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Abstract

Study of the use of antidepressants for depression in dementia: the HTA-SADD trial — a multicentre, randomised, double-blind, placebo-controlled trial of the clinical effectiveness and cost-effectiveness of sertraline and mirtazapine

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Objective: Depression is common in dementia, causing considerable distress and other negative impacts. Treating it is a clinical priority, but the evidence base is sparse and equivocal. This trial aimed to determine clinical effectiveness of sertraline and mirtazapine in reducing depression 13 weeks post randomisation compared with placebo.

Design: Multicentre, parallel-group, double-blind placebo-controlled randomised controlled trial of the clinical effectiveness of sertraline and mirtazapine with 13- and 39-week follow-up.

Setting: Nine English old-age psychiatry services.

Participants: A pragmatic trial. Eligibility: probable or possible Alzheimer's disease (AD), depression (4+ weeks) and Cornell Scale for Depression in Dementia (CSDD) score of 8+ . Exclusions: clinically too critical

(e.g. suicide risk); contraindication to medication; taking antidepressants; in another trial; and having no carer.

Interventions: (1) Sertraline; (2) mirtazapine; and (3) placebo, all with normal care. Target doses: 150 mg of sertraline or 45 mg of mirtazapine daily.

Main outcome measures: Outcome: CSDD score. Randomisation: Allocated 1 : 1 : 1 through Trials Unit, independently of trial team. Strati ed block randomisation by centre, with randomly varying block sizes; computer-generated randomisation. Blinding: Double blind: medication and placebo identical for each antidepressant. Referring clinicians, research workers, participants and pharmacies were blind. Statisticians blind until analyses completed.

Results: Numbers randomised: 326 participants randomised (111 placebo, 107 sertraline and 108 mirtazapine). Outcome: Differences in CSDD at 13 weeks from an adjusted linear-mixed model: mean difference (95% CI) placebo sertraline 1.17 (0.23 to 2.78; p = 0.102); placebo mirtazapine 0.01 (1.37 to 1.38; p = 0.991); and mirtazapine sertraline 1.16 (0.27 to 2.60; p = 0.112). Harms: Placebo group had fewer adverse reactions (29/111, 26%) than sertraline (46/107, 43%) or mirtazapine (44/108, 41%; p = 0.017); 39-week mortality equal, ve deaths in each group.

Conclusions: This is a trial with negative ndings but important clinical implications. The data suggest that the antidepressants tested, given with normal care, are not clinically effective (compared with placebo) for clinically signi cant depression in AD. This implies a need to change current practice of antidepressants being the rst-line treatment of depression in AD. From the data generated we formulated the following recommendations for future work. (1) The secondary analyses presented here suggest that there would be value in carrying out a placebo-controlled trial of the clinical effectiveness and cost-effectiveness of mirtazapine in the management of Behavioural and Psychological Symptoms of Dementia. (2) A conclusion from this study is that it remains both ethical and essential for trials of new medication for depression in dementia to have a placebo arm. (3) Further research is required to evaluate the impact that treatments for depression in people with dementia can have on their carers not only in terms of any impacts on their quality of life, but also the time they spend care-giving. (4) There is a need for research into alternative biological and psychological therapies for depression in dementia. These could include evaluations of new classes of antidepressants (such as venlafaxine) or antidementia medication (e.g. cholinesterase inhibitors). (5) Research is needed to investigate the natural history of depression in dementia in the community when patients are not referred to secondary care services. (6) Further work is needed to investigate the cost modelling results in this rich data set, investigating carer burden and possible moderators to the treatment effects. (7) There is scope for reanalysis of the primary outcome in terms of carer and participant CSDD results.

Trial registration: EudraCT Number 2006 000105 38.

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Contents

List of abbreviations

AD	Alzheimer's disease
AS	Alzheimer's Society
BADL	Bristol Activities of Daily Living
BPSD	Behavioural and Psychological Symptoms of Dementia
CEAC	cost-effectiveness acceptability curve
CI	con dence interval
CONSORT	Consolidated Standards of Reporting Trials
CSDD	Cornell Scale for Depression in Dementia
CSRI	Client Service Receipt Inventory
CTU	Clinical Trials Unit
DEMQOL	Dementia Quality of Life
DeNDRoN	Dementia and Neurodegenerative Disease Research Network
DIADS	Depression in Alzheimer's Disease Study
DMEC	Data Monitoring and Ethics Committee
DSM	Diagnostic and Statistical Manual
ENT	ear, nose and throat
EQ-5D	European Quality of Life-5 Dimensions
GHQ-12	General Health Questionnaire version 12
GP	general practitioner
HRQL	health-related quality of life
HTA	Health Technology Assessment
ICER	incremental cost effectiveness ratio
MH&N CTU	Mental Health & Neurosciences Clinical Trials Unit
MHRN	Mental Health Research Network
MMSE	Mini Mental State Examination
NASSA	noradrenergic and speci c serotonergic antidepressant
NB	net bene t
NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute for Health Research
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association
NPI	Neuropsychiatric Inventory
OR	odds ratio
QALY	quality-adjusted life-year
QRD	Quality Research in Dementia
RCT	randomised controlled trial
SADD	Study of Antidepressants for Depression in Dementia
SCIE	Social Care Institute for Excellence
SD	standard deviation
SE	standard error
SES	standardised effect size
SF-12	Short Form questionnaire-12 items

SSRI	selective serotonin reuptake inhibitor	TSC	Trial Steering Committee
TCA	tricyclic antidepressant	VAS	visual analogue scale

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background

Dementia is one of the most common and serious disorders in later life. Worldwide it affects 35 million people, and this will treble by 2050. In the UK there are 750,000 people with dementia and 200,000 new cases every year. It causes irreversible decline in global intellectual, social and physical functioning. In the UK dementia costs around £17B per year; worldwide, its annual cost is US$600B, with this set to at least triple in the next 20 years. The negative impacts of dementia on those with the disorder, in terms of deteriorating function, and on carers are profound. Dementia has a devastating impact across culture, gender, ethnicity and class. The need to improve care for people with dementia is a policy priority.

Depression is common in dementia, with prevalence of > 20%, causing distress, reducing quality of life, exacerbating cognitive and functional impairment, increasing mortality, and increasing carer stress and depression. Treating depression is therefore a key clinical priority to improve the well-being, quality of life and level of function of people with Alzheimer's disease (AD).

A Cochrane review (Bains J, Birks JS, Dening TR. The efficacy of antidepressants in the treatment of depression in dementia. Cochrane Database Syst Rev 2002;4:CD003944) identified only three studies, comprising 107 subjects, which had data that could be subject to a meta-analysis of efficacy. It concluded that, despite its clinical seriousness, there was only weak evidence of the effectiveness of antidepressants in dementia. Two studies used tricyclic antidepressants – 'drugs not commonly used in this population' (because of anticholinergic side effects that may negatively affect cognition, and cardiac side effects); only one used the most commonly used class (selective serotonin reuptake inhibitors). None covered newer classes of antidepressants and all were of short duration. Subsequently, the Depression in Alzheimer's Disease Study-II (DIADS)-II compared 67 people prescribed sertraline with 64 given placebo. In contrast with the DIADS study included in the Cochrane review, they found no benefit whatsoever of sertraline.

Despite the equivocal evidence, current practice is to use antidepressants, often sertraline, as a first-line treatment for depression in dementia. Given the limited evidence in this clinically important area, the Health Technology Assessment (HTA) programme of the UK National Institute for Health Research prioritised antidepressant treatment of depression in dementia as an area for primary research. They commissioned the study reported here to fill gaps in the evidence base definitively and enable the formulation of good-quality guidance on care for people with dementia and their carers.

Trial design

Multicentre parallel group double-blind placebo-controlled randomised controlled trial of the clinical effectiveness of sertraline and mirtazapine with 13- and 39-week follow-up.

Methods

Participants

This was a pragmatic trial, with inclusion criteria designed to mirror clinical practice closely. Those eligible met the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria for probable or possible AD and co-existing depression of at least 4 weeks' duration with a Cornell Scale for Depression in Dementia (CSDD) of 8+. The only exclusions were being too critical for randomisation (e.g. suicide risk); absolute contraindication

to trial medications; currently taking antidepressants; being in another trial; and having no informant to give collateral information. Participants were recruited from community old-age psychiatry services in nine English centres.

Interventions

There were three groups, (1) sertraline, (2) mirtazapine and (3) placebo, all with normal clinical care. The target dose for all participants was 150 mg of sertraline or 45 mg of mirtazapine per day.

Primary outcomes

Depression in dementia, measured by CSDD, and costs measured by the Client Service Receipt Inventory at 13 weeks.

Secondary outcomes and moderators

These included disease-specific health-related quality of life [Dementia Quality of Life (DEMQOL) and DEMQOL-Proxy]; generic quality of life [European Quality of Life-5 Dimensions (EQ-5D) interview administered to carer]; withdrawal from treatment; cognitive impairment (Mini Mental State Examination); medication adherence; adverse events; carer mental health [General Health Questionnaire version 12 (GHQ-12)]; carer quality of life (Short Form questionnaire-12 items version 2; SF-12v2); carer burden (Zarit Scale); behavioural disorder [Neuropsychiatric Inventory (NPI)]; and (at baseline) a dementia vascularity index (modified Hachinski scale).

Sample size

Initially a sample size of 507 was calculated to provide 90% power to detect a two-point CSDD difference [standard deviation (SD) 5; standardised effect size 0.4] for the sertraline–placebo and the mirtazapine–placebo comparisons at 13 weeks, and 86% power at 39 weeks.

Change to protocol

Owing to a call for extra funding following slower recruitment than predicted, the sample size needed for the trial was reassessed by statistical review by the Data Monitoring and Ethics Committee when there were 75 subjects available with 13-week follow-up data. The parameters of the sample size calculation were not changed, but the new target was calculated on the basis of reported values with greater precision than pre-study assumptions. An extended recruitment was agreed with a revised target of 339 participants.

Randomisation

Participants were allocated to placebo, sertraline or mirtazapine (1 : 1 : 1) through the Clinical Trials Unit (CTU) after baseline assessment and obtaining consent. The CTU database programmer independently undertook treatment allocation. Random allocation was stratified by centre and undertaken with a computer-generated randomisation sequence with randomly varying block sizes.

Blinding

The trial was double blind, with medication and placebo identical in appearance for each antidepressant. Referring clinicians and research workers completing assessments were kept blind to group allocation, as were patients and pharmacies. Statisticians were blind to group identity until after the analyses were completed.

Statistical methods

Significance was tested at 5%. Analyses were pragmatic, based on intention to treat. CSDD differences between treatment groups (sertraline–placebo and mirtazapine–placebo), were estimated with mixed linear regression models. Covariates were treatment group, baseline CSDD score, time and the stratification factor, and centre. A time-by-treatment interaction term was included to allow estimates at the individual time points to be summarised. The model for the CSDD incorporated random intercepts by participant. Model assumptions were checked by use of diagnostic plots. We compared categorical variables by use

of Fisher's exact test. We analysed secondary outcomes with mixed linear regression models with random participant intercepts and a time-by-treatment interaction term; covariates in the model were treatment group, baseline value of outcome, time, and treatment centre. NPI analyses utilised the generalised linear model framework, specifying a negative binomial distribution and logit link.

