primary 72-month analysis are those collected while the carer was still actively looking after the patient (i.e. patient was still living at home). Data collected after the patient had died or was admitted to a care home was excluded.

To be included in the primary long term analysis, the individual must have had at least one follow-up HADS-T score. Those excluded therefore have no follow-up measurements at any time point. Analyses compare the group as randomised, regardless of the number of therapy sessions attended in the intervention group

We used mixed effects linear regression models to assess the effect of the START intervention on repeated measurements of HADS-T over 72 months. Initially we adjusted for treatment centre, HADS-T at baseline and time, but then extended this model to include adjustments for carer age, carer sex, baseline NPI score and Zarit score. We also investigated whether the treatment effect changed over time by including a treatment by time interaction. We

chose not to allow for therapist clustering in these models since previous analyses of data up to 24 months had indicated that clustering effects were negligible. As a sensitivity analysis however models were refitted allowing for therapist clustering. For all cases estimates obtained were not substantially different.

We used scatter plots of residuals and fitted values to check model assumptions. The correlation structure assumed in the main analyses was compound symmetry; however, models were refitted in sensitivity analyses with alternative structures (autoregressive (order 1) and linear spatial correlation assumptions). For all models these investigations supported the models used for the main analyses.

The analyses described for the HADS total score were repeated for anxiety and depression subscales of the HADS.

We investigated the effect of the START intervention on the occurrence of cases of anxiety/depression, using mixed effects logistic regression models, with a participant-level random effect.

If care home admission or death of the care recipient occurred prior to 72 months, the carer was not followed-up beyond the last visit prior to death or care home admission. Given the possibility of a relationship between HADS scores and death/care home admission, we conducted sensitivity analyses to consider the impact of such informative censoring. Joint mixed effect models for the longitudinal HADS scores and time to institutionalisation or death were fitted to account for the correlation between the longitudinal and survival outcomes(26). The HADS component treatment effect estimates were compared with those obtained from the previously fitted mixed models. [Note: Joint models were fitted using the `JM` package in R(27)].

Time until care home admission

We employed a multi-state model (depicted pictorially in supplementary Figure 1)(28) to analyse time until care home admission while accounting for the possibility of patient death. The model was set up to allow transition from living at home to one of two states, care home admission or death. Effect estimates from the model are 'intensity ratios' which are analogous to hazard ratio estimates in a Cox proportional hazards model but pertain to the specific transitions within the multi-state model. As before, models were fitted adjusting for centre, carer age, carer sex, baseline NPI and Zarit score. [Note: Multi state models were fitted using the `msm` package in R(28)).

Time spent at home

In a further analysis of patient time spent at home (i.e. time prior to care home admission or death), we fitted models for time to admission or death using a standard survival analysis. We used a log rank test to make a comparison between the randomised groups and then fitted a Cox regression model to provide a treatment effect estimate adjusted for centre, carer age, carer sex, baseline HADS total, baseline NPI total and Zarit total score.

Costs

The difference in costs between treatment arms at 72 months was assessed using the non-parametric Wilcoxon Rank-Sum test(29).

Patient involvement

This study was devised and conducted with patient and public involvement (PPI) in the questions of the study and PPI representatives were on the management and steering group. They helped shape the original questions, added qualitative questions about the experience and took part in interpreting the findings. They have also presented them.

Results

Participant flow and recruitment

The Consort diagram (Figure 1) shows participant flow through the study. We randomised 260/472 (55%) of the carers referred. Others refused (n=181; 38%), did not meet inclusion criteria (n=22; 5%) or were uncontactable (n=9, 2%). We randomised 173 (67%) participants to intervention and 87 (33%) to TAU. The characteristics of the randomised groups generally achieved good balance in terms of socio-demographic and clinical characteristics (see supplementary table 1). Carers were mostly spouses/partners (109; 42%) or children (113; 44%). The proportions of patients who died (before they were admitted to a care home), were admitted to care homes and withdrew by randomised group is shown in supplementary table 2. There is no evidence of significant differences in the proportions of participants in each end-status category between the START and TAU groups.

Intervention adherence and fidelity

130 (75%) carers in the intervention group attended ≥5 therapy sessions, 8 (5%) withdrew before any therapy sessions. Ten therapists delivered the intervention, to between 11 and 32 carers each. The mean fidelity score was 4.7 (SD 0.66).

Primary outcome

Table 1 summarises HADS-T scores at each follow-up point. Analysis of HADS-T, adjusting for centre, baseline score, time and factors related to outcome (carer age and sex, NPI, Zarit) over the 6-year period, showed an average improvement in HADS-T of 2.00 points compared with TAU (95% CI: -3.38 to -0.63; p=0.005) (Table 2). In the model adjusting only for centre, baseline score and time, average score decrease was smaller but still significant and in favour of the intervention group (Table 2). A model including an interaction with time showed no evidence of differential effects of the intervention over time (p=0.98).

Secondary outcomes

Depression and anxiety caseness and scores

In the fully adjusted analyses there was a reduced odds of HADS-depression caseness in the intervention group compared to TAU, (odds ratio (OR) =0.20 (95% CI: 0.08 to 0.52), p = 0.001). Reduction in HADS-anxiety caseness however was not significant (OR= 0.50, 95% CI: 0.24 to 1.07, p = 0.07) (Table 2).

Fully adjusted models for HADS-A and HADS-D continuous scores indicated significant beneficial intervention effects over 6 years, with average decreases of -0.97 (95% CI= -1.78 to -0.15,) and -1.06 (95% CI-1.78 to -0.35) respectively. Models showed no evidence of differential intervention effects with time for HADS-A or HADS-D (p= 0.98 and p=0.94, respectively).

Adjusted joint models were used as sensitivity analyses to allow for the possibility of a relationship between HADS scores and time to care home admission or death gave similar results to previous models for HADS-T, HADS-D and HADS-A (HADS-T: 2.01 (95% CI -3.38 to -0.63), HADS-D: -1.07 (-1.78 to -0.37)), HADS-A: -0.97 (-1.78 to -0.16)). This suggests that censoring by death/care home admission is not problematic.

Analysis of time until patient care home admission and death

Figure 2 shows the cumulative incidence of care home admission and death over time by randomised group and indicates little difference between the groups for either outcome. The multi-state model adjusted for centre, carer age, carer sex, baseline HADS-T, baseline NPI and baseline Zarit gave intensity ratios for the START intervention versus

TAU of 0.88 (95% CI 0.58 to 1.35) for the home-to-care-home transition and 0.81 (95% CI 0.50 to 1.30) for the home-to-death transition, both showing no evidence of a between group difference in transition rates to care homes or in death rates. .

Analysis of time spent at home

Based on Kaplan Meier estimates, the estimated median time spent at home (i.e. time until death or institutionalisation) for the TAU group was 39.0 months (95% CI 31.1 to 49.4) and for START was 42.2 months (95% CI 33.3 to 54.7). Cox regression with adjustments for centre, carer age, baseline HADS total, NPI score and Zarit score, showed no evidence of a difference between the randomised groups (hazard ratio estimate: 0.81 (95% CI 0.59 to 1.11)).

Costs

Costs for carer and patient service use are shown in Table 3. Costs of services used by patients were much higher than costs for services used by carers across the full study period. In the final year of follow-up (61-72 months) median patient service use costs were £16,964 for TAU and £5,759 for START, (p=0.072), Median carer service use costs were £377 for TAU and £274 for START.

Discussion

Main findings

This is the first RCT to demonstrate that family carers of people with dementia referred to specialist care experience benefits from an intervention delivered by supervised psychology graduates in terms of depression and anxiety symptoms and depression caseness, not only in the short-term but for up to 6 years. The difference is small but is statistically significant, greater than the minimally clinically important difference (that which is clinically significant to patients)and is sustained(30). The difference in costs appears to be economically large (cost per patient in the intervention group is around a third of the cost in the treatment as usual group) although there was no significant difference in time to care home admission or death. The reduced sample size, however, means that the test for differences in cost is underpowered (particularly given highly skewed cost data), but the estimated costs of health and care services used by patients appear to be lower for the intervention group compared to treatment as usual in the final year of follow-up. It is encouraging that this intervention does not therefore increase costs, and might actually be cost-saving. Carers in the control group were five times more likely to have clinically significant depression on a rating scale validated against caseness using ICD criteria. Predictably, health and social care costs increase over time for both groups, as a result of the worsening condition. There is a bigger increase in TAU group.

Strengths and limitations

The trial is randomised, with blinded follow-ups and we recruited the numbers of participants needed according to the power analysis based on the primary clinical outcome (7). The intervention was manual-based, standardised and supervised. High fidelity ratings and very low inter-cluster correlations show the results do not differ according to therapists, suggesting that the intervention can be delivered consistently.

We planned a pragmatic trial to include all family carers who presented to services so they had varied sociodemographic and clinical characteristics and came from a variety of services; consequently, our study has some external generalisability, that is, it suggests the intervention can be used in a variety of NHS settings. We did not have

the power to analyse whether this intervention was more effective in subgroups; for example, those with more education or without a mental health history or with more family support. At the time of the START intervention most patients had only recently presented to services and thus the intervention can be offered at the beginning of the patient pathway but may not be applicable to those who have had the diagnosis for many years. It was preventative as well as improving depression and so can be offered to this with and without depression (7). START's preventative effect that carers used different components of the intervention and some continued to use these consciously over two years but we did not ask about this at six year follow up(11). Only patient care home admission and death and carer HADS were directly collected after 2 years and therefore the economic analysis involved modelling. Although the differences in costs were striking, the nature of dementia which inevitably meant attrition by death of some of those with it over six years, meant the numbers were smaller. In addition, the data were skewed and they only approached the usual level taken as significant.

Comparison with other studies, meaning and implications

The practical nature of the intervention, in which carers were encouraged to develop and continue to use successful strategies, might also account for the longevity of the positive effects on carer mental health that we found – the most successful strategies were likely to be used repeatedly and therefore remembered and integrated into caring routines. The intervention included a final session on planning for the future. It is likely that the nature of caring difficulties will have evolved over six years. Intervention group participants were given a manual in which strategies they had found helpful for managing caring challenges, as well as pleasant events were recorded, and recordings of the relaxation exercises so that they had something to refer to during future caring.

Our findings would suggest that carers were able to continue using the skills and strategies they had practiced in the longer term; a focus on planning for the future, accessing support, and explicit consideration of how difficulties may change and emotion focused and acceptance based strategies, might have helped support this. It is also possible that carers revisited previously less personally relevant aspects of the manualised intervention as certain issues or challenges became more salient to their caring.