Health economics method

The primary economic evaluation was a cost-effectiveness analysis comparing differences in treatment costs for patients receiving sertraline, mirtazapine or placebo with CSDD score, over 0 13 weeks and 0 39 weeks. The secondary analysis was a cost utility analysis using quality-adjusted life-years (QALYs) computed from the EQ-5D and societal weights. Both the primary and secondary economic evaluations were undertaken from the perspective of (a) health and social care agencies and (b) health, social care agencies and informal carers. Health and social care costs for 0 13 months and 0 39 months (and health, social care and costs of informal care costs for the parallel analysis from the broader perspective for the same time periods) were regressed in turn on treatment allocation, baseline cost, baseline CSDD and centre. To mitigate the effects of skewness, non-parametric bootstrapping methods were used to estimate 95% con dence intervals for mean costs. Estimates of bootstrapped mean cost and effectiveness were used to estimate an incremental cost-effectiveness ratio for each analysis. The value of health effects was then expressed in terms of QALYs. Uncertainty around the costs and effectiveness estimates was addressed by plotting cost-effectiveness acceptability curves.

Results

Trial recruitment

A total of 664 individuals were screened; 326 (49%) were randomised 111 to placebo, 107 to sertraline and 108 to mirtazapine. Groups were evenly matched, and the majority of participants were female, with a mean age of 79 years; 146 (45%) were married.

Outcomes and estimation

Primary outcome: Cornell Scale for Depression in Dementia

The absolute change from baseline at 13 weeks was greatest for placebo, 5.6 (SD 4.7), compared with 3.9 (SD 5.1) for sertraline and 5.0 (SD 4.9) for mirtazapine. This difference was maintained through to 39 weeks, with change scores of 4.8 (SD 5.5) for placebo, 4.0 (SD 5.2) for sertraline and 5.0 (SD 6.1) for mirtazapine. The results from the linear-mixed modelling, after adjusting for baseline depression and centre, made clear that there was no evidence of a difference between sertraline and placebo or mirtazapine and placebo, on the CSDD score at 13 or 39 weeks. This analysis provides robust evidence of an absence of clinical effectiveness of the antidepressants tested here compared with placebo.

Secondary outcomes

There were fewer neuropsychiatric symptoms and higher carer-rated health-related quality-of-life (HRQL) scores (DEMQOL-Proxy) in participants given mirtazapine compared with sertraline; these differences did not persist to 39 weeks. Carers whose relatives were receiving placebo had higher HRQL scores at 13 weeks (SF-12v2 mental component score) and higher mental-health scores (GHQ-12) than did those whose relatives were on sertraline. Carers of participants in the mirtazapine group had better quality of life as measured by HRQL score (SF-12v2 mental component score) at 13 weeks than did those in the sertraline group.

Safety data

A total of 19 participants reported 240 adverse reactions: 29/111 (26%) in the placebo group had adverse reactions compared with 46/107 (43%) in the sertraline group ($p = 0.010$) and 44/108 (41%) in the mirtazapine group ($p = 0.031$; overall p-value for placebo vs either drug = 0.017). Overall, the number of serious adverse events reported did not differ between groups but more of these events were severe in

those on antidepressants compared with placebo (p = 0.003). Mortality did not differ between groups (ve deaths in each group by 39 weeks).

Economic analyses

In the 0- to 13-week period, there were no differences in service use between the treatment groups reaching statistical signi cance. However, taking the whole 0- to 39-week period, it was striking that the mean number of hours per week spent by unpaid carers caring for patients in the placebo-treated group and the sertraline group was almost twice that for patients in the mirtazapine-treated group. This difference in unpaid carer time between the placebo and mirtazapine-treated group was statistically signi cant at the 5% level. On the secondary measure of outcome, the mean QALY gain at 39 weeks between placebo and sertraline was 0.03 (95% CI 0.09 to 0.03); between placebo and mirtazapine 0.05 (95% CI 0.10 to 0.10); and between mirtazapine and sertraline 0.02 (95% CI 0.03 to 0.07). There were no statistically signi cant differences in either the primary or secondary measure of outcome between groups at 13 or 39 weeks. After adjustment for baseline costs, CSDD score at baseline and site, there were no statistically signi cant differences in health and social care costs (or health, social care and unpaid carer costs) in any pair-wise comparison in either time period. Mirtazapine had a low likelihood (around 30%) of being more cost-effective than placebo if society was not willing to pay anything for a unit improvement in the CSDD depression score, with this rising to 80% if society was willing to pay 5000 for a unit improvement in CSDD score. In the secondary economic evaluation, where costs were considered alongside QALYs, mirtazapine was 89% likely to be more cost-effective than placebo even if society was willing to pay nothing for a QALY gain.

Conclusions

This is a trial with negative ndings but important clinical implications. The data suggest that the antidepressants tested, given with normal care, are not clinically effective (compared with placebo) for clinically signi cant depression in AD. The data do not support the use of antidepressants as the rst-line treatment of depression in AD.

As far as we are aware, this is the rst study to explore the cost-effectiveness of mirtazapine and sertraline in treating depression in dementia. Our results show that mirtazapine and sertraline are not cost-effective compared with placebo as a treatment for depression in dementia when looking at the primary outcome of change in depressive symptoms. However, mirtazapine did halve unpaid carer time and therefore carer costs. So, when costs were considered alongside QALY gains, a different picture emerged. Mirtazapine had the highest likelihood of cost-effectiveness compared with sertraline and placebo.

We considered possible reasons for the nding that mirtazapine treatment had a good chance of being cost-effective compared with placebo or sertraline when the outcome under consideration is the QALY. The trend towards lower incremental costs for mirtazapine was driven by the statistically signi cantly lower unpaid carer inputs. The small improvements in quality of life for mirtazapine relative to the other treatments also contributed to the cost-effectiveness result, and can, perhaps, be mediated plausibly via the putative ability of mirtazapine to ameliorate sleep disturbances and anxiety. Improvements in sleep could potentially improve life quality and therefore patient-reported EQ-5D scores; they could also release carer time directly and so ameliorate an important source of carer distress. In this way mirtazapine might have a general effect, bene cial for both the patient and the carer, without exerting a speci c antidepressant effect. The potential positive effects of mirtazapine seem to act more in the realm of general behavioural and psychological symptoms in dementia than depression per se.

The data from this study provide evidence to support antidepressants not being prescribed as a rst-line treatment for people with depression in AD, who are referred to old-age psychiatry, for all but the most critical of cases (by reason, for example, of self-harm or other risk), as many cases will resolve with usual care and without sertraline or mirtazapine. Alternatives to antidepressants include the stepped

care, with `watchful waiting', which is advocated currently as best practice for the general treatment of depression (without dementia) in the community. The first step is provision of `low-intensity psychosocial interventions', with more complex psychosocial interventions as an alternative to antidepressants at the next stage of severity. Those recruited into the trial will have received non-drug `treatment as usual' provided by the community mental-health teams to whom they were referred. This will have included a broad range of supportive and problem-solving interventions, commonly delivered by a community psychiatric nurse, often in their own household. This will have focused on problems encountered by the person with dementia and the carer, covering aspects of dementia as well as depression, and ranging in intensity from low to high as needed. Identifying which components of `usual care' may be effective is an important area for future research. Other explanations for the observed changes for all cases over time include regression to the mean, and Hawthorne and placebo effects. As we find no evidence to support the use of antidepressants, we suggest that potential cases might be more appropriately managed by specialist services that are able to offer non-drug interventions for depression, perhaps avoiding the use of medication with potential for adverse reactions.

From the data generated we formulated the following recommendations for future work.

1. The secondary analyses presented here suggest that there would be value in carrying out a placebo-controlled trial of the clinical effectiveness and cost-effectiveness of mirtazapine in the management of Behavioural and Psychological Symptoms of Dementia.
2. A conclusion from this study is that it remains both ethical and essential for trials of new medication for depression in dementia to have a placebo arm.
3. Further research is required to evaluate the impact that treatments for depression in people with dementia can have on their carers, not only in terms of any impacts on their quality of life, but also the time they spend care-giving.
4. There is a need for research into alternative biological and psychological therapies for depression in dementia. These could include evaluations of new classes of antidepressants (such as venlafaxine) or antidementia medication (e.g. cholinesterase inhibitors).
5. Research is needed to investigate the natural history of depression in dementia in the community when cases are not referred to secondary care services.
6. Further work is needed to investigate the cost modelling results in this rich data set, investigating carer burden and possible moderators to the treatment effects.
7. There is scope for reanalysis of the primary outcome in terms of carer and participant CSDD results.

Trial registration

EudraCT Number 2006 000105 38.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1 Introduction

Scientific background

Dementia is one of the most common and serious disorders in later life, with a prevalence of 5% and an incidence of 2% per year in the over 65s.[1,2] Worldwide it affects 35 million people, and this will treble by 2050.[3] In the UK there are 750,000 people with dementia currently[4] and 200,000 new cases every year. It causes irreversible decline in global intellectual, social and physical functioning. Abnormalities in behaviour, insight and judgement are part of the disorder, as are neuropsychiatric symptoms such as psychosis, anxiety and depression. The economic cost of caring for people with dementia is immense. In the UK, the cost of dementia is around 17B per year,[4] greater than stroke (3B), heart disease (4B) and cancer (2B).[5] Worldwide, its annual cost is US$600B, 1% of world gross domestic product,[6] and these costs are set to at least triple in the next 20 years.[3,6] The need to improve care for people with dementia is a policy priority.[7–10] More importantly, the negative impacts of dementia on those with the disorder, in terms of deteriorating function, and on carers,[11,12] are profound. Dementia has a devastating impact across culture, gender, ethnicity and class.

Depression is common in dementia, with prevalence of > 20%,[13,14] causing distress, reducing quality of life, exacerbating cognitive and functional impairment, increasing mortality, and increasing carer stress and depression.[14–16] Treating depression is therefore a key clinical priority to improve the well-being, quality of life and level of function of people with Alzheimer's disease (AD).

We searched the PubMed and The Cochrane Library databases to 1 March 2011, without language restrictions, for full articles reporting randomised controlled trials (RCTs), systematic reviews, and meta-analyses with the search terms `depression', `dementia', `Alzheimer's disease', `antidepressant', `meta-analysis', and `CSDD' (Cornell Scale for Depression in Dementia). We excluded trials without recognised depression outcome measures, placebo controls or specified thresholds for depressive disorder. We identified one Cochrane review[17] and three systematic reviews.[18–20]

The Cochrane review Antidepressants for treating depression in dementia,[17] completed in July 2002, identified six studies with 739 subjects meeting inclusion criteria (`all relatively unconfounded, double-blind, randomized trials comparing any antidepressant drug ... with placebo, for patients diagnosed as having dementia and diagnosed as having a depression according to established criteria'). Only three studies, comprising 107 subjects, had data that could be subject to a meta-analysis of efficacy. Petracca et al.[21] studied 24 subjects in a neurological outpatient clinic in Argentina in a double-blind, placebo-controlled crossover trial of clomipramine [a tricyclic antidepressant (TCA)] with two 6-week treatment periods with a 2-week washout period. There was a mean change of 10.7 on the Hamilton Depression Scale in the intervention group and 4.5 in the control group, an equivocal outcome. Reifler et al.[22] selected 61 subjects from two university outpatient clinics in an 8-week, double-blind trial of imipramine (a TCA). The study showed no treatment effect. The third trial[23] was an interim analysis of data on 22 subjects, which, subsequently, was reported fully in Lyketsos et al.[24] These final data from the Depression in Alzheimer's Disease Study (DIADS) were not available to the Cochrane review. In the final study, 44 subjects were recruited from a single university outpatient clinic into a 12-week, double-blind, placebo-controlled trial of sertraline [a specific serotonin reuptake inhibitor (SSRI)]. An effect size of 0.51 was reported, with a mean change of 10.5 on the Hamilton Depression Scale in the intervention group and 4.5 in the control group, and 9.9 and 3.2 on the CSDD.[25] Other than the further data on the additional 22 cases reported in Lyketsos et al.,[24] and the group`s subsequent DIADS-II study,[26] which was negative and which is discussed below, we are not aware of any other studies published since then that would have met the criteria for inclusion in the Cochrane review.