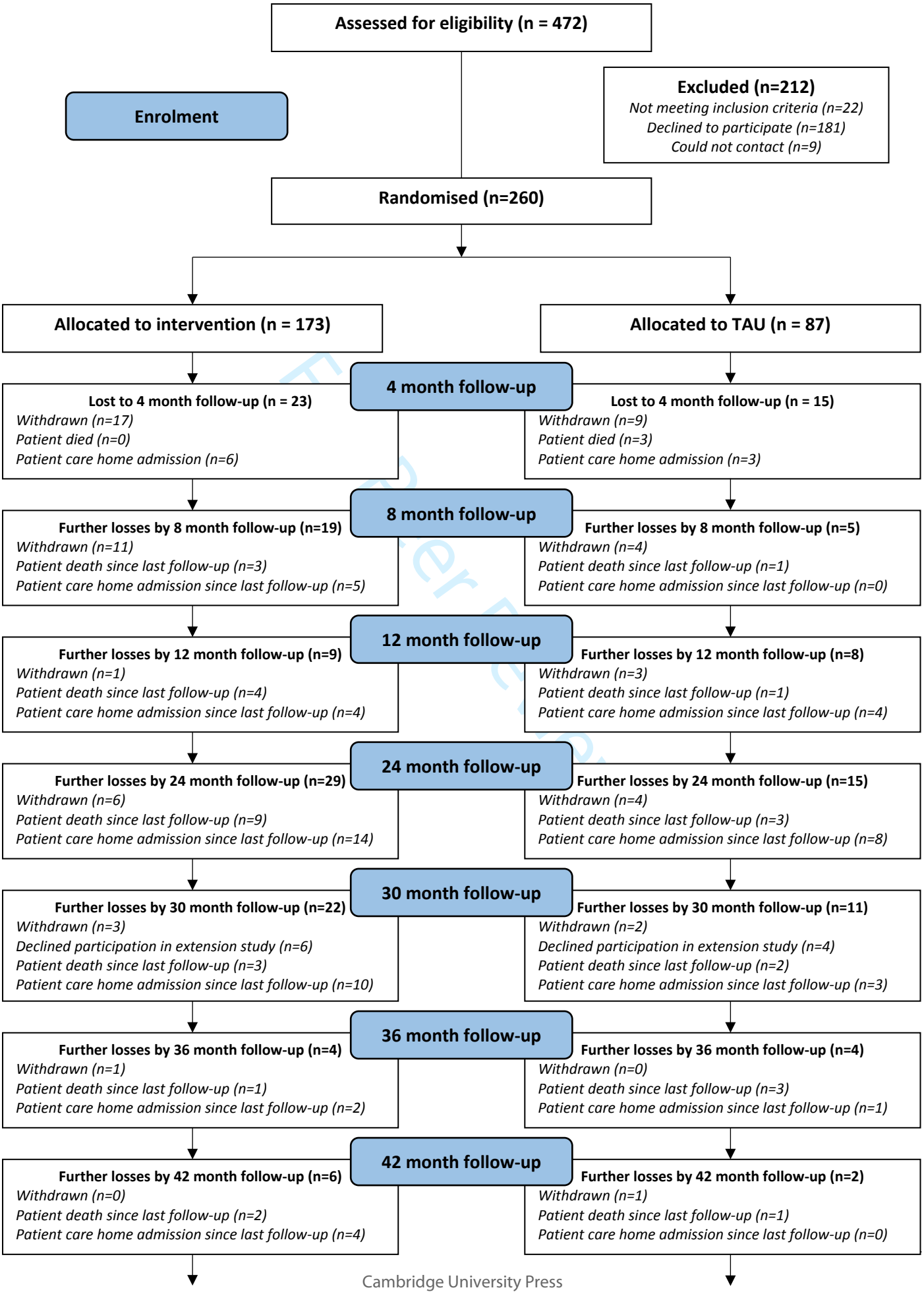
Many interventions for family carers of people with dementia have not worked in improving mood (31-33). Others have been effective but the effects have not been sustained(34). Most have not considered prevention. In general those that have been effective are multicomponent and delivered to individuals rather than groups for at least six sessions (35) (36) and our study was designed to follow this model. Some earlier interventions for family carers have been effective and had sustained effects which have continued for between one and five years(12) (13, 14). Our study is in line with this but because it is manual-based and delivered by non-clinically trained psychology graduates it is designed to be scalable and practical and has economic findings to support this. We have more fully considered cost than most other studies although there is some evidence that interventions can generate saving(37) (38). There is little evidence that carer stress predicts care home admission in community-dwelling older people in general (39) but psychological interventions for family carers may reduce care home admission for people living with dementia, with a meta-analysis of the best-quality studies finding a significant reduction in the odds of care home admission, although

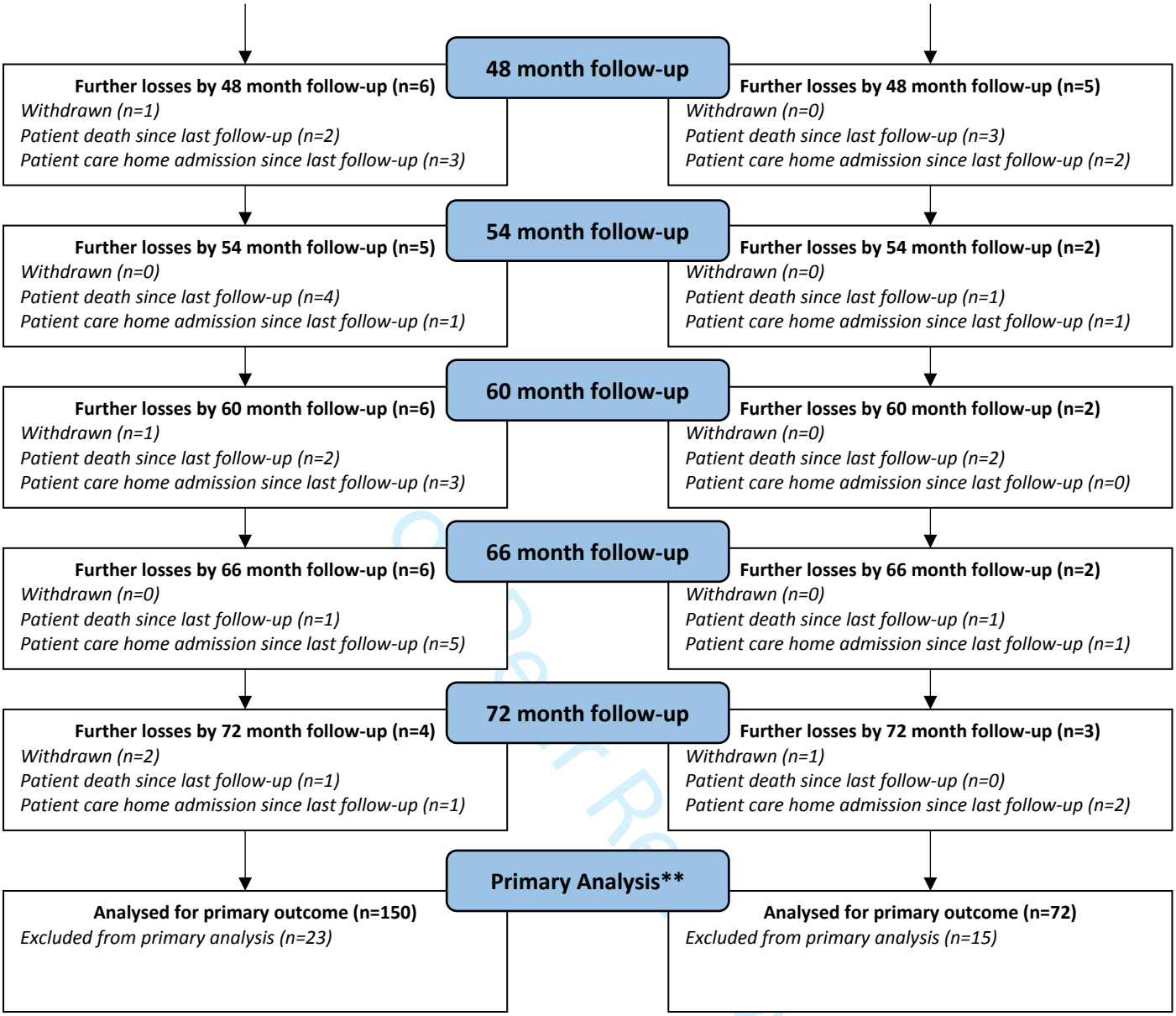
the time to admission difference did not reach significance(40). Family carers become more anxious and depressed over time without intervention; thus we included carers who were not depressed at presentation (3, 4).

Future research

The START intervention is clinically effective, improving carer mood over six years. It does not increase patient or carer service-related costs and thus should be available. The numbers of people with dementia and the diversity of culture, geographic location and available NHS resources mean that further research is necessary to widen access and optimise implementation. For example, consider whether the intervention can be delivered remotely (through a skype or similar application), through the existing voluntary sector carer support infrastructure (as some carers do not see themselves as patients) and be adapted for ethnic groups with different cultures.

Figure 1: CONSORT diagram for long-term outcomes (up to 72 months)*.