The Cochrane review concluded that, despite its clinical seriousness, there was only weak evidence of the effectiveness of antidepressants in dementia. Two studies used TCAs `drugs not commonly used in this population' because anticholinergic side effects may negatively affect cognition, and cardiac side effects; only one used the most commonly used class (SSRIs). None covered newer classes of antidepressants and all were of short duration. Lyketsos et al.[24] acknowledged the need for research into the efficacy of antidepressants in a wider range of depression type and severity, longer-term treatment, and the comparative efficacy of different classes of antidepressants. Therefore, they completed a follow-up study, the DIADS-II study. This compared 67 people who were prescribed sertraline with 64 people who were given placebo. In contrast with DIADS, this study found no benefit whatsoever of sertraline at 12 or 24 weeks, and concluded that this was not a function of depression severity, depression type or severity of dementia.[26,27]

One systematic review[18] used a different quality assessment and included data from five studies of 165 participants, and concluded that antidepressants were better than was placebo for treatment response [odds ratio (OR) 2.32; 95% confidence interval (CI) 1.04 to 5.16] and remission of depression (OR 2.75; 95% CI 1.13 to 6.65) with rates of discontinuation equivalent to placebo. This did not include the DIADS-II data. The positive message of the meta-analysis of the 2010 systematic review[19] is questionable because, although it includes the DIADS-II data,[26,27] it seems to count the data from the first DIADS trial twice (i.e. by treating the interim[23] and the final trial data[24] as separate data sets when the first is a subset of the second). Finally, the 2011 study[18] concluded that the efficacy of antidepressants in people with depression and dementia is not established. The reviews and meta-analyses taken together are not conclusive but all reported that the limitations of previous trials were their small sizes, low numbers of participants taking drugs that were used in clinical practice, and short follow-up.

It is clear that the subjects recruited into all of the trials discussed above were highly selected and so there may be limitations in the generalisability of the data derived from them. One element of this is the severity of depression recruited, with Lyketsos et al.[24] and Reifler et al.[22] requiring depression to meet Diagnostic and Statistical Manual (DSM) criteria for major depressive episode. Such disorders form only a small proportion of clinically significant depression requiring intervention in older adults in the community.

All of these studies, except DIADS-II, were of short duration, and so could not tackle the crucial issue of whether or not there is longer-term benefit associated with antidepressant treatment. It is unclear whether the differential efficacy between the published studies relates to the choice of antidepressant, differences in study design and power or chance variation. Importantly, the literature does indicate that the successful resolution of depression may be associated with cognitive and functional improvements.[17] There are, however, several cautions. For example, one study of the TCA imipramine indicated that active treatment increased cognitive impairment and disability, whilst several studies of falls indicate that most antidepressants increase risk of falling. In addition, there have been safety concerns relating to the SSRI sertraline and gastrointestinal bleeding,[28] and the SSRI paroxetine and withdrawal.

Despite the equivocal evidence, current practice is to use antidepressants, often sertraline, as a first-line treatment for depression in dementia. The Quality Standards Subcommittee of the American Academy of Neurology[29] cited only `moderate clinical certainty' for antidepressants in treating depression in dementia but concluded that `SSRIs may offer some benefit with greater tolerability'. A UK primary care guideline suggests antidepressants as the only form of management for depression in dementia[30] and the UK National Institute for Health and Clinical Excellence/Social Care Institute for Excellence (NICE/SCIE) clinical guideline on dementia[31] also advocates antidepressants for depression in dementia.

Given the limited evidence in this clinically important area, the Health Technology Assessment (HTA) programme of the UK National Institute for Health Research (NIHR) prioritised antidepressant treatment of depression in dementia as an area for primary research. They commissioned the study reported here to fill gaps in the evidence base definitively and enable the formulation of good-quality guidance on care for people with dementia and their carers.

Explanation of rationale

Experimental: inclusion of an arm of the study using tricyclic antidepressants

As discussed above, there are unanswered questions concerning what class of antidepressant to choose and how long to treat. This trial was designed to attempt provide best-quality data on all of these clinically important areas.

One possible area of contention is the appropriateness of including a TCA arm in the trial. This was referred to in the original research brief. Prior to our initial submission we carried out a local consultation with people with dementia, family carers and clinicians in London, Manchester and within the Alzheimer's Society (AS). The findings of this exercise were clear. Patients, carers and clinicians all believed that it would be unacceptable to randomise people with dementia to medication with a predictable set of negative (anticholinergic, e.g. constipation, increased confusion, blurred vision, low blood pressure, drowsiness) side effects, even given the fact that the competing classes of medication had their own profile of side effects.

In addition, clinicians reported to us that their clinical practice was not to use TCAs as a first-line treatment for depression in dementia and that they believed people with dementia to be at a higher risk of harm from TCA side effects than people without dementia. Therefore, they raised questions of the clinical acceptability of a trial that included the possibility of randomisation to a TCA. To be successful we needed a large number of clinical teams to take part in case finding, and if the trial were to generate real effectiveness data then these participants needed to be an unbiased sample of all potential prescribers. On these grounds we therefore decided not to include a TCA arm but instead to compare the clinical effectiveness and cost-effectiveness (including discontinuation and adverse events) of examples of the two classes of antidepressants most in use.

In the subsequent feedback from the HTA Commissioning Board we were invited to reconsider our decision not to include a TCA arm. Therefore, we consulted the AS Quality Research in Dementia (QRD) Network. This was a panel made up of people with dementia and their carers, who advised the UK AS on research issues. The consultation was carried out by the AS Director of Research (Professor Clive Ballard). He consulted regional co-ordinators of the AS QRD and individual members of the network, representing the views of 45 QRD members, most with experience of caring for someone with dementia who has been treated with antidepressants. The purpose was to inform them about key aspects of the study, in particular whether or not it was appropriate to include TCAs as one of the treatments. All but one of the people responding strongly expressed the view that TCAs were an inappropriate treatment for people with dementia, describing a number of personal experiences where serious falls, increased confusion, urinary retention and other adverse events had resulted in a serious detrimental impact to the quality of life of the person with dementia.

We also consulted clinicians through the potential collaborating centres more widely and, again, there was a near unanimous view that it was not clinically supportable to initiate people with depression in dementia on a TCA. They also reported that the existence of such a possibility in randomisation would discourage them from entering patients into the trial. At the very least it was therefore likely that there would be substantial selection bias (both in patient acceptability and clinician referral) introduced by the inclusion of a TCA arm. We therefore decided not to include a TCA arm.

Experimental: choice of antidepressants

The selection of the best candidate antidepressants for this trial is not straightforward. Cost and power considerations dictate that an optimal design should include two active antidepressant treatments and a placebo. However, there are several cautions. One previous small RCT has indicated equivocal benefit with the TCA clomipramine[21] but other data indicate marked side effects and exacerbation of disability associated with TCA treatment. For example, one study of the TCA imipramine indicated that active

treatment increased cognitive impairment and disability,[22] and several studies of falls indicate that most antidepressants increase the risk of falls.[32] In addition, there have been safety concerns with SSRIs, with respect to withdrawal effects and the potential risk of self-harm.

Within this framework, the choice of specific antidepressant agents required careful consideration. For example, the best evidence of efficacy in people with dementia at the time of the trial design was for the SSRI sertraline, as that was the compound used in the original DIADS study.[23] But this was a very small trial and other SSRIs, such as citalopram, have also been reported to be effective in treating depression in later life, including those with dementia, but in less-well-designed studies.[33] Citalopram may have less interactions with other drugs than other SSRIs and people with dementia are usually recipients of polypharmacy. The most effective antidepressant in people without dementia available at that time was probably venlafaxine[34] but there are no RCTs in people with dementia and there are potential concerns regarding side effects in these individuals.[35] A newer antidepressant, mirtazapine, appeared to have a good safety profile and a different mode of effect and was becoming widely used in clinical practice to treat depression in people with dementia but had not been evaluated in a RCT for this indication.

In order to design and cost a trial of this sort there is a need to identify the compounds to be tested. We therefore made the decision that our trial design should include sertraline (the SSRI with the best evidence and which would be off licence by the end of the trial) and mirtazapine (the novel antidepressant with the least safety concerns). The doses chosen reflect common clinical practice for the treatment of depression in dementia and (in the case of sertraline) direct trial evidence,[24] with higher doses than those suggested here (i.e. > 150 mg of sertraline or 45 mg of mirtazapine) being seen as less appropriate in people with dementia as well as depression.

Controls: use of placebo

The research brief referred to comparison with standard care. Despite the evidence base, standard care for depression in dementia is the provision of antidepressants, with SSRIs being the most commonly used drugs.[29] Standard secondary care (and it was stipulated in the brief that the study should be people referred to secondary care) is, however, much more than just medication. It involves a detailed multidisciplinary assessment of the person with dementia and their family carers with the generation of an individualised care package for each, often with continuing monitoring and follow-up.[36] We therefore developed a study design whereby all participants receive full standard care with only the antidepressant element subject to investigation against placebo and between classes of compound.

We concluded that, at the time of the trial design, there was little convincing evidence that antidepressant treatments were more effective than placebo in treating depression in dementia in real-world clinical practice. As discussed above, the data available were generally from small-scale studies of highly selected groups of patients with depression in dementia. The research brief required a trial that could take the evidence base and clinical practice forward significantly. In these circumstances we came to the belief that a placebo group was not just ethical, but also essential. If antidepressants were indeed not effective then the placebo group might do better, as they should have had fewer side effects. We carried out a further consultation exercise on the acceptability of the inclusion of a placebo group with local people with dementia, family carers and clinicians. They were supportive of the strategy of using placebo in these circumstances, as long as its use was minimised and that the information derived from the trial would yield a definitive answer.

Run-in period

One possible element of a trial such as this is the inclusion of a run-in period. The potential value of this is to identify a group of people more likely to comply with subsequent data collection (i.e. to minimise loss to follow-up) and to identify a group of people with depression who are less likely to spontaneously recover.[37–39] It is also possible that depression scores may be reduced by psychosocial interventions,[40] some of which may be provided as part of routine care. The result of these factors is a potentially high placebo response rate in clinical trials. The research brief was clear in its call for an evaluation of antidepressants in

routine clinical practice, and it is not routine clinical practice to precede the prescription of antidepressants for depression in dementia with a trial of a non-pharmacological treatment such as exercise. Instead, we proposed the clinically relevant inclusion criterion for the trial that the depression should have been present for at least 4 weeks.

Specific objectives

The primary objective was to determine the clinical effectiveness and cost-effectiveness of a SSRI (sertraline) and a noradrenergic and specific serotonergic antidepressant (NASSA; mirtazapine) in reducing depression (measured by CSDD) 13 weeks post randomisation compared with placebo.

Secondary objectives included clinical effectiveness at 39 weeks; differences in adverse events; other outcomes (e.g. quality of life, cognition, carer burden, carer quality of life); and the influence of clinical characteristics (e.g. dementia severity, dementia type, depression type, depression severity, and neuropsychiatric symptoms).

Chapter 2 Methods

Trial design

A multicentre, parallel group, double-blind placebo-controlled RCT of the clinical effectiveness of two antidepressants, mirtazapine and sertraline, with 13- and 39-week follow-up (1 : 1 : 1 allocation).

Participants

Eligibility

This was a pragmatic trial, with inclusion criteria designed to mirror clinical practice closely. Those eligible met NINCDS/ADRDA criteria for probable or possible AD[41] and co-existing depression of at least 4 weeks' duration. A local research worker then assessed their depression severity using the CSDD.[25] Those scoring 8+ were eligible for the trial. The only exclusions were those who were clinically too critical for randomisation (e.g. suicide risk); absolute contraindication to trial medications; those currently taking antidepressants; those in another trial; and those having no family or professional carer to give collateral information.

Settings and location

Participants were recruited from community old-age psychiatry services in nine English centres (Birmingham, Cambridge, Leicester, Liverpool, Manchester, Newcastle, north London, Southampton, and south London and Kent).

Interventions

There were three groups: (1) sertraline, (2) mirtazapine and (3) placebo, all with normal clinical care. The target dose was for all participants was 150 mg of sertraline or 45 mg of mirtazapine per day. Drugs and their placebo were identically presented with participants aiming to take six tablets orally once a day (up to three sertraline 50 mg or sertraline placebo; and up to three mirtazapine 15 mg or mirtazapine placebo).

Outcomes

Co-primary outcomes

Depression in dementia, measured by CSDD,[25] and costs measured by the Client Service Receipt Inventory (CSRI)[42] at 13 weeks.

Secondary outcomes and moderators

These included: disease-specific health-related quality of life [Dementia Quality of Life (DEMQOL) and DEMQOL-Proxy];[43] generic quality of life [European Quality of Life-5 Dimensions (EQ-5D) interview administered to carer][44] withdrawal from treatment; cognitive impairment [Mini Mental State Examination (MMSE)];[45] medication adherence; adverse events; carer mental health [General Health Questionnaire (GHQ-12)];[46] carer quality of life (SF-12v2)[47] and carer burden (Zarit Scale);[48] behavioural disorder [Neuropsychiatric Inventory (NPI)];[49] and (at baseline) a dementia vascularity index (modified Hachinski scale).[50]

Data entry

The data arising from each baseline or follow-up interview were entered at each centre via the internet using the InferMed Macro electronic data capture system by the researchers as the study proceeded. The data entry system used was Macro version 3.0 (InferMed, London, UK). Prior to data base lock, all of the primary outcome measures and 10% of all other outcome measures were source data veri ed. Table 1 summarises the measures that were used at each assessment time point.

Sample size

Initially a sample size of 507 was calculated to provide 90% power to detect a two-point CSDD difference [standard deviation (SD) 5; standardised effect size (SES) 0.4] for the sertraline placebo and the mirtazapine placebo comparisons at 13 weeks, and 86% power at 39 weeks. This allowed 20% loss to follow-up, correlation between baseline and outcome CSDD ≥ 0.6, and up to 12.5% of participants to either drop out or drop in using an analysis of covariance with two-sided 5% signi cance levels. This allowed for two-sided 95% CIs for the difference in the proportion of adverse events between the groups of (a clinically signi cant) 10%.

Change to protocol

Owing to a call for extra funding following slower recruitment than predicted, the sample size needed for the trial was reassessed by statistical review by the Data Monitoring and Ethics Committee (DMEC) when there were 75 subjects available with 13-week follow-up data. The parameters of the sample size calculation were not changed (SD 5, SES 0.4), but the new target was calculated on the basis of reported values that had greater precision than did the pre-study assumptions. An extended recruitment period was agreed, with a revised target of 339 participants for the sample (113 in every group). This change involved unmasking of a statistician (Clare Rutterford, Clinical Trials Unit, King's College London, UK), who was not involved in the nal analyses, to the identity of patients in the placebo group.

Randomisation

Participants were allocated to placebo, sertraline or mirtazapine (1 : 1 : 1) through the Mental Health & Neurosciences Clinical Trials Unit (MH&N CTU) after baseline assessment and obtaining consent. The MH&N CTU database programmer independently undertook treatment allocation. Random allocation was strati ed by centre and undertaken with a computer-generated randomisation sequence with randomly varying block sizes (block sizes of three or six). Allocation was physically carried out during working hours from Monday to Friday.

Blinding

The trial was double blind, with medication and placebo identical in appearance for each antidepressant. Referring clinicians and research workers completing baseline and follow-up assessments were kept blind to group allocation, as were patients and pharmacies. Statisticians were blind to group identity until after the analyses were completed.

TABLE 1 Research assessment by time point

Assessment	Informant	Screening	Registration	Baseline	Randomisation	Ongoing	Week 4	Week 8	Week 13	Week 39	Withdrawal
Verbal consent to referral to recruiting PI	Patient/carer	7									
Eligibility assessment	Referring and recruiting, PI/RW	7									
Exclusions	Patient/carer	7									
Informed consent and registration	Patient/carer		7								
Demographics	Patient/carer		7								
Randomisation	Patient				7						
Carer medication preference	Carer			7							
Pill count	Carer					7					
Medical history	Carer					7					
CSDD	Patient/carer, RW			7			7	7	7	7	7
NPI	Carer			7					7	7	
DEMQOL-Proxy	Carer			7					7	7	
DEMQOL	Patient			7					7	7	
BADL	Carer			7					7	7	
CSRI	Carer			7					7	7	
Zarit Carer Burden Scale	Carer			7					7	7	
SF-12 v2 (carer)	Carer			7					7	7	
GHQ-12 (carer)	Carer			7					7	7	

continued

TABLE 1 Research assessment by time point (continued)

Assessment	Informant	Screening	Registration	Baseline	Randomisation	Ongoing	Week 4	Week 8	Week 13	Week 39	Withdrawal
CGI	Carer								7	7	
MMSE	Patient			7					7	7	
EuroQol (participant)	Patient			7					7	7	
EuroQol (carer)	Carer			7					7	7	
Olin (Depression in Dementia)	Carer			7					7	7	
Medication guess	Patient/carer								7	7	
Concomitant therapies	Patient/carer					7					
Concomitant medications	Patient/carer					7					
Trial medication log	Patient/carer					7					
Non-serious adverse event	Patient/carer					7					
Serious adverse event	Patient/carer					7					
Withdrawal form	Patient/carer										7

BADL, Bristol Activities of Daily Living; CGI, Carer Global Impression; PI, principal investigator; RW, research worker.

Statistical methods

The statistical analysis plan was nalised and approved by the Trial Steering Committee and the DMEC. Signi cance was tested at 5% level for all analyses. Analyses were completed in Stata version 11 (StataCorp LP, College Station, TX, USA). Analyses were pragmatic, based an intention to treat sample.

Descriptive statistics

All baseline data were summarised by treatment groups. Only descriptive statistics were utilised; no formal statistical comparisons were undertaken. Continuous variables were reported as means and SDs, categorical variables are presented as frequencies (n) and percentages (%).

Primary analyses

The CSDD differences between treatment groups (sertraline placebo and mirtazapine placebo) were estimated with mixed linear regression models. Covariates were treatment group, baseline CSDD score, time and the strati cation factor, and centre. A time-by-treatment interaction term was included to allow estimates at the individual time points to be summarised. The model for the CSDD incorporated random intercepts by participant. Model assumptions were checked by use of diagnostic plots.

We did modelling with the assumption that data were missing at random, and included predictors of missing data (treatment group and centre) in the modelling. We used a logistic model to assess predictors of missing data (examination of all baseline clinical and demographic variables).

Secondary analyses

We compared categorical variables by use of Fisher's exact test. We analysed secondary outcomes with mixed linear regression models with random participant intercepts and a time-by-treatment interaction term; covariates in the model were treatment group, baseline value of outcome, time, and treatment centre. The more detailed NPI analyses utilised the generalised linear model framework, specifying a negative binomial distribution and logit link. The modelling was cross sectional at each time point (13 and 39 weeks); covariates in the model were treatment group, baseline value of outcome and treatment centre. All analyses results are summarised at 13 weeks and 39 weeks with two-sided 95% CIs.

Health economics: methods

Economic evaluation

The primary economic evaluation was a cost-effectiveness analysis comparing differences in treatment costs for patients receiving sertraline, mirtazapine or placebo with differences in effectiveness as measured by the primary outcome, total CSDD score, over two time periods: 0 13 weeks and 0 39 weeks. The secondary analysis was a cost utility analysis using quality-adjusted life-years (QALYs) computed from the EQ-5D and societal weights over those same periods. Both the primary and secondary economic evaluations were undertaken from the perspective of (a) health and social care agencies and (b) health, social care agencies and informal carers. A measure of quality of life was appropriate for the secondary analysis as it was recognised that trial medication not only has a potential impact on depressive symptoms, but also may affect areas of functioning including self-care and usual activities.

Resource use

Resource-use data for each person were collected over a retrospective period of 6 months before randomisation. At 13 weeks, follow-up data were collected retrospectively for a 3-month period and at 39 weeks for a retrospective period of 6 months. Services and support received by the study participants were recorded on a resource-use questionnaire adapted from the Client Service Receipt Inventory (CSRI),[51] including inpatient stays, outpatient attendances, day hospital treatment, visits to social clubs, meals at lunch clubs, day care visits, hours spent in contact with community-based professionals, such as community teams for older people, community psychologists, community psychiatrists, general

practitioners (GPs), nurses (either practice, district or community psychiatric), social workers, occupational therapists, paid home help or care workers, and physiotherapists. The study also collected data on the use of voluntary organisation services, such as volunteer support, befriending and telephone care line support, and also on unpaid support provided by friends and relatives. Contacts made with voluntary support and support provided by friends and relatives were also measured in physical units, such as hours of care support time. The prescribed daily doses for the medications were calculated from the trial medication log, and prescribing periods were weighted to the changing dose regime.

Unit costs

All unit costs were estimated at 2009 10 prices and were collected from sources in the public domain. Unit costs are summarised in Table 2. Costs per unit of measurement for each type of service (such as per inpatient day, per appointment, per attendance, per visit or per contact with health and community-based professionals including voluntary services) were taken from Curtis.[52] The National Health Service Schedule of Reference Costs[53] was used to estimate the cost of outpatient attendances. The unit cost of medication was obtained from the British National Formulary.[54]

We collected information on the volume and nature of informal care inputs, mindful of the dif culties of measuring such dimensions and of their interpretation as inputs to the care process. Costs were attached to informal care inputs using a replacement cost the unit cost of a paid local authority home care worker.[52] This approach allowed us to quantify how much it would cost to replace the informal carer with the services from the market. In sensitivity analyses we examined whether or not the cost-effectiveness results would change under other assumptions.