** HADS data included in the primary 72 month analysis are collected while the carer was still looking after the patient at home. Prior to 24 months, carers were followed up for HADS even after the patient had died or had been admitted to a care home. After 24 months, follow up was terminated when the patient died or was no longer at home. For the purposes of the six year follow-up analysis, observation of HADS has been censored for all patients if either death or care home admission occurred. ** To be included in the primary long term analysis, the individual must have at least one follow up score available for the HADS total.*

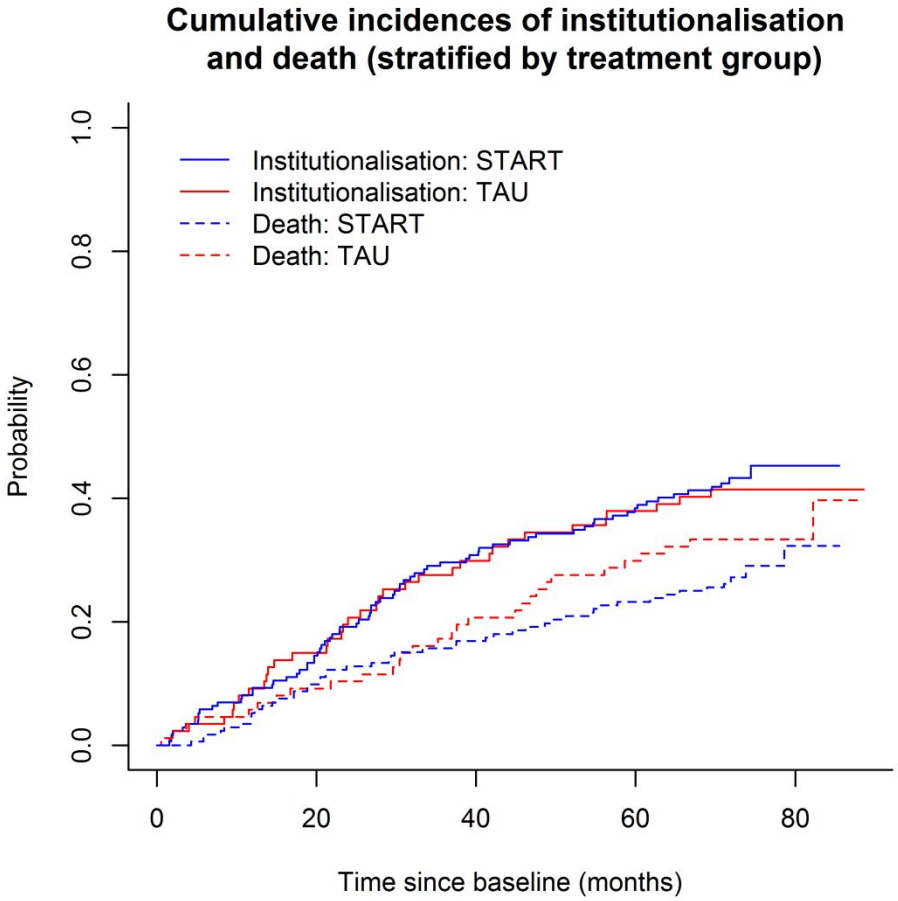


Figure 2: Plot of estimated cumulative incidence functions for the events 'care home admission' and 'death' over time, stratified by treatment group.

Table 1: Summaries of HADS total score at each follow-up time by treatment group.

Follow-up time (month)	Group	Number of observations (n)	Mean (SD)
0	TAU	87	14.8 (7.4)
	START	172	13.5 (7.3)
4	TAU	70	14.3 (7.6)
	START	146	12.3 (7.3)
8	TAU	67	14.9 (8.1)
	START	125	12.8 (7.9)
12	TAU	57	15.1 (9.0)
	START	122	12.5 (7.8)
24	TAU	44	15.6 (8.7)
	START	93	12.7 (7.2)
30	TAU	33	15.5 (7.8)
	START	65	13.0 (7.5)
36	TAU	28	15.6 (7.5)
	START	65	12.3 (7.3)
42	TAU	27	15.7 (8.7)
	START	59	13.8 (8.0)
48	TAU	22	16.5 (8.9)
	START	54	13.2 (7.3)
54	TAU	20	16.2 (7.6)
	START	49	12.1 (7.0)
60	TAU	18	17.3 (10.3)
	START	44	12.3 (8.0)
66	TAU	15	15.1 (9.5)
	START	38	13 (7.9)
72	TAU	13	17.5 (11.1)
	START	34	12.5 (9.0)

Table 2; Estimates of the effect of the START intervention compared with TAU on HADS measures over 6 years.

HADS measure	Estimates comparing intervention and TAU	
	Adjusted for centre, baseline score and time (n=222)	Adjusted for centre, baseline score, time, age, sex, NPI & Zarit (n=213)
	Difference in means (95% CI)	
HADS-T (total score)	-1.45 (-2.80 to -0.10)	-2.00 (-3.38 to -0.63)
HADS-D	-0.93 (-1.63 to -0.24)	-1.06 (-1.78 to -0.35)
HADS-A	-0.58 (-1.39 to 0.22)	-0.97 (-1.78 to -0.15)
	Odds ratio (95% CI)	
HADS-D caseness	0.30 (0.13 to 0.71)	0.20 (0.08 to 0.52)
HADS-A caseness	0.64 (0.31 to 1.32)	0.50 (0.24 to 1.07)

Table 3: Annual costs of services used by carers and patients, by year, from 25 to 72 months

		Intervention			Treatment as usual		
Time period	Services for patient or carer	N	Median	Inter-quartile range	N	Median	Inter-quartile range
25 to 36 months	Carer	82	364	132 to 704	35	269	103 to 622
	Patient	109	5764	1922 to 18,869	54	5303	1573 to 21,866
37 to 48 months	Carer	83	402	130 to 702	35	279	166 to 601
	Patient	94	6098	1767 to 20,219	44	7200	1452 to 22,346
49 to 60 months	Carer	73	390	137 to 666	28	274	178 to 587
	Patient	83	4619	1744 to 23,116	33	16,574	1524 to 24,920
61 to 72 months	Carer	53	377	184 to 635	24	274	191 to 587
	Patient	68	5759	1892 to 18,254	30	16,964	2369 to 24,077

Note: Differences between groups were tested using the non-parametric Wilcoxon rank-sum test. None were statistically significant, although the difference for 61-72 months approached statistical significance (p=0.0717).

Supplementary table 1: Baseline carer and patient demographic and clinical characteristics by randomisation group

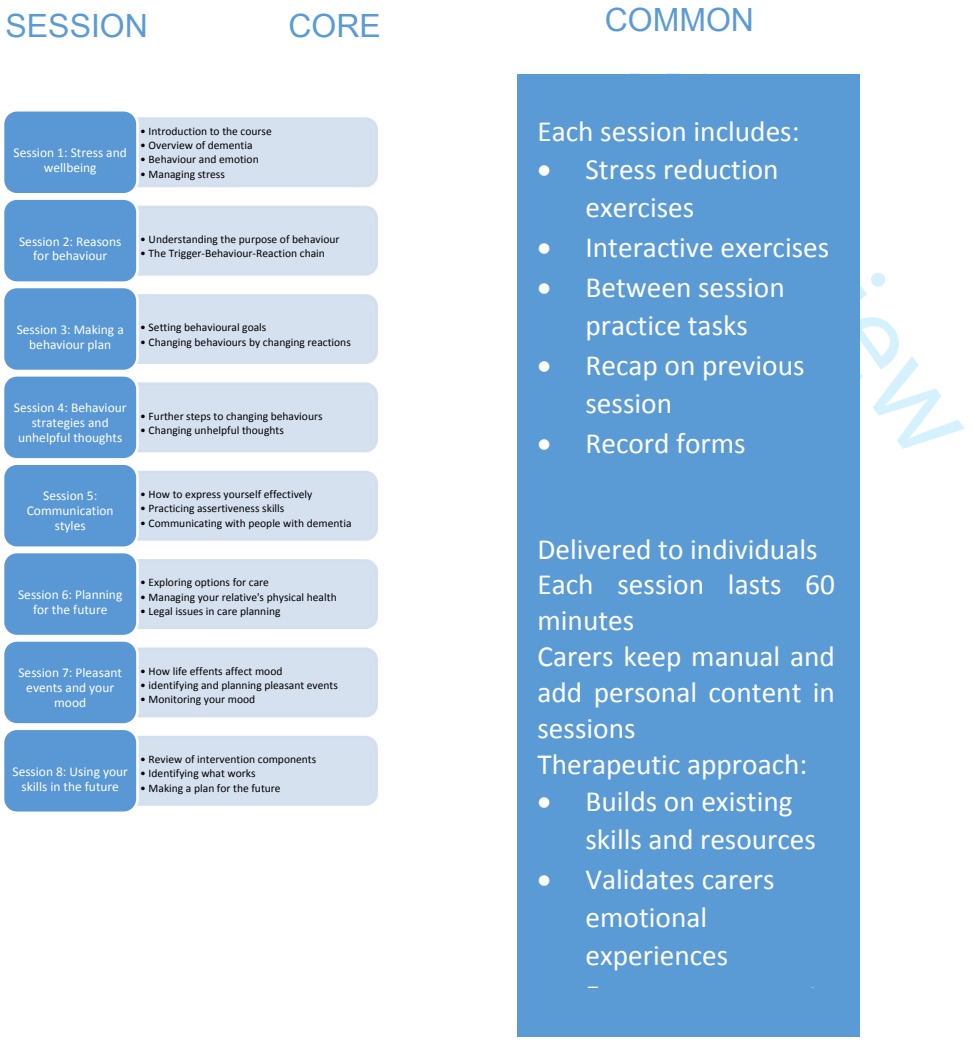
-	Carer		Patient	
	TAU (n=87)	**Intervention (n=173)**	**TAU (n=87)**	**Intervention (n=17**
Age (years)~	56.1 (12.3) range: 27,89	62.0 (14.6) range: 18,88	78.0 (9.9) range: 53,96	79.9 (8.3) range: 55,95
Sex*Female	62 (71.3%)	116 (67.1%)	50 (57.5%)	102 (59.0%)
Ethnicity*White UK	65 (74.7%)	131 (76.2%)	61 (70.1%)	126 (72.8%)
White other	5 (5.8%)	10 (5.8%)	6 (6.9%)	14 (8.1%)
Black and minority	17 (19.5%)	31 (18.0%)	20 (23.0%)	33 (19.1%)
Marital Status*Not currently married	25 (28.7%)	61 (35.3%)	47 (54.0%)	92 (53.2%)
Education*No qualifications	18 (20.7%)	45 (26.0%)	44 (51.2%)	73 (44.5%)
School level	33 (37.9%)	51 (29.5%)	16 (18.6%)	28 (17.1%)
Further education	36 (41.4%)	77 (44.5%)	26 (30.2%)	63 (38.4%)
Work *Full time	28 (32.2%)	36 (20.8%)	n/a	n/a
Part time	20 (23.0%)	27 (15.6%)	n/a	n/a
Retired	23 (26.4%)	80 (46.2%)	n/a	n/a
Not working	16 (18.4%)	30 (17.3%)	n/a	n/a
Living With Carer*	n/a	n/a	50 (57.5%)	113 (65.3%)
Relationship to patient * Partner	31 (35.6%)	78 (45.1%)	n/a	n/a
Child	42 (48.3%)	71 (41.0%)	n/a	n/a
Other	14 (16.1%)	24 (13.9%)	n/a	n/a
NPI Total~	n/a	n/a	26.6 (20.1)(n=86)	24.0 (19.0)(n=171
CDR overall Score~	n/a	n/a	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)	n/a	n/a
HADS-T score	14.8 (7.4)	13.5 (7.3)	n/a	n/a
HADS-A score	9.3 (4.3)	8.1 (4.4)	n/a	n/a

HADS-D	5.5 (3.9)	5.4 (3.8)	n/a	n/a
QOL-AD	n/a	n/a	29.9 (6.9)	30.2(6.9)
HADS Anxiety Case(score of ≥9)*	48 (55.2%)	85 (49.4%)	n/a	n/a
HADS Depression Case (score ≥9)*	17 (19.5%)	36 (20.9%)	n/a	n/a
Cost (£, over 4-month period pre-baseline)	315	218	3205	2446

HADS= Hospital Anxiety and Depression Scale, CDR =Clinical Dementia Scale MCTS= Modified Conflict Tactics Scale, Zarit = Zarit Burden Interview, NPI = Neuropsychiatric Inventory, Qol-AD = Quality of Life- Alzheimer's disease, HSQ = Health Status Questionnaire ~ Data are mean (Standard deviation) *Data are number and percentage. If some people did not complete the measure n is indicated in the table.