Cost estimation

Three main categories of costs were analysed: medication costs, aggregated health and social care costs (primary care and hospital outpatient visits, inpatient admissions and community-based health and social care), and cost of time spent care-giving by relatives and friends. Costs were categorised in this way to facilitate the comparison of costs alongside measures of effectiveness from the perspectives of the economic analysis previously de ned. The costs of services and support used by patients were derived by combining medication, health and social care resource utilisation data with estimated unit costs. Costs were calculated for the periods 0 13 weeks and 0 39 weeks.

Statistical analysis

Cost data were analysed in a similar way to the effectiveness data. Health and social care costs for 0 13 months and 0 39 months (and health, social care and costs of informal care costs for the parallel analysis from the broader perspective for the same time periods) were regressed in turn on treatment allocation, baseline cost, baseline CSDD and centre. To mitigate the effects of skewness, non-parametric bootstrapping methods which avoid the distributional assumptions of parametric testing by use of resampling were used to estimate 95% CIs for mean costs. Where the bias-corrected 95% CIs of between-group change scores excluded zero, they could be judged to be signi cant at $p = 0.05$.

Estimates of bootstrapped mean cost and effectiveness were used to estimate an incremental cost-effectiveness ratio (ICER) for each analysis. The incremental cost-effectiveness ratio for each replication was calculated as $[(cost_b - cost_a)/(effect_b - effect_a)]$, which summarises the cost difference between two treatments per incremental difference in the outcome (CSDD and EQ-5D in turn). The EQ-5D was measured directly from patients as recommended by NICE guidelines (2008) and weighted by a valuation of changes in quality of life reported from UK population data. The value of health effects was then expressed in terms of QALYs. The ratio statistic compared the treatments in terms of observed differences in costs and effects, regardless of whether or not the difference in costs and effects was statistically signi cant.

Uncertainty around the costs and effectiveness estimates was addressed by plotting cost-effectiveness acceptability curves (CEACs). A CEAC assesses trade-offs between costs and outcomes, showing the

TABLE 2 Unit costs for 2009 10

Service	Unit cost ( )	Source
Inpatient (bed-days)	299	Curtis 2010[52]
Day hospital (attendance)	50 205	NHS reference costs 2009 10,[53] Curtis 2007,[55] Curtis 2010[52]
Outpatient (appointment)	21 165	NHS reference costs 2009 10[53]
Accident and Emergency (attendance)	37, 97	Curtis 2010[52]
GP (per surgery consultation)	28	Curtis 2010[52]
Geriatrician (minutes)	1.83	Curtis 2010[52]
Nurse (minutes)[a]	0.43 0.52	Curtis 2010[52]
Occupational therapist (minutes)	0.65	Curtis 2010[52]
Community psychiatrist (minutes)	1.83	Curtis 2010[52]
Counsellor (minutes)	0.57	Curtis 2010[52]
Psychologist (minutes)	1.20	Curtis 2010[52]
Chiropodist (contact)	0.37	Curtis 2010[52]
Social worker (minutes)	0.67	Curtis 2010[52]
Care manager (minutes)	0.82	Curtis 2010[52]
Home care worker/care attendant (minutes)	0.35	Curtis 2010[52]
Sitting scheme (minutes)	0.45	Curtis 2010[52]
Self-help group (minutes)	0.57	Curtis 2010[52]
Meals on wheels (meal)	4.8	www.ic.nhs.uk/web les/publications/009_Social_Care/pss0910exp nal/pss0910updateOct2011/Personal_Social_Services_Expenditure_Report_2009_10.pdf
Dentist (minutes)	2.90	NHS reference costs 2009 10[53]
Optician (minutes)	0.48	Individual calculation[b]
Day care (day)	42 66	Curtis 2010[52]
Lunch club (meal)	7	http://cash-online.org.uk/content/1/6/3/; uprated using the Consumer Price Index (CPI)
Social club (session)	5	Cost of adult social club at 2004 5, uprated using the pay and prices in ator (Curtis 2010[52])

a Practice nurse, district nurse health visitor, community psychiatric nurse, cardiac nurse and incontinence nurse.

b There is a recommended fee payable to for ophthalmic medical practitioners who administer sight tests; however, optometrists undertake the majority of tests. The salaries of optometrists can vary, depending on the setting in which they practice (private, hospital, or combination of the two). The range of typical salaries in private practice based on salary data collected June 2009 (www.prospects.ac.uk/optometrist_salary.htm) was 19,500 28,000, whereas in hospital optometrists are usually covered by the Agenda for Change pay scale consisting of nine pay bands. Typical salaries for the pre-registration year start at 18,152 (band 4). Typical starting salaries range from 25,472 34,189 (band 6). Specialist optometrists can earn 30,460 40,157 (band 7) and principal optometrists 38,851 55,945 (band 8a/8b). Typical salaries for consultant optometrists range from 54,454 to 80,810 (band 8c/8d). Working hours are usually 0900 to 1730, Monday to Saturday. Hours worked can vary, but optometrists generally work 38 hours per week. The average salary for private practice was used. The cost per hour was estimated, based on 41 weeks per annum, 38 hours per week.

likelihood of each of the two medications in turn being seen as cost-effective relative to the other or relative to placebo, given different (implicit monetary) values placed on incremental outcome improvements. In this net bene t (NB) approach, monetary values of incremental effects and incremental costs for each case are combined, and the net bene t derived as:

$$NB = (effect_b \quad effect_a) \quad (cost_b \quad cost_a) \tag{1}$$

where a = control, b = drug treatment, NB = net bene t and = willingness to pay for unit improvement in CSDD-depression severity score or an additional QALY.

The impact on costs given uncertainty around the value attached to informal care inputs was assessed in one-dimensional sensitivity analysis.

All analyses were carried out in Stata version 11 and SPSS 17 (SPSS Inc., Chicago, IL, USA).

Chapter 3 Results

Participant flows

The CONSORT (Consolidated Standards of Reporting Trials) diagram, below, shows the flow of participants through the trial (Figure 1).

Withdrawal from treatment implies that the participant remains in the trial. Withdrawal from the trial implies the participant withdrawal from the trial and treatment. These two categories are mutually exclusive.

Trial recruitment

Over the course of the trial there were nine recruiting sites, all in the UK. These were Birmingham, Cambridge, Leicester, Liverpool, Manchester, Newcastle, north London, Southampton and south London and Kent. Randomisation was stratified by site; all sites successfully recruited. Recruitment began in December 2006 and ended in January 2010. Follow-up interviews were completed by October 2010. In total, 664 individuals were screened as potential participants; of these 326 (49%) were randomised. The overall recruitment rate is shown in Figure 2. The number of participants recruited per site ranged from 7 to 60.

Baseline data

In total 326 participants were randomised in the trial; 111 to the placebo arm, 107 to the sertraline arm and 108 to the mirtazapine group. All participants completed the CSDD baseline questionnaire. Baseline demographics are summarised for participant and carers. The total number of collected questionnaires completed is featured. Table 3 shows the participant and carer demographics, whereas data collected on clinical characteristics is summarised in Table 4. Groups were evenly matched.

The majority of participants were female, and had a mean age of 79 years, ranging from 47 to 98 years. In total, 146 (45%) of participants were married and the majority ethnicity was white.

The carers ranged in age from 22 to 95 years, with a mean age of 61 years. Again, the majority were female, but a higher proportion of the carers were married (63%) compared with the participants. On average 23% of carers were paid workers.

Clinical characteristics of participants and carers are shown in Table 4. Completeness of data varies from 74% MMSE to 100% CSDD, primary outcome measure. Clinical characteristics are balanced over treatment arms. Participant qualities of life have worst outcomes when rated by carers in comparison with the participant rating of equivalent scales.

The mean overall dosages (including participants who withdrew from medication) were 70 mg (SD 52) per day for sertraline and 24 mg (16) per day for mirtazapine. For participants who remained on prescribed medication the mean dose was 95 mg (36) per day for sertraline and 30 mg (23) per day for mirtazapine.

Data collection

The mean (SD) time interval between randomisation and completion of questionnaires was 18.2 (14.19) weeks at the 13-week assessment time point and 42.15 (10.7) weeks at the 39-week assessment. The

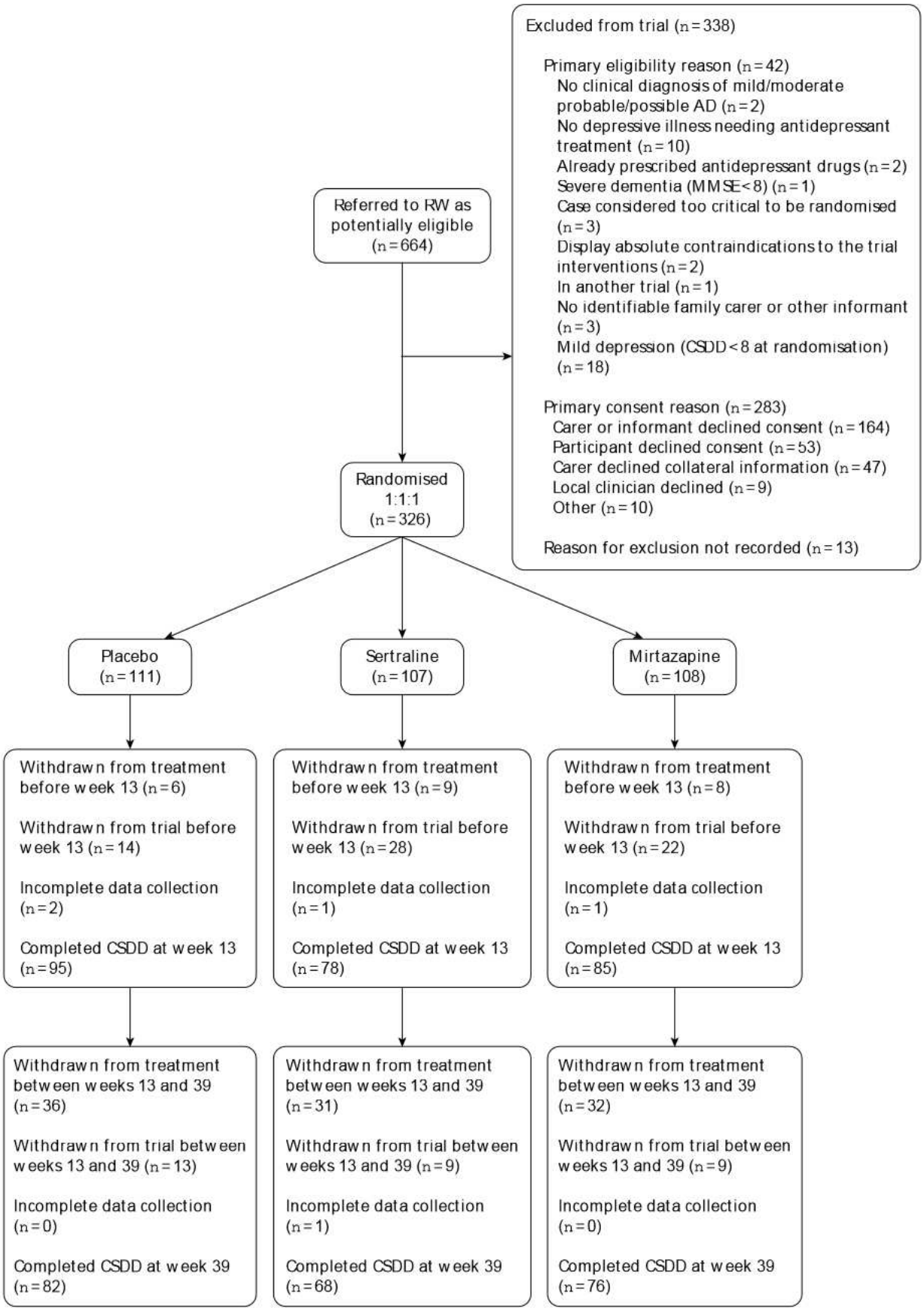

FIGURE 1 Participant flows in the Health Technology Assessment-Study of Antidepressants for Depression in Dementia (HTA-SADD) trial. RW, research worker.