Supplementary figure 1

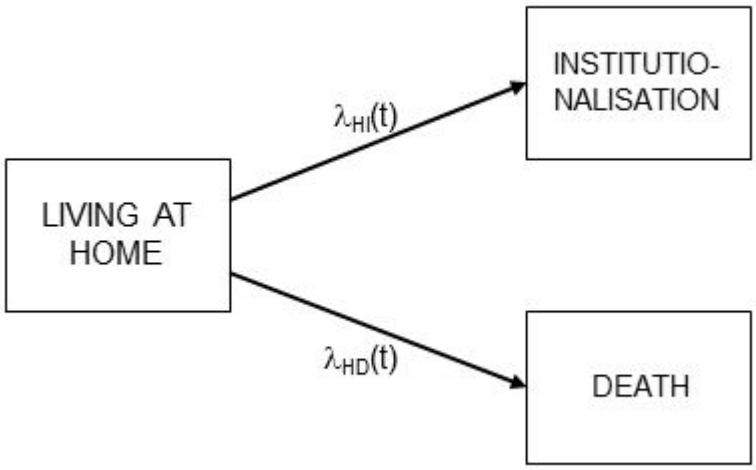
Supplementary figure 1: The START intervention



Supplementary table 2: Summaries of patient death, care home admission, withdrawal and complete follow-up by treatment group.

End Status	Number (Percentage) of participants per group		All Participants	P-value
	TAU Group	START Group		
Death	21 (24.1%)	32 (18.5%)	53 (20.4%)	0.37
Care home admission	25 (28.7%)	58 (33.5%)	83 (31.9%)	0.52
Remain in study at 72 months and not known to have died or been admitted to care home	13 (14.9%)	34 (19.7%)	47 (18.1%)	0.45
Lost to follow up/withdrawal prior to 72 months	24 (27.6%)	43 (24.9%)	67 (25.8%)	0.75
Censored at 24 months due to non-participation in extension study	4 (4.6%)	6 (3.5%)	10 (3.8%)	0.74
Total	87	173	260	

Supplementary figure 1 Multi-state model for patient care home admission and death. Direction of arrows represent the passage of time.



$\lambda_{HI}(t)$ denotes the instantaneous rate of transition from the 'living at home' state to the 'care home admission' state.

$\lambda_{HD}(t)$ denotes the instantaneous rate of transition from the 'living at home' state to the 'death' state

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: the submitted **work was supported by NIHR HTA,** no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work . GL, ZW and CC are supported by the UCLH NIHR Biomedical Research Centre. GL and PR were in part supported by the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care (CLAHRC) North Thames at Bart's Health NHS Trust. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Dr Walker reports during the conduct of the study; personal fees from GE Healthcare, grants from GE Healthcare, grants from Lundbeck, other from GE Healthcare, outside the submitted work. All other authors declare no conflicts of interest.

Transparency declaration: The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Details of contributors: GL, CC, JH, ZW, CM, PR, MK contributed to the conception and design of the study and acquisition of funding, JB GL A O'K MK, DK, RR contributed to the analytic plan. JB and A O'K analysed the clinical data. MK, DK and RR analysed the economic data. GL, CC, ZW, JH and CM led recruitment from their trusts. MM collected follow-up data to 6 years. GL drafted the article and all authors revised it critically for important intellectual content and gave final approval of the version to be published. The researchers/therapists Monica Manela, Ryan Li, Elanor Lewis-Holmes, Ruth Shanley, Amy Waugh, Lynsey Kelly, Allana Austin, Peter Keohane, Shilpa Bavishi, Amanda Shulman and Jonathan Bradley collected and entered the baseline and follow-up data to 2 years and implemented the manual. Shirley Nurock gave advice throughout as an expert family carer. GL will act as guarantor

The trial was conducted in accordance with Good Clinical Practice guidelines, the Declaration of Helsinki, the Clinical Trials Regulations and local laws and regulations. We obtained written ethics approval for the study from East London and the City Research Ethics Committee 1 for the trial (ID: 09\H0703\84) and Research and Development permission from the local trusts. All participants gave written informed consent.

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The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the HTA programme, NIHR, NHS or the Department of Health. The study was sponsored by UCL. Neither funders nor sponsors had a role in the study design and the collection, analysis, and interpretation of data and the writing of the article and the decision to submit it for publication. The researchers were independent from funders and sponsors. All researchers could access all the data.

All authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Data sharing: no additional data available

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Clinical effectiveness of START (STrAtegies for RelaTives) psychological intervention for family carers and the effects on cost of care for people with dementia: six year follow-up of a randomised controlled trial

Short title START: Six year clinical and dementia cost outcome

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Abstract

Background

START (STrAtegies for RelaTives) intervention reduced depressive and anxiety symptoms of family carers of relatives with dementia at home over two years and was cost-effective.

Aims

To assess clinical-effectiveness over six years and impact on costs and care home admission.

Methods

We conducted a randomised, parallel group, superiority trial recruiting from 04/11/2009 to 08/06/2011 with six year follow-up. 260 self-identified family carers of people with dementia were randomised 2:1 to START, an eight-session manual-based coping intervention delivered by supervised psychology graduates or Treatment as Usual (TAU). The primary outcome was affective symptoms (hospital anxiety and depression total score; HADS-T). ~~and S~~secondary outcomes included patient and carer service costs, and care home admission.

Results

222 (85.8%) of 173 carers randomised to START and 87 to TAU~~,~~ were included in the 6-year clinical efficacy analysis. Over 72-months, the intervention group compared to TAU was better on HADS-T (adjusted mean difference -2.00 points; 95% confidence interval [CI]: -3.38 to -0.63). Patient-related (START versus TAU respectively: median £5759 versus £16964 in the final year; p =0.07) and carer-related costs (median £377 versus £274 in the final year) were not significantly different between groups nor were ~~There were no significant~~ group differences in time until care home [Intensity ratio START:TAU = 0.88 (CI: 0.58 to 1.35)].

Conclusions

START is clinically effective and this effect lasts for six years without increasing costs. This is the first intervention with such a long-term clinical and possible economic benefit and has potential to make a difference to individual carers ~~whilst not increasing costs~~.

Declarations of interest

None

Word count 250

Trial Registration: ISCTRN 70017938

Word count- 3927

Introduction

Families provide most of the care to people with dementia living at home. Family carers have worse physical health, more absences from work, lower quality of life and are more likely to be anxious or depressed than non-carers(1-4). Currently around 50 million people globally have dementia, projected to nearly triple by 2050, while the present annual global cost is US$818 billion(5). Nearly 85% of costs are family and social rather than medical costs(6).

The START (STrAtegies for RelaTives) multicomponent intervention for family carers, individually delivered by supervised psychology graduates (with a first degree in psychology and ~~with~~ no clinical training), was tested by our research team in a randomised controlled trial and was the first to show both clinical-effectiveness (reduced anxiety and depressive symptoms, decreased depression caseness, improved quality of life) and cost-effectiveness for family carers of people with dementia(7, 8). ~~In summary START is a parallel-group, superiority, single-blind, randomised controlled trial (RCT) conducted in the UK (four sites). Participants were selected to represent varied clinical services, so we could see if the intervention was generalisable- a mental health trust based in a large city; a trust in a semi-rural area, a tertiary neurological clinic for rare and young-onset dementia; and a mental health trust where patients were allocated to a specialist nurse (Admiral Nurse). We recruited self-identified family carers providing at least weekly support to people with a clinical diagnosis of dementia, living in their own homes and referred to the service we recruited from during the previous year. We excluded those who were unable to give informed consent or who lived more than 1.5 hours travelling time from the researchers' base. We recruited from 04/11/2009 to 08/06/2011 through three mental health trusts and a tertiary neurology clinic. Last follow up was 28/04/2017. Participants were randomised 2:1 to intervention: TAU in order to maintain study power given the potential for clustering of outcomes by therapist in the intervention arm. We recruited 260 participants to the study.~~ Methods and results up to two years follow-up have been reported in detail elsewhere (7-11). We found that START carers had a decrease in symptom score which was greater than the minimum clinically important difference and at 8 months were one fifth as likely to have case-level depression. These benefits persisted for two years(9), when the intervention was also cost-neutral when considering health and care services used by both family carers and patients(9). To the best of our knowledge, there are no clinically and cost-effective interventions that have demonstrated effects beyond five years(12) (13, 14), and none are manualised; ~~set out in a manual~~ so the intervention can be delivered consistently to participants; ~~and delivered~~ by graduates without clinical training, with potential to implement at scale.

Objectives

Our aim is to determine the long-term (up to 6 years from baseline) clinical effectiveness of START for family carers' affective symptoms and costs compared to Treatment as Usual (TAU) in terms of:

1) Our primary outcome-Total HADS score (hospital anxiety and depression total score; HADS-T) in carers of people with dementia
2) Secondary outcomes
    - Anxiety and depression caseness and scores
    - Time until care home admission and death of the person with dementia
    - Time spent at home

- Cost of care for both people with dementia and carers

Methods

We registered a trial protocol before recruitment began https://doi.org/10.1186/ISRCTN70017938. After registration we requested and received a 5-year no-cost extension to the trial and that our primary outcome would be repeated measures of the HADS-T and registered this prior to analyses. A standard reporting protocol was used.

Intervention and delivery

We recruited 260 participants to the study. We developed the eight-session START manual-based individual coping intervention for dementia family carers from the American "Coping with Caregiving"(15). We trained and supervised non-clinically trained psychology graduates to deliver the intervention (see supplementary figure 1), and PR supervised them clinically as a group with additional time available for individual support~~and monitored intervention fidelity, which was satisfactory; researchers rated other therapist's session fidelity using a checklist out of a possible five points~~. There was a strong practical focus in the training programme on how to deliver the therapy, potential clinical dilemmas, empathic listening, effective use of supervision, safe working practise and when to ask for help. They were trained to adhere to the manual and we used role-play with senior members of the team completing a competency checklist to ensure they could deliver each session competently.~~-~~ We monitored intervention fidelity using a checklist out of a possible five points, and it was satisfactory. ~~Psychology graduates were trained as therapists and PR supervised them clinically as a group with additional time available for individual support~~. Therapists worked with carers to identify individual difficulties and to find workable solutions rather than give answers or recommendations, and implement strategies including: behavioural management, communication strategies, identifying and changing unhelpful thoughts, positive reframing, accessing support, future planning and increasing pleasant events. Each session included a relaxation exercise and we asked carers to put into practise the individualised strategies and relaxation between sessions. The final session was used to agree a plan of what to do in future based upon what that carer had felt worked. The carer kept their own manual and relaxation CDs.

~~TAU~~

In summary START is a parallel-group, superiority, single-blind, randomised controlled trial (RCT) conducted in the UK (four sites). Participants were selected to represent varied clinical services, so we could see if the intervention was generalisable- a mental health trust based in a large city; a trust in a semi-rural area, a tertiary neurological clinic for rare and young-onset dementia; and a mental health trust where patients were allocated to a specialist nurse (Admiral Nurse. ~~All carers were referred from National Health Service (NHS) clinics in the trusts in the trial.~~ We recruited self-identified family carers providing at least weekly support to people with a clinical diagnosis of dementia, living in their own homes and referred to the service we recruited from during the previous year. We excluded those who were unable to give informed consent or who lived more than 1.5 hours travelling time from the researchers' base. We recruited from 04/11/2009 to 08/06/2011 through three mental health trusts and a tertiary neurology clinic. Last follow up was 28/04/2017. Standard treatment includes medical, psychological and social interventions, consisting of assessment, diagnosis and information-giving, risk assessment and management (e.g. fire, driving, adequate nutrition and self-care, vulnerability, managing money), drug treatment, cognitive stimulation therapy, practical support,

treatment of neuropsychiatric and cognitive symptoms, assessment of capacity, help in making long-term decisions, and carer support. Patients in both groups received TAU and the use of services in both groups has been described in detail(16).

Randomisation and masking

Participants were randomised 2:1 to intervention: TAU in order to maintain study power given the potential for clustering of outcomes by therapist in the intervention arm Randomisation was stratified by centre using random permuted blocks via an online computer-generated randomisation system from an independent Clinical Trials Unit. Assessors were blinded to randomisation status, but study participants knew their allocation.

Outcome measures

We collected carer and patient socio-demographic details at baseline and we measured dementia severity using the clinical dementia rating (CDR)(17). We also administered the Neuropsychiatric Inventory (NPI)(18), as neuropsychiatric symptoms have been shown to be associated with carer psychological morbidity, and the Zarit burden interview(19). Each NPI item is scored as the product of severity and frequency giving a potential score of 0-12 and scores are summed giving a possible total from 0-144. Higher scores indicate more neuropsychiatric symptoms and more burden, respectively. We also measured carers' anxiety and depressive symptoms, using the Hospital Anxiety and Depression Scale HADS(20, 21) at baseline, 4, 8, 12 and 24 months. In an agreed extension with our funders and ethics committees we continued to collect carer HADS scores and place of residence for patients six-monthly from 24 until 72 months. We recorded the date that a patient was admitted to a care home or had died, and stopped measuring the HADS at that point. HADS is a scale, validated for all age groups and settings, in people who are physically well or ill, and in Asian and African ethnic groups(19); summarised as HADS-D (depression) HADS-A (anxiety) with scores from 0 to 21 and a total HADS score (HADS-T) from 0 to 42 (higher scores indicating more symptoms). The total score (HADS-T) is our chosen primary outcome as it has better sensitivity and positive predictive value than either of the individual scales in identifying depression, when compared to International Classification of Diseases (ICD) depression diagnosis criteria(21). HADS-D and HADS-A are also validated as scores for "caseness" and were dichotomised as "case" and "non-case", with a cut-point of ≥9 (19).

The Client Service Receipt Inventory (CSRI)(22) measured health and social care service use retrospectively until 24 months, but not beyond that point. Each carer reported their own and the patient's service use over the previous 4 months, covering the full range of services (8). Service contacts were multiplied by their unit costs (2009-10 prices) obtained from publicly available sources: NHS reference costs(23) for inpatient and outpatient attendances, and the PSSRU volume(24) for other services. Costs were discounted to present values at an annual rate of 3.5% (25).

Beyond the 24-month point, we estimated costs of services used by patients and carers up to the earliest of either withdrawal from the study, death of either patient or carer, or end of follow-up period (72 months). For patients who continued living in the community, we assumed that weekly costs remained the same as at 24 months. For patients moving to a care home, we attached a unit cost equal to the weekly charge for a private nursing home for older people (24), the most likely type of admission for someone with dementia, for the duration of stay, and we assumed that carer service use costs continued. Costs were carried forward as long as the patient/carer remained alive.

Statistical analysis

Analyses were conducted as intention-to- treat based on a predefined statistical analysis plan. Most analyses were carried out in STATA (version 14), but some models (as detailed) were fitted using R.

HADS scores

HADS data included in the primary 72-month analysis are those collected while the carer was still actively looking after the patient (i.e. patient was still living at home). Data collected after the patient had died or was admitted to a care home was excluded.

To be included in the primary long term analysis, the individual must have had at least one follow-up HADS-T score. Those excluded therefore have no follow-up measurements at any time point. Analyses compare the group as randomised, regardless of the number of therapy sessions attended in the intervention group

We used mixed effects linear regression models to assess the effect of the START intervention on repeated measurements of HADS-T over 72 months. Initially we adjusted for treatment centre, HADS-T at baseline and time, but then extended this model to include adjustments for carer age, carer sex, baseline NPI score and Zarit score. We also investigated whether the treatment effect changed over time by including a treatment by time interaction. We chose not to allow for therapist clustering in these models since previous analyses of data up to 24 months had indicated that clustering effects were negligible. As a sensitivity analysis however models were refitted allowing for therapist clustering. For all cases estimates obtained were not substantially different.

We used scatter plots of residuals and fitted values to check model assumptions. The correlation structure assumed in the main analyses was compound symmetry; however, models were refitted in sensitivity analyses with alternative structures (autoregressive (order 1) and linear spatial correlation assumptions). For all models these investigations supported the models used for the main analyses.

The analyses described for the HADS total score were repeated for anxiety and depression subscales of the HADS.

We investigated the effect of the START intervention on the occurrence of cases of anxiety/depression, using mixed effects logistic regression models, with a participant-level random effect.

If care home admission or death of the care recipient occurred prior to 72 months, the carer was not followed-up beyond the last visit prior to death or care home admission. Given the possibility of a relationship between HADS scores and death/care home admission, we conducted sensitivity analyses to consider the impact of such informative censoring. Joint mixed effect models for the longitudinal HADS scores and time to institutionalisation or death were fitted to account for the correlation between the longitudinal and survival outcomes(26). The HADS component treatment effect estimates were compared with those obtained from the previously fitted mixed models. [Note: Joint models were fitted using the `JM` package in R(27)].

Time until care home admission

We employed a multi-state model (depicted pictorially in supplementary Figure 1)(28) to analyse time until care home admission while accounting for the possibility of patient death. The model was set up to allow transition from living at home to one of two states, care home admission or death. Effect estimates from the model are 'intensity ratios' which are analogous to hazard ratio estimates in a Cox proportional hazards model but pertain to the specific

transitions within the multi-state model. As before, models were fitted adjusting for centre, carer age, carer sex, baseline NPI and Zarit score. [Note: Multi state models were fitted using the `msm` package in R(28)).

Time spent at home

In a further analysis of patient time spent at home (i.e. time prior to care home admission or death), we fitted models for time to admission or death using a standard survival analysis. We used a log rank test to make a comparison between the randomised groups and then fitted a Cox regression model to provide a treatment effect estimate adjusted for centre, carer age, carer sex, baseline HADS total, baseline NPI total and Zarit total score.

Costs

~~Costs of services used by patients and carers were estimated up to the earliest of either their withdrawal from the study, death of either the patient or carer, or end of the follow-up period (72 months). For patients who remained at home, costs of NHS and social care services used by them or their carers were extrapolated from the last complete year of data (in most cases, 12-24 months post-randomisation). For patients admitted to care homes, unit costs of care home residence were applied for the duration of stay, and we assumed that carer service use costs would continue. Costs were carried forward as long as the patient/carer remained alive. In an initial analysis, t~~The difference in costs between treatment arms at 72 months was assessed ~~statistically~~ using the non-parametric Wilcoxon Rank-Sum test(29).

Patient involvement

This study was devised and conducted with patient and public involvement (PPI) in the questions of the study and PPI representatives were on the management and steering group. They helped shape the original questions, added qualitative questions about the experience and took part in interpreting the findings. They have also presented them.

Results

Participant flow and recruitment

The Consort diagram (Figure 1) shows participant flow through the study. We randomised 260/472 (55%) of the carers referred. Others refused (n=181; 38%), did not meet inclusion criteria (n=22; 5%) or were uncontactable (n=9, 2%). We randomised 173 (67%) participants to intervention and 87 (33%) to TAU. The characteristics of the randomised groups generally achieved good balance in terms of socio-demographic and clinical characteristics (see supplementary table 1). Carers were mostly spouses/partners (109; 42%) or children (113; 44%). The proportions of patients who died (before they were admitted to a care home), were admitted to care homes and withdrew by randomised group is shown in supplementary table 2. There is no evidence of significant differences in the proportions of participants in each end-status category between the START and TAU groups.

Intervention adherence and fidelity

130 (75%) carers in the intervention group attended ≥5 therapy sessions, 8 (5%) withdrew before any therapy sessions. Ten therapists delivered the intervention, to between 11 and 32 carers each. The mean fidelity score was 4.7 (SD 0.66).

Primary outcome

Table 1 summarises HADS-T scores at each follow-up point. Analysis of HADS-T, adjusting for centre, baseline score, time and factors related to outcome (carer age and sex, NPI, Zarit) over the 6-year period, showed an average improvement in HADS-T of 2.00 points compared with TAU (95% CI: -3.38 to -0.63; p=0.005) (Table 2). In the model adjusting only for centre, baseline score and time, average score decrease was smaller but still significant and in favour

of the intervention group (Table 2). A model including an interaction with time showed no evidence of differential effects of the intervention over time (p=0.98).