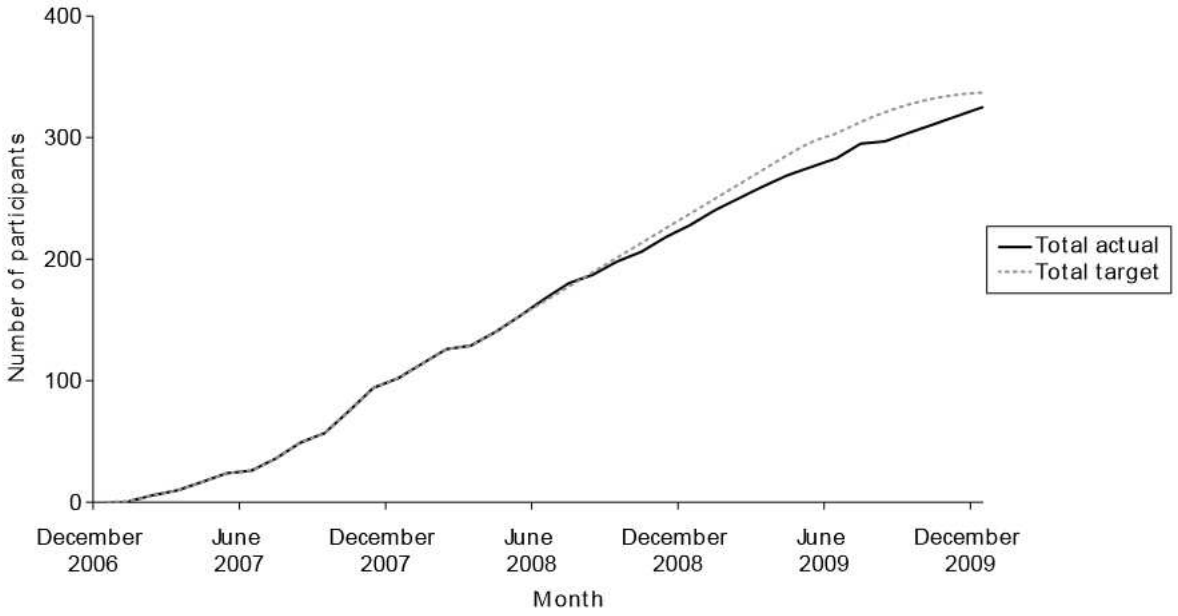

FIGURE 2 Cumulative recruitment over the trial period (revised target).

TABLE 3 Baseline demographics of participants and carers

	Participant			Carer		
Characteristic	Placebo (n = 111)	Sertraline (n = 107)	Mirtazapine (n = 108)	Placebo (n = 111)	Sertraline (n = 107)	Mirtazapine (n = 108)
Age (years)	79 (8.8)	80 (8.4)	79 (8.4)	59 (14.8)	61 (13.9)	61 (17.1)
Sex (male)	40 (36)	34 (32)	31 (29)	46 (30)	37 (30)	48 (35)
Ethnicity (white)	104 (94)	98 (92)	101 (94)	119 (79)	109 (89)	119 (86)
Marital status (married)	48 (43)	51 (48)	60 (56)	93 (62)	82 (67)	85 (61)
Residence (lives in care home)	20 (18)	13 (12)	17 (16)			
Relation to participant (paid carer)				40 (26)	19 (15)	34 (24)

Data are mean (SD) or n (%).

TABLE 4 Baseline participant and carer clinical characteristics

Clinical characteristics	Placebo	Sertraline	Mirtazapine
Duration of depression			
Data available	111 (100%)	102 (95%)	106 (98%)
1 month	7 (6%)	3 (3%)	
1 2 months	4 (4%)	6 (6%)	10 (9%)
2 6 months	24 (22%)	18 (17%)	26 (25%)
> 6 months	76 (68%)	75 (71%)	70 (66%)
Severity of depression			
CSDD 8 11	43 (39%)	45 (42%)	54 (50%)
CSDD ≥ 12	68 (61%)	64 (58%)	54 (50%)
Dementia vascularity	2.1 (1.3)	2.2 (1.3)	2.2 (1.3)
Carer-rated scores			
Participant SF-12			
Data available	103 (93%)	101 (94%)	96 (89%)
Physical component (0 100)	43.2 (10.6)	45.2 (11.2)	44.9 (12.4)
Mental component (0 100)	50.1 (11.8)	47.9 (11.1)	46.1 (12.5)
Participant generic quality of life			
Data available	109 (99%)	106 (99%)	105 (97%)
EuroQoL VAS (0 100)	52.3 (21.1)	53.8 (19.6)	51.9 (22.4)
Participant depression			
Data available	111 (100%)	107 (100%)	108 (100%)
CSDD (0 38)	13.6 (5.2)	12.8 (3.6)	12.5 (3.7)
Participant activity limitation			
Data available	111 (100%)	106 (99%)	107 (99%)
BADL (0 60)	18.2 (11.1)	16.6 (11.2)	18.4 (10.9)
Participant quality of life			
Data available	91 (82%)	97 (91%)	91 (84%)
DEMQOL-Proxy (31 124)	88.4 (15.3)	86.5 (15.6)	86.9 (13.1)
Carer mental health			
Data available	105 (95%)	103 (96%)	98 (91%)
GHQ-12 (0 36)	12.6 (5.1)	12.5 (4.9)	13.0 (5.9)
Carer burden			
Data available	87 (78%)	93 (87%)	91 (84%)
Zarit Score (0 88)	27.2 (16.6)	27.8 (14.7)	26.1 (16.0)
Participant neuropsychiatric symptoms			
Data available	106 (95%)	104 (97%)	108 (100%)
NPI (0 144)	30.2 (17.6)	26.9 (16.8)	29.9 (20.9)

TABLE 4 Baseline participant and carer clinical characteristics (continued)

Clinical characteristics	Placebo	Sertraline	Mirtazapine
Participant-rated scores			
Participant cognition			
Data available	82 (74%)	79. (74%)	90 (83%)
Standardised MMSE (0 33)	18.2 (7.4)	18.5 (6.7)	17.6 (6.0)
Participant generic quality of life			
Data available	92 (83%)	86 (80%)	91 (84%)
EuroQoL VAS (0 100)	60.3 (24.1)	66.6 (17.8)	66.9 (18.5)
Participant generic quality of life			
Data available	87 (78%)	82 (77%)	91 (84%)
DEMQOL (28 122)	83.7 (17.2)	82.5 (14.3)	85.1 (12.8)

BADL, Bristol Activities of Daily Living; SF, short form health survey; VAS, visual analogue scale.
Data are n (%) or mean (SD).

distribution of initiation of treatment following randomisation is shown in Figure 3. Out of the 326 participants randomised, 321 received allocated treatment.

Numbers analysed

In total, 111 participants were randomised to placebo, 107 to sertraline, and 108 to mirtazapine. The number of participants included in each analysis is indicated in the tables.

Outcomes and estimation

Primary outcome: Cornell Scale for Depression in Dementia

In total, 258 participants completed the research worker rated CSDD at 13 weeks post randomisation, with 226 participants going on to complete the measure at 39 weeks. As measured by the CSDD severity of depression was shown to decrease in all three intervention groups, compared with baseline, the results of which can be seen in Figure 4. The absolute change from baseline at 13 weeks was greatest for placebo 5.6 (SD 4.7), compared with 3.9 (5.1) for sertraline and 5.0 (4.9) for mirtazapine. This difference was maintained through to 39 weeks, with change scores of 4.8 (5.5) for placebo, 4.0 (5.2) for sertraline and 5.0 (6.1) for mirtazapine.

The results from the linear-mixed modelling (Table 5), after adjusting for baseline depression and the strati cation factor centre, highlighted that there was no evidence of a difference between sertraline and placebo or mirtazapine and placebo, on the CSDD score at 13 or 39 weeks. This analysis provides robust evidence of an absence of clinical effectiveness of the antidepressants tested here compared with placebo.

On exploratory analysis of the primary outcome measure, we classi ed the participants as suffering from depression based on the CSDD; a score of ≥ 8 is the threshold for depression (Table 6). As part of our eligibility criteria all participants at baseline had depression. This criteria was examined at 13 and 39 weeks. By 13 weeks the same proportion of participants in all treatment arms had moved to the no depression classi cation (49%); the main deviation from this trend was seen at 39 weeks when mirtazapine showed the largest percentage of non-depressive arm (55%). On evaluation with a generalised linear-mixed model (using the a logit link for the dichotomous data), adjusting for baseline depression and the strati cation

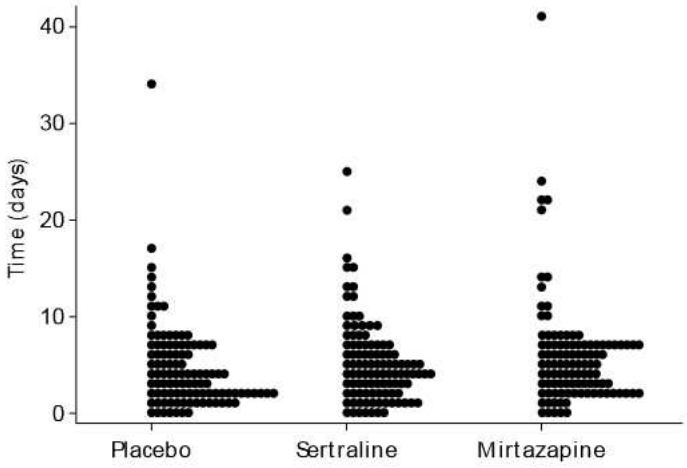

FIGURE 3 Distribution of initiation of treatment from randomisation.

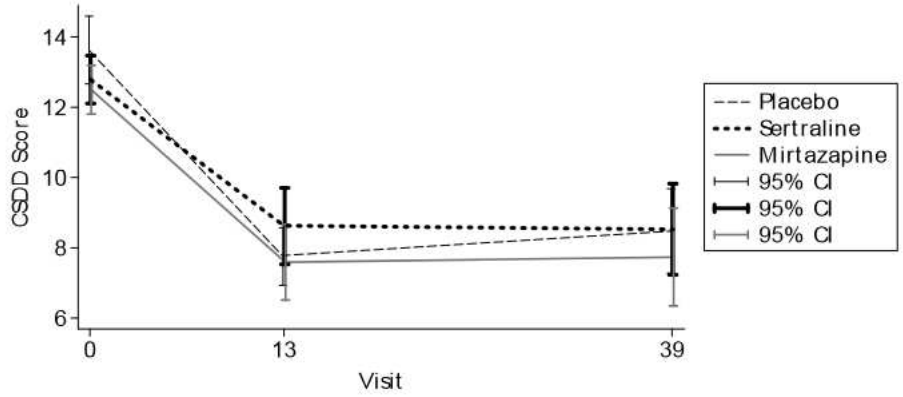

FIGURE 4 The CSDD scores by treatment group, unadjusted means with 95% CI (a lower CSDD score means fewer depressive symptoms).

factor centre, there was no evidence for a difference in the proportion of participants classi ed with depression by the CSDD between treatment arms at 13 or 39 weeks (Table 7).

Secondary outcomes

Table 8 shows the effectiveness of the medications compared with placebo and between each other on secondary outcomes in participants and carers. Again, few differences can be attributed to the antidepressants. However, there were fewer neuropsychiatric symptoms and higher carer-rated participant scores for health-related quality of life (HRQL) (DEMQOL-Proxy) in participants given mirtazapine compared with sertraline, but these differences did not persist to 39 weeks (see Table 4).

Our ndings did not differ in subgroup analyses examining outcomes by baseline depression severity (CSDD score 8 11 vs ≥ 12). All but eight participants (one in the placebo group, three in the sertraline group and four in the mirtazapine group) met criteria for categorical diagnosis of depression in AD as per Olin criteria.[56] Sensitivity analyses with the Olin criteria[56] as a moderator were not appropriate because of the low frequency of participants who did not meet Olin criteria.[56] However, this gives reassurance of the clinical signi cance of the depression in dementia investigated here.

Carers whose relatives were receiving placebo had higher quality-of-life scores at 13 weeks (SF-12 mental component score) and higher mental-health scores (GHQ-12) than those whose relatives were on sertraline (see Table 8). Finally, carers of participants in the mirtazapine group had higher quality-of-life scores (SF-12

TABLE 5 Primary outcomes of research worker rated CSDD score

	CSDD score		
Time point	Placebo	Sertraline	Mirtazapine
Baseline: mean (SD), n	13.6 (5.2), 111	12.8 (3.6), 107	12.5 (3.7), 108
Week 13: mean (SD), n	7.8 (4.1), 95	8.6 (4.9), 78	7.9 (5.0), 85
Week 39: mean (SD), n	8.5 (5.5), 82	8.6 (5.5), 68	7.7 (6.2), 76
Mean difference from placebo			
13 weeks: mean difference (SE); (95% CI); p-value; n		1.17 (0.72); (0.23 to 2.78); 0.10; 173	0.01 (0.70); (1.37 to 1.38); 0.99; 180
39 weeks: mean difference (SE); (95% CI); p-value; n		0.38 (0.76); (1.12 to 1.87); 0.63; 150	0.67 (0.74); (2.12 to 0.79); 0.37; 158
Mean difference from mirtazapine			
13 weeks: mean difference (SE); (95% CI); p-value; n		1.16 (0.72); (0.25 to 2.57); 0.11; 163	
39 weeks: mean difference (SE); (95% CI); p-value; n		1.04 (0.76); (0.48 to 2.56); 0.18; 144	

TABLE 6 Proportion of participants with depression

	Visit					
	Baseline		Week 13		Week 39	
Treatment	No depression	Depression	No depression	Depression	No depression	Depression
Placebo		111	47 (49%)	48	40 (49%)	42
Sertraline		107	38 (49%)	40	33 (47%)	37
Mirtazapine		108	42 (49%)	43	42 (55%)	34
Total		326	127	131	115	111

Number (%) of cases of depression.

TABLE 7 Generalised linear-mixed modelling of depression classi cation

Comparison		OR	SE	p-value	(95% CI)
Week 13	Sertraline vs placebo	1.050	0.349	0.883	0.547 to 2.016
	Mirtazapine vs placebo	1.008	0.327	0.979	0.534 to 1.906
	Sertraline vs mirtazapine	1.042	0.351	0.904	0.538 to 2.018
Week 39	Sertraline vs placebo	1.077	0.408	0.845	0.512 to 2.263
	Mirtazapine vs placebo	0.692	0.256	0.319	0.335 to 1.428
	Sertraline vs mirtazapine	1.557	0.596	0.247	0.736 to 3.296

SE, standard error.
Adjusted logistic model for depression status at 13 and 39 weeks, full adjusted model.

TABLE 8 Comparisons of secondary participant carer outcome (including depression severity)

Outcome		Week 13			Week 39		
		Sertraline vs placebo: coef cient (SE); 95% CI; (p-value)	Mirtazapine vs placebo: coef cient (SE); 95% CI; (p-value)	Sertraline vs mirtazapine: coef cient (SE); 95% CI; (p-value)	Sertraline vs placebo: coef cient (SE); 95% CI; (p-value)	Mirtazapine vs placebo: coef cient (SE); 95% CI; (p-value)	Sertraline vs mirtazapine: coef cient (SE); 95% CI; (p-value)
Cognition; MMSE		0.22 (0.65); 1.50 to 1.05; (0.73)	0.27 (0.61); 1.48 to 0.94; (0.66)	0.05 (0.64); 1.21 to 1.31; (0.94)	0.55 (0.68); 1.89 to 0.79; (0.42)	1.71 (0.67); 2.48 to 0.14; (0.08)	0.62 (0.69); 0.73 to 1.97; (0.37)
Activity limitation; BADL		1.40 (1.26); 1.07 to 3.88; (0.27)	0.04 (1.23); 2.44 to 2.36); (0.97)	1.44 (1.30); 1.10 to 3.99; (0.27)	1.63 (1.35); 1.01 to 4.27; (0.26)	1.19 (1.30); 1.37 to 3.75; (0.36)	0.44 (1.38); 2.26 to 3.14; (0.75)
Behaviour, problems; NPI		2.72 (2.41); 2.01 to 7.45; (0.26)	3.56 (2.30); 8.07 to 0.96; (0.12)	6.28 (2.42); 1.53 to 11.03; (0.010)	2.02 (2.53); 2.94 to 6.97; (0.43)	1.51 (2.42); 6.25 to 3.24; (0.53)	3.53 (2.53); 1.44 to 8.49; (0.164)
Depression severity	Low CSDD score: 8 11	1.12 (1.01); 0.85 to 3.10; (0.26)	0.30 (0.98); 2.21 to 1.61; (0.76)	1.43 (0.99); 0.51 to 3.36; (0.15)	0.33 (1.04); 1.72 to 2.37; (0.76)	0.99 (1.02); 2.98 to 1.00; (0.33)	1.31 (1.04); 0.72 to 3.34; (0.20)
	High CSDD score: 12+	1.18 (0.91); 0.60 to 2.96; (0.34)	0.27 (0.89); 1.47 to 2.01; (0.76)	0.91 (0.91); 0.95 to 2.77; (0.34)	0.38 (0.94); 1.47 to 2.23; (0.69)	0.41 (0.91); 2..20 to 1.37; (0.65)	0.0.80 (0.97); 1.10 to 2.69; (0.41)
Life quality; DEMQOL		0.30 (1.89); 3.40 to 4.01; (0.87)	0.06 (1.76); 3.52 to 3.39; (0.97)	0.37 (1.89); 3.52 to 3.39; (0.85)	1.76 (2.04); 5.75 to 2.23; (0.39)	0.03 (1.92); 3.80 to 3.75; (0.99)	1.74 (2.07); 5.79 to 2.32; (0.40)
Life quality; DEMQOL-Proxy		1.98 (2.14); 6.16 to 2.21; (0.36)	3.13 (2.15); 1.09 to 7.35; (0.15)	5.11 (2.22); 9.45 to 0.76; (0.021)	2.69 (2.28); 1.77 to 7.15; (0.24)	3.69 (2.28); 0.77 to 8.16; (0.11)	1.00 (2.35); 5.61 to 3.60; (0.67)
Life quality; self rated; EQ-5D		3.44 (3.78); 10.86 to 3.98; (0.36)	2.00 (3.67); 5.18 to 9.19; (0.59)	5.44 (3.72); 5.18 to 9.19; (0.14)	4.34 (4.19); 12.56 to 3.88; (0.30)	1.18 (4.12); 9.25 to 6.89; (0.78)	3.16 (4.21); 9.25 to 6.89; (0.45)
Life quality; carer rated; EQ-5D		0.61 (3.05); 5.38 to 6.59; (0.84)	3.62 (3.03); 2.31 to 9.55; (0.23)	3.02 (3.17); 9.23 to 3.20; (0.34)	0.27 (3.32); 6.77 to 6.24; (0.94)	1.11 (3.23); 7.44 to 5.21; (0.73)	0.85 (3.42); 5.86 to 7.56; (0.80)
Carer burden; Zarit		0.50 (1.93); 4.28 to 3.27; (0.80)	1.14 (1.83); 4.93 to 0.65; (0.56)	0.64 (1.98); 3.23 to 4.51; (0.75)	0.09 (2.07); 4.15 to 3.98; (0.97)	2.80 (2.14); 6.99 to 1.38; (0.19)	2.71 (2.13); 1.45 to 6.88; (0.20)
Carer mental health; GHQ		1.47 (0.72); 0.06 to 2.89; (0.042)	0.57 (1.23); 0.84 to 1.98; (0.43)	0.90 (0.75); 0.56 to 2.37; (0.23)	0.43 (0.77); 1.09 to 1.95; (0.58)	0.61 (0.77); 2.12 to 0.90; (0.43)	1.04 (0.80); 0.53 to 2.61; (0.20)
Life quality; SF-12 physical component score		1.28 (1.40); 1.48 to 4.03; (0.36)	0.53 (1.39); 2.20 to 3.26; (0.70)	0.75 (1.45); 2.10 to 3.59; (0.61)	1.68 (1.48); 4.58 to 1.22; (0.26)	0.02 (1.46); 2.84 to 2.88; (0.99)	1.70 (1.53); 2.84 to 2.88; (0.27)
Life quality; SF-12 mental component score		2.99 (1.47); 5.87 to 0.11; (0.042)	0.52 (1.45); 2.31 to 3.36; (0.72)	3.52 (1.52); 6.50 to 0.54; (0.021)	0.09 (1.54); 2.94 to 3.11; (0.96)	0.31 (1.51); 3.28 to 2.66; (0.84)	0.40 (1.60); 2.74 to 3.54; (0.80)

mental component score) at 13 weeks than the carers of participants in the sertraline group. However, these differences did not persist at 39 weeks.

Neuropsychiatric Inventory

The distributional assumptions of the regression model were improved by specifying a negative binomial distribution for the NPI data. The data were examined cross-sectionally, thus missing data were accounted for by inverse probability weighting. The subscales of the NPI can be combined to yield four factors: factor 1, agitation, disinhibition and irritability; factor 2, delusions, depression and anxiety; factor 3, hallucinations, aberrant motor behaviour and sleep; and factor 4, elation, apathy and appetite. The summaries for the factors came be seen in Table 9. Under the new regression model, there is evidence for a bene cial effect of mirtazapine in comparison with sertraline. The difference in odds between sertraline and placebo, although non-signi cant, trends towards a better outcome in placebo. These differences are seen at 13 weeks (Table 10).

The signi cant odds seen for the total score (OR 1.39; 95% CI 1.08 to 1.78; p = 0.009), is supported by factors 2 and 3. These effects are not continued into week 39.