Secondary outcomes

Depression and anxiety caseness and scores

In the fully adjusted analyses there was a reduced odds of HADS-depression caseness in the intervention group compared to TAU, (odds ratio (OR) =0.20 (95% CI: 0.08 to 0.52), p = 0.001). Reduction in HADS-anxiety caseness however was not significant (OR= 0.50, 95% CI: 0.24 to 1.07, p = 0.07) (Table 2).

Fully adjusted models for HADS-A and HADS-D continuous scores indicated significant beneficial intervention effects over 6 years, with average decreases of -0.97 (95% CI= -1.78 to -0.15,) and -1.06 (95% CI-1.78 to -0.35) respectively. Models showed no evidence of differential intervention effects with time for HADS-A or HADS-D (p= 0.98 and p=0.94, respectively).

Adjusted joint models were used as sensitivity analyses to allow for the possibility of a relationship between HADS scores and time to care home admission or death gave similar results to previous models for HADS-T, HADS-D and HADS-A (HADS-T: 2.01 (95% CI -3.38 to -0.63), HADS-D: -1.07 (-1.78 to -0.37)), HADS-A: -0.97 (-1.78 to -0.16)). This suggests that censoring by death/care home admission is not problematic.

Analysis of time until patient care home admission and death

Figure 2 shows the cumulative incidence of care home admission and death over time by randomised group and indicates little difference between the groups for either outcome. The multi-state model adjusted for centre, carer age, carer sex, baseline HADS-T, baseline NPI and baseline Zarit gave intensity ratios for the START intervention versus TAU of 0.88 (95% CI 0.58 to 1.35) for the home-to-care-home transition and 0.81 (95% CI 0.50 to 1.30) for the home-to-death transition, both showing no evidence of a between group difference in transition rates to care homes or in death rates. .

Analysis of time spent at home

Based on Kaplan Meier estimates, the estimated median time spent at home (i.e. time until death or institutionalisation) for the TAU group was 39.0 months (95% CI 31.1 to 49.4) and for START was 42.2 months (95% CI 33.3 to 54.7). Cox regression with adjustments for centre, carer age, baseline HADS total, NPI score and Zarit score, showed no evidence of a difference between the randomised groups (hazard ratio estimate: 0.81 (95% CI 0.59 to 1.11)).

Costs

Costs for carer and patient service use are shown in Table 3. Costs of services used by patients were much higher than costs for services used by carers across the full study period. In the final year of follow-up (61-72 months) median patient service use costs were £16,964 for TAU and £5,759 for START, ~~which is striking but not statistically significant~~ (p=0.072) ~~possibly because of the small sample by this point, and the skewed cost distribution~~. Median carer service use costs were £377 for TAU and £274 for START.

Discussion

Main findings

This is the first RCT to demonstrate that family carers of people with dementia referred to specialist care experience benefits from an intervention delivered by supervised psychology graduates in terms of depression and anxiety symptoms and depression caseness, not only in the short-term but for up to 6 years. The difference is small but is statistically significant, greater than the minimally clinically important difference (that which is clinically significant to patients)and is sustained(30). The difference in costs appears to be economically large ~~significant~~ (cost per patient in the intervention group is around a third of the cost in the treatment as usual group) although there was no significant difference in time to care home admission or death. The reduced sample size, however, means that the test for differences in cost is underpowered (particularly given highly skewed cost data), but the estimated costs of health and care services used by patients appear to be lower for the intervention group compared to treatment as usual in the final year of follow-up. It is encouraging that this intervention does not therefore increase costs, and might actually be cost-saving. Carers in the control group were five times more likely to have clinically significant depression on a rating scale validated against caseness using ICD criteria. Predictably, health and social care costs increase over time for both groups, as a result of the worsening condition. There is a bigger increase in TAU group.

Strengths and limitations

The trial is randomised, with blinded follow-ups- and we recruited the numbers of participants needed according to the power analysis based on the primary clinical outcome (7). ~~and accounts for all participants~~ The intervention was manual-based, standardised and supervised. High fidelity ratings and very low inter-cluster correlations show the results do not differ according to therapists, suggesting that the intervention can be delivered consistently.

We planned a pragmatic trial to include all family carers who presented to services so they had varied sociodemographic and clinical characteristics and came from a variety of services; consequently, our study has some external generalisability, that is, it suggests the intervention can be used in a variety of NHS settings. We did not have the power to analyse whether this intervention was more effective in subgroups; for example, those with more education or without a mental health history or with more family support. At the time of the START intervention most patients had only recently presented to services and thus the intervention can be offered at the beginning of the patient pathway but may not be applicable to those who have had the diagnosis for many years. It was preventative as well as improving depression and so can be offered to ~~everyone~~this with and without depression (7). START's preventative effect ~~highlights that carers can benefit from early intervention. A qualitative analysis confirmed~~ that carers used different components of the intervention and some continued to use these consciously over two years but we did not ask about this at six year follow up(11). Only patient care home admission and death and carer HADS were directly collected after 2 years and therefore the economic analysis involved modelling. Although the differences in costs were striking, the nature of dementia which inevitably meant attrition by death of some of those with it over six years, meant the numbers were smaller. In addition, the data ~~was~~ were skewed and they only approached the usual level taken as significant.

Comparison with other studies, meaning and implications

The practical nature of the intervention, in which carers were encouraged to develop and continue to use successful strategies, might also account for the longevity of the positive effects on carer mental health that we found – the most successful strategies were likely to be used repeatedly and therefore remembered and integrated into caring routines. The intervention included a final session on planning for the future. It is likely that the nature of caring difficulties will have evolved over six years. Intervention group participants were given a manual in which strategies they had found helpful for managing caring challenges, as well as pleasant events were recorded, and recordings of the relaxation exercises so that they had something to refer to during future caring.

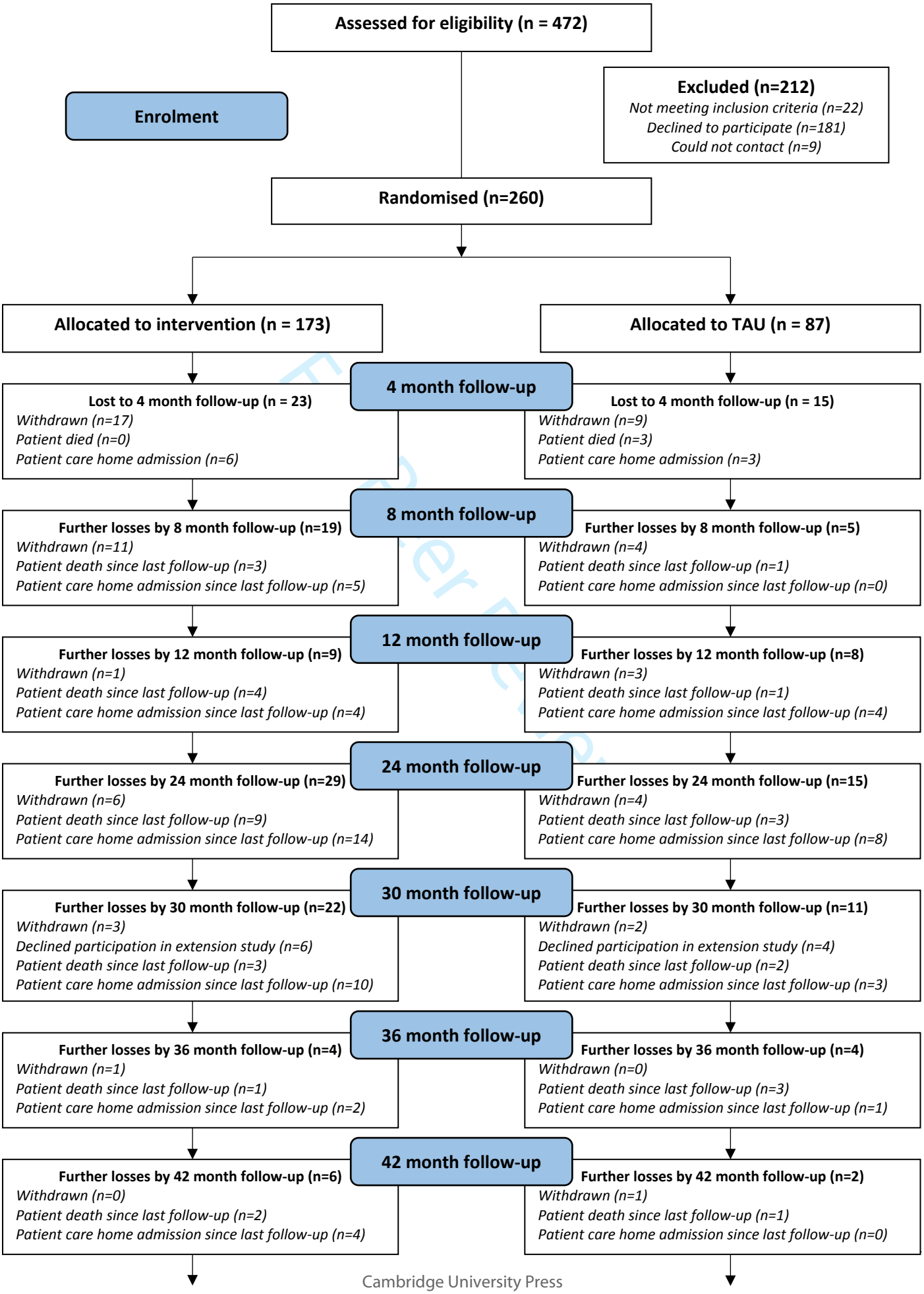
Our findings would suggest that carers were able to continue using the skills and strategies they had practiced in the longer term; a focus on planning for the future, accessing support, and explicit consideration of how difficulties may change and emotion focused and acceptance based strategies, might have helped support this. It is also possible that carers revisited previously less personally relevant aspects of the manualised intervention as certain issues or challenges became more salient to their caring.