Safety data

In total, 119 participants reported 240 adverse reactions. Table 11 shows adverse reactions by week 39. 29 of 111 participants (26%) in the placebo group had adverse reactions, compared with 46 of 107 (43%) in the sertraline group (p = 0.010) and 44 of 108 (41%) in the mirtazapine group (p = 0.031; overall p-value for placebo vs either drug 0.017). Gastrointestinal reactions were most common with sertraline (usually nausea) and psychological reactions were most common with mirtazapine (usually drowsiness and sedation). At 13 weeks, there were 15 serious adverse events in the placebo group of which three (20%) were rated severe, compared with 12 in the sertraline group [eight severe (67%)] and 14 [10 severe (71%)] in the mirtazapine group. Overall, the number of serious adverse events reported did not differ

TABLE 9 Mean (SD) of the NPI factors

Time	Placebo: data available; mean (SD)	Sertraline: data available; mean (SD)	Mirtazapine: data available; mean (SD)
Baseline			
Factor 1	110; 6.89 (6.44)	107; 5.87 (5.53)	108; 6.5 (6.67)
Factor 2	111; 9.18 (6.65)	105; 8.76 (6.33)	108; 9.42 (7.55)
Factor 3	111; 6.41 (6.73)	106; 5.71 (5.57)	108; 6.36 (7.21)
Factor 4	107; 7.43 (6.25)	105; 6.62 (5.18)	108; 7.58 (6.44)
Week 13			
Factor 1	97; 4.30 (4.65)	79; 4.58 (5.32)	88; 4.28 (5.68)
Factor 2	96; 5.21 (5.59)	79; 5.85 (6.62)	88; 4.17 (5.54)
Factor 3	97; 4.41 (5.14)	79; 5.43 (6.02)	88; 4.02 (5.74)
Factor 4	93; 5.53 (5.56)	75; 5.25 (5.65)	88; 4.42 (4.73)
Week 39			
Factor 1	84; 5.08 (5.58)	70; 4.91 (6.03)	78; 4.36 (5.88)
Factor 2	84; 5.37 (5.48)	69; 5.61 (6.44)	78; 5.32 (7.08)
Factor 3	83; 3.39 (4.83)	70; 4.46 (5.35)	78; 4.34 (6.22)
Factor 4	81; 5.59 (5.57)	68; 5.68 (5.38)	78; 5.19 (6.45)

TABLE 10 Odds ratio, the NPI and derived factor scores[a]

	Week 13			Week 39		
NPI factor: OR (SE); 95% CI; (p-value)	Sertraline vs placebo	Mirtazapine vs placebo	Sertraline vs mirtazapine	Sertraline vs placebo	Mirtazapine vs placebo	Sertraline vs mirtazapine
Total score	1.098 (0.12); 0.884 to 1.363; (0.397)	0.790 (0.10); 0.618 to 1.009; (0.059)	1.390 (0.18); 1.084 to 1.782; (0.009)	1.150 (0.15); 0.884 to 1.495; (0.298)	0.933 (0.14); 0.693 to 1.256; (0.647)	1.232 (0.18); 0.926 to 1.640; (0.151)
Factor 1	1.104 (0.19); 0.782 to 1.558; (0.573)	1.013 (0.21); 0.678 to 1.516; (0.948)	1.090 (0.24); 0.706 to 1.681; (0.698)	1.101 (0.233); 0.728 to 1.666; (0.649)	0.913 (0.19); 0.608 to 1.372; (0.663)	1.206 (0.28); 0.760 to 1.911; (0.427)
Factor 2	1.203 (0.22); 0.840 to 1.723; (0.313)	0.738 (0.13); 0.516 to 1.054; (0.095)	1.631 (0.30); 1.141 to 2.331; (0.007)	0.996 (0.18); 0.697 to 1.425; (0.984)	0.886 (0.17); 0.609 to 1.287; (0.524)	1.125 (0.21); 0.775 to 1.634; (0.536)
Factor 3	1.395 (0.26); 0.964 to 2.018; (0.078)	0.716 (0.17); 0.451 to 1.138; (0.158)	1.946 (0.45); 1.239 to 3.056; (0.004)	1.663 (0.42); 1.020 to 2.713; (0.042)	1.398 (0.35); 0.856 to 2.283; (0.181)	1.190 (0.26); 0.779 to 1.819; (0.422)
Factor 4	1.064 (0.18); 0.762 to 1.486; (0.715)	0.853 (0.13); 0.633 to 1.148; (0.294)	1.248 (0.22); 0.887 to 1.755; (0.204)	1.141 (0.21); 0.786 to 1.656; (0.488)	0.842 (0.17); 0.570 to 1.244; (0.387)	1.355 (0.27); 0.912 to 2.015: (0.133)

a Fully adjusted modelling.

TABLE 11 Adverse reactions de nite, probable, and possibly related to study intervention by week 39

	Treatment group			
Classi cation	Placebo	Sertraline	Mirtazapine	Total events
Psychological	10 (22)	9 (18)	24 (44)	53 (84)
Neurological	8 (9)	16 (25)	18 (21)	42 (55)
Gastrointestinal	7 (7)	20 (24)	11 (13)	38 (44)
Other	2 (2)	5 (5)	3 (3)	10 (10)
Genitourinary	4 (4)	3 (3)	2 (3)	9 (10)
Musculoskeletal	2 (3)	3 (3)	3 (3)	8 (9)
Dermatological	3 (4)	3 (3)	2 (2)	8 (9)
Respiratory	2 (2)	1 (1)	2 (2)	5 (5)
Cardiovascular	1 (1)	0 (0)	2 (4)	3 (5)
Infection	1 (1)	1 (1)	1 (1)	3 (3)
ENT	2 (2)	1 (1)	0 (0)	3 (3)
Haematological	1 (1)	1 (1)	0 (0)	2 (2)
Endocrine	0 (0)	1 (1)	0 (0)	1 (1)
Total[a]	29 (58)	46 (86)	44 (96)	119 (240)

ENT, ear, nose and throat.
a Data are number of participants (number of events).

between groups but more of these events were severe in those on antidepressants compared with placebo (p = 0.003). Mortality did not differ between groups (ve deaths in each group by 39 weeks).

Health economic results

Baseline comparisons

At baseline, full service use data were available for 326 participants (111 placebo, 107 sertraline, 108 mirtazapine). At 13 weeks, economic data were available for 97 participants in the placebo group, 78 in the sertraline group and 88 in the mirtazapine group. By 39 weeks, there were 84 participants in the placebo group, 69 in the sertraline group and 77 in the mirtazapine group.

Service use and support

Contacts made by patients with services and support over weeks 0 13 and 0 39 are shown in Table 12. There were few differences between the three patient groups in either time period, except when mirtazapine and sertraline were compared with placebo and mirtazapine was compared with sertraline. There were no statistically signi cant differences between the groups in the number of contacts with any services.

Costs

Daily medication costs of 0.05 for sertraline 50 mg and 0.23 for mirtazapine 15 mg were applied. Mean cost of medication per person was estimated to be 7 (CI 6 to 9) and 37 (CI 32 to 41).

Mean total costs over 0 13 weeks and 0 39 weeks are detailed in Table 13. Pair-wise comparisons were made between the two antidepressants and placebo using regression analysis and bootstrapping. There

TABLE 12 Service use

Time period	Placebo (n = 97)		Sertraline (n = 78)		Mirtazapine (n = 88)	
	No. using	Mean[a] (SD)	No. using	Mean[a] (SD)	No. using	Mean[a] (SD)
Weeks 0 13						
Hospital-based care						
Inpatient (bed-day)[b]	8	1.65 (7.98)	5	1.58 (6.82)	5	0.49 (2.19)
Outpatient (attendance)	33	0.53 (1.08)	25	0.60 (1.10)	26	0.53 (1.10)
Accident and Emergency (attendance)	8	0.12 (0.48)	5	0.08 (0.27)	4	0.57 (0.28)
Day hospital (contact)	3	0.23 (1.44)	6	0.83 (4.11)	4	0.32 (1.66)
Community-based care						
GP (contact)	57	1.36 (2.36)	44	1.09 (1.44)	49	1.22 (2.84)
Geriatrician (contact)	3	0.03 (0.17)	0	0	88	0.03 (0.18)
Nurse[c] (contact)	41	0.87 (1.49)	29	2.50 (10.83)	43	1.56 (3.71)
Occupational therapist (contact)	11	0.21 (0.66)	7	0.35 (1.70)	5	0.08 (0.38)
Community psychiatrist (contact)	21	0.26 (0.54)	14	0.24 (0.63)	19	0.27 (0.58)
Psychologist (contact)	2	0.82 (0.64)	3	0.06 (0.37)	2	0.09 (0.62)
Counsellor (contact)	1	0.01 (0.10)	3	0.36 (2.94)	2	0.17 (1.32)
Care manager (contact)	7	0.10 (0.42)	1	0.01 (0.11)	4	0.05 (0.21)
Social worker (contact)	15	0.21 (0.69)	10	0.19 (0.58)	12	0.28 (0.87)
Home care worker/care attendant (contact)	19	18.57 (60.57)	17	21.92 (72.77)	22	28.33 (72.19)
Chiropodist (contact)	33	0.43 (0.710	16	0.26 (0.57)	23	0.40 (0.88)
Sitting scheme (contact)	5	1.21 (6.71)	5	0.68 (4.29)	3	0.59 (3.75)
Self-help group (contact)	0	0	0	0	1	0.03 (0.32)
Meals on wheels (contact)	3	0.30 (1.77)	3	5.82 (33.95)	4	2.32 (12.74)
Dentist (contact)	10	0.13 (0.49)	10	0.15 (0.43)	15	0.23 (0.58)
Optician (contact)	10	0.12 (0.39)	13	0.19 (0.46)	12	0.15 (0.39)
Day services						
Day services (day)	15	4.15 (11.95)	17	6.50 (15.64)	16	5.47 (13.33)
Lunch club (visit)	3	1.88 (15.92)	0	0	3	1.18 (8.51)
Social club (visit)	2	0.27 (1.86)	4	0.67 (2.89)	2	0.44 (3.08)
Informal care						
Care giving (hours/week)	45	10.05 (17.65)	37	11.63 (21.59)	42	9.84 (23.85)

TABLE 12 Service use (continued)

Time period	Placebo (n = 84)		Sertraline (n = 69)		Mirtazapine (n = 78)	
	No. using	Mean[a] (SD)	No. using	Mean[a] (SD)	No. using	Mean[a] (SD)
Weeks 0 39						
Hospital-based care						
Inpatient (bed-day)[b]	9	3.05 (10.48)	11	2.55 (9.26)	14	4.54 (15.08)
Outpatient (attendance)	44	0.83 (1.15)	33	0.90 (1.41)	29	0.69 (1.15)
Accident and Emergency (attendance)	13	0.17 (0.41)	8	0.25 (0.86)	7	0.10 (0.35)
Day hospital (contact)	1	0.01 (0.11)	8	2.61 (9.42)	3	0.56 (3.30)
Community-based care						
GP (contact)	57	1.51 (1.83)	40	1.52 (2.15)	55	1.88 (2.40)
Geriatrician (contact)	4	0.05 (0.21)	0	0	2	0.03 (0.16)
Nurse[c] (contact)	37	1.24 (2.34)	33	5.84 (29.57)	34	1.46 (3.53)
Occupational therapist (contact)	9	0.17 (0.53)	8	0.45 (2.23)	5	0.10 (0.44)
Community psychiatrist (contact)	22	0.33 (0.67)	15	0.26 (0.53)	29	0.60 (1.48)
Psychologist (contact)	5	0.21 (1.34)	2	0.03 (0.17)	1	0.01 (0.11)
Counsellor (contact)						
Care manager