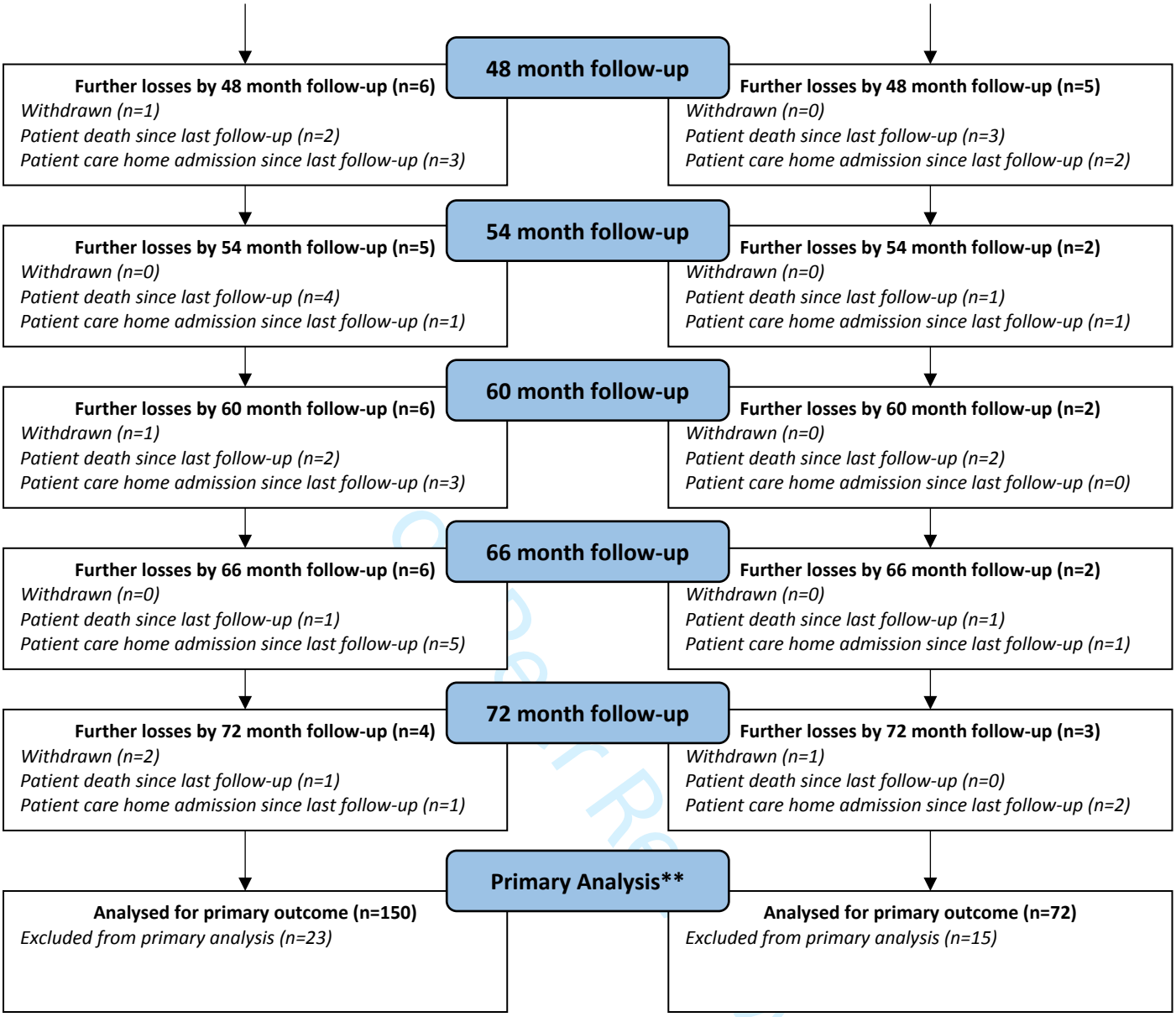
Many interventions for family carers of people with dementia have not worked in improving mood (31-33). Others have been effective but the effects have not been sustained(34). Most have not considered prevention. In general those that have been effective are multicomponent and delivered to individuals rather than groups for at least six sessions (35) (36) and our study was designed to follow this model. Some earlier interventions for family carers have been effective and had sustained effects which have continued for between one and five years(12) (13, 14). Our study is in line with this but because it is manual-based and delivered by non-clinically trained psychology graduates it is designed to be scalable and practical and has economic findings to support this. We have more fully considered cost than most other studies although there is some evidence that interventions can generate saving(37) (38). There is little evidence that carer stress predicts care home admission in community-dwelling older people in general (39) but psychological interventions for family carers may reduce care home admission for people living with dementia, with a meta-analysis of the best-quality studies finding a significant reduction in the odds of care home admission, although the time to admission difference did not reach significance(40). Family carers become more anxious and depressed over time without intervention; thus we included carers who were not depressed at presentation (3, 4).

Future research

The START intervention is clinically effective, improving carer mood over six years. It does not increase patient or carer service-related costs and thus should be available. The numbers of people with dementia and the diversity of culture, geographic location and available NHS resources mean that further research is necessary to widen access and optimise implementation. For example, consider whether the intervention can be delivered remotely (through a skype or similar application), through the existing voluntary sector carer support infrastructure (as some carers do not see themselves as patients) and be adapted for ethnic groups with different cultures.

Figure 1: CONSORT diagram for long-term outcomes (up to 72 months)*.





** HADS data included in the primary 72 month analysis are collected while the carer was still looking after the patient at home. Prior to 24 months, carers were followed up for HADS even after the patient had died or had been admitted to a care home. After 24 months, follow up was terminated when the patient died or was no longer at home. For the purposes of the six year follow-up analysis, observation of HADS has been censored for all patients if either death or care home admission occurred. ** To be included in the primary long term analysis, the individual must have at least one follow up score available for the HADS total.*

Table 1: Summaries of HADS total score at each follow-up time by treatment group.

Follow-up time (month)	Group	Number of observations (n)	Mean (SD)
0	TAU	87	14.8 (7.4)
	START	172	13.5 (7.3)
4	TAU	70	14.3 (7.6)
	START	146	12.3 (7.3)
8	TAU	67	14.9 (8.1)
	START	125	12.8 (7.9)
12	TAU	57	15.1 (9.0)
	START	122	12.5 (7.8)
24	TAU	44	15.6 (8.7)
	START	93	12.7 (7.2)
30	TAU	33	15.5 (7.8)
	START	65	13.0 (7.5)
36	TAU	28	15.6 (7.5)
	START	65	12.3 (7.3)
42	TAU	27	15.7 (8.7)
	START	59	13.8 (8.0)
48	TAU	22	16.5 (8.9)
	START	54	13.2 (7.3)
54	TAU	20	16.2 (7.6)
	START	49	12.1 (7.0)
60	TAU	18	17.3 (10.3)
	START	44	12.3 (8.0)
66	TAU	15	15.1 (9.5)
	START	38	13 (7.9)
72	TAU	13	17.5 (11.1)
	START	34	12.5 (9.0)

Table 2; Estimates of the effect of the START intervention compared with TAU on HADS measures over 6 years.

HADS measure	Estimates comparing intervention and TAU	
	Adjusted for centre, baseline score and time (n=222)	Adjusted for centre, baseline score, time, age, sex, NPI & Zarit (n=213)
	Difference in means (95% CI)	
HADS-T (total score)	-1.45 (-2.80 to -0.10)	-2.00 (-3.38 to -0.63)
HADS-D	-0.93 (-1.63 to -0.24)	-1.06 (-1.78 to -0.35)
HADS-A	-0.58 (-1.39 to 0.22)	-0.97 (-1.78 to -0.15)
	Odds ratio (95% CI)	
HADS-D caseness	0.30 (0.13 to 0.71)	0.20 (0.08 to 0.52)
HADS-A caseness	0.64 (0.31 to 1.32)	0.50 (0.24 to 1.07)

Table 3: Annual costs of services used by carers and patients, by year, from 25 to 72 months

		Intervention			Treatment as usual		
Time period	Services for patient or carer	N	Median	Inter-quartile range	N	Median	Inter-quartile range
25 to 36 months	Carer	82	364	132 to 704	35	269	103 to 622
	Patient	109	5764	1922 to 18,869	54	5303	1573 to 21,866
37 to 48 months	Carer	83	402	130 to 702	35	279	166 to 601
	Patient	94	6098	1767 to 20,219	44	7200	1452 to 22,346
49 to 60 months	Carer	73	390	137 to 666	28	274	178 to 587
	Patient	83	4619	1744 to 23,116	33	16,574	1524 to 24,920
61 to 72 months	Carer	53	377	184 to 635	24	274	191 to 587
	Patient	68	5759	1892 to 18,254	30	16,964	2369 to 24,077

Note: Differences between groups were tested using the non-parametric Wilcoxon rank-sum test. None were statistically significant, although the difference for 61-72 months approached statistical significance (p=0.0717).

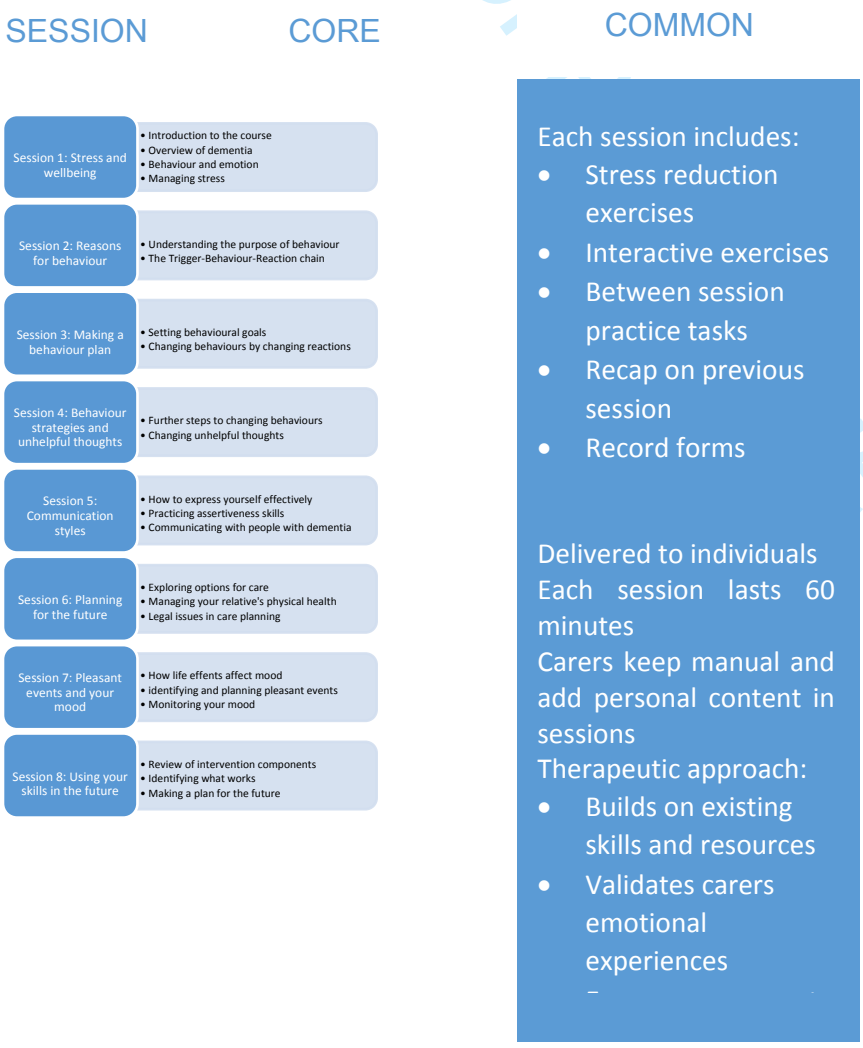
Supplementary table 1: Baseline carer and patient demographic and clinical characteristics by randomisation group

-	Carer		Patient	
	TAU (n=87)	**Intervention (n=173)**	**TAU (n=87)**	**Intervention (n=17**
Age (years)~	56.1 (12.3) range: 27,89	62.0 (14.6) range: 18,88	78.0 (9.9) range: 53,96	79.9 (8.3) range: 55,95
Sex*Female	62 (71.3%)	116 (67.1%)	50 (57.5%)	102 (59.0%)
Ethnicity*White UK	65 (74.7%)	131 (76.2%)	61 (70.1%)	126 (72.8%)
White other	5 (5.8%)	10 (5.8%)	6 (6.9%)	14 (8.1%)
Black and minority	17 (19.5%)	31 (18.0%)	20 (23.0%)	33 (19.1%)
Marital Status*Not currently married	25 (28.7%)	61 (35.3%)	47 (54.0%)	92 (53.2%)
Education*No qualifications	18 (20.7%)	45 (26.0%)	44 (51.2%)	73 (44.5%)
School level	33 (37.9%)	51 (29.5%)	16 (18.6%)	28 (17.1%)
Further education	36 (41.4%)	77 (44.5%)	26 (30.2%)	63 (38.4%)
Work *Full time	28 (32.2%)	36 (20.8%)	n/a	n/a
Part time	20 (23.0%)	27 (15.6%)	n/a	n/a
Retired	23 (26.4%)	80 (46.2%)	n/a	n/a
Not working	16 (18.4%)	30 (17.3%)	n/a	n/a
Living With Carer*	n/a	n/a	50 (57.5%)	113 (65.3%)
Relationship to patient * Partner	31 (35.6%)	78 (45.1%)	n/a	n/a
Child	42 (48.3%)	71 (41.0%)	n/a	n/a
Other	14 (16.1%)	24 (13.9%)	n/a	n/a
NPI Total~	n/a	n/a	26.6 (20.1)(n=86)	24.0 (19.0)(n=171
CDR overall Score~	n/a	n/a	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)	n/a	n/a
HADS-T score	14.8 (7.4)	13.5 (7.3)	n/a	n/a
HADS-A score	9.3 (4.3)	8.1 (4.4)	n/a	n/a

HADS-D	5.5 (3.9)	5.4 (3.8)	n/a	n/a
QOL-AD	n/a	n/a	29.9 (6.9)	30.2(6.9)
HADS Anxiety Case(score of ≥9)*	48 (55.2%)	85 (49.4%)	n/a	n/a
HADS Depression Case (score ≥9)*	17 (19.5%)	36 (20.9%)	n/a	n/a
Cost (£, over 4-month period pre-baseline)	315	218	3205	2446

HADS= Hospital Anxiety and Depression Scale, CDR =Clinical Dementia Scale MCTS= Modified Conflict Tactics Scale, Zarit = Zarit Burden Interview, NPI = Neuropsychiatric Inventory, Qol-AD = Quality of Life- Alzheimer's disease, HSQ = Health Status Questionnaire ~ Data are mean (Standard deviation) *Data are number and percentage. If some people did not complete the measure n is indicated in the table.

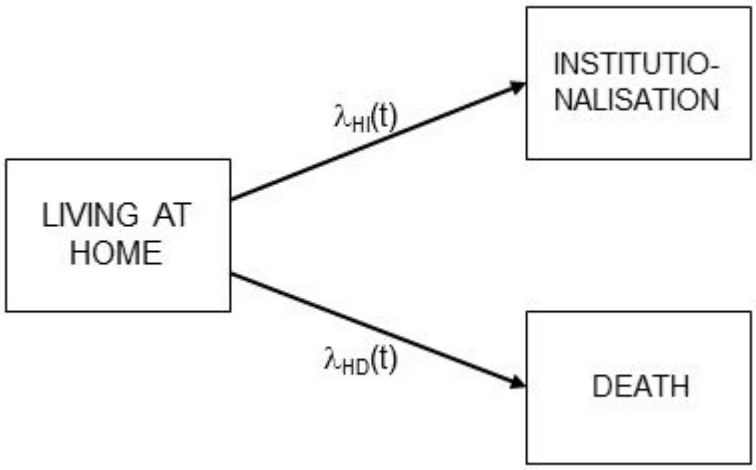
Supplementary figure 1: The START intervention



Supplementary table 2: Summaries of patient death, care home admission, withdrawal and complete follow-up by treatment group.

End Status	Number (Percentage) of participants per group		All Participants	P-value
	TAU Group	START Group		
Death	21 (24.1%)	32 (18.5%)	53 (20.4%)	0.37
Care home admission	25 (28.7%)	58 (33.5%)	83 (31.9%)	0.52
Remain in study at 72 months and not known to have died or been admitted to care home	13 (14.9%)	34 (19.7%)	47 (18.1%)	0.45
Lost to follow up/withdrawal prior to 72 months	24 (27.6%)	43 (24.9%)	67 (25.8%)	0.75
Censored at 24 months due to non-participation in extension study	4 (4.6%)	6 (3.5%)	10 (3.8%)	0.74
Total	87	173	260	

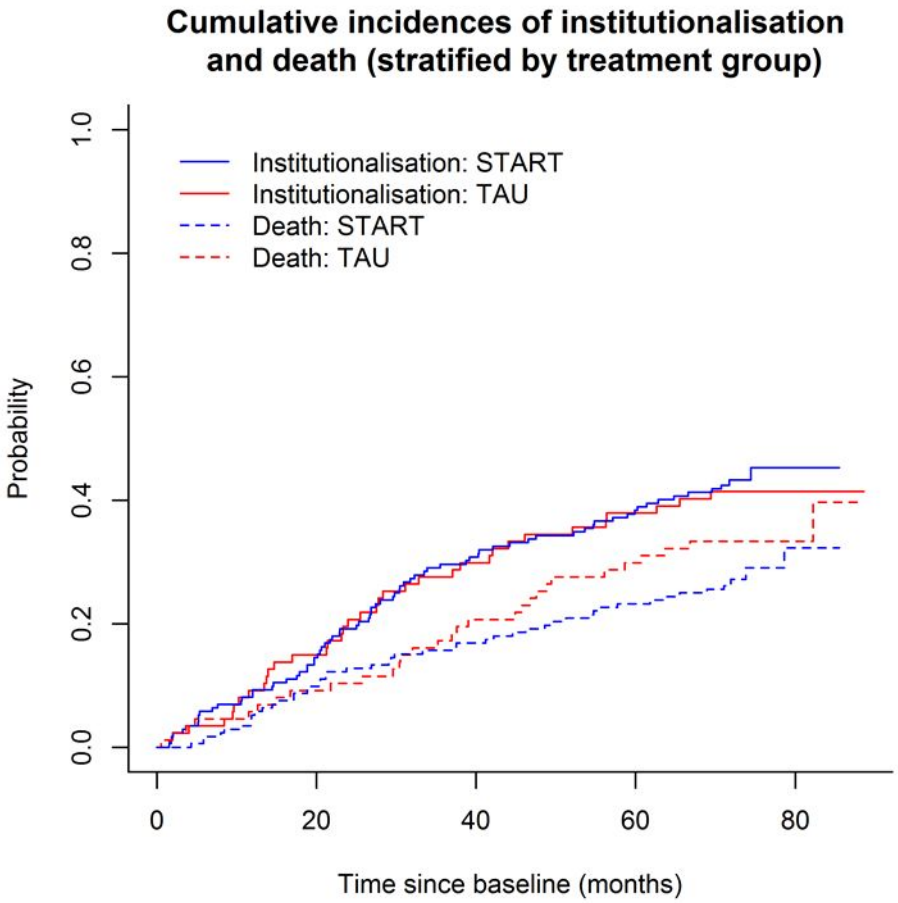
Supplementary figure 2 Multi-state model for patient care home admission and death. Direction of arrows represent the passage of time.



$\lambda_{HI}(t)$ denotes the instantaneous rate of transition from the 'living at home' state to the 'care home admission' state.

$\lambda_{HD}(t)$ denotes the instantaneous rate of transition from the 'living at home' state to the 'death' state

Supplementary Figure 3: Plot of estimated cumulative incidence functions for the events 'care home admission' and 'death' over time, stratified by treatment group.



Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: the submitted **work was supported by NIHR HTA,** no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work . GL, ZW and CC are supported by the UCLH NIHR Biomedical Research Centre. GL and PR were in part supported by the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care (CLAHRC) North Thames at Bart's Health NHS Trust. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Dr Walker reports during the conduct of the study; personal fees from GE Healthcare, grants from GE Healthcare, grants from Lundbeck, other from GE Healthcare, outside the submitted work. All other authors declare no conflicts of interest.

Transparency declaration: The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Details of contributors: GL, CC, JH, ZW, CM, PR, MK contributed to the conception and design of the study and acquisition of funding, JB GL A O'K MK, DK, RR contributed to the analytic plan. JB and A O'K analysed the clinical data. MK, DK and RR analysed the economic data. GL, CC, ZW, JH and CM led recruitment from their trusts. MM collected follow-up data to 6 years. GL drafted the article and all authors revised it critically for important intellectual content and gave final approval of the version to be published. The researchers/therapists Monica Manela, Ryan Li, Elanor Lewis-Holmes, Ruth Shanley, Amy Waugh, Lynsey Kelly, Allana Austin, Peter Keohane, Shilpa Bavishi, Amanda Shulman and Jonathan Bradley collected and entered the baseline and follow-up data to 2 years and implemented the manual. Shirley Nurock gave advice throughout as an expert family carer. GL will act as guarantor

The trial was conducted in accordance with Good Clinical Practice guidelines, the Declaration of Helsinki, the Clinical Trials Regulations and local laws and regulations. We obtained written ethics approval for the study from East London and the City Research Ethics Committee 1 for the trial (ID: 09\H0703\84) and Research and Development permission from the local trusts. All participants gave written informed consent.

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All authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Data sharing: no additional data available

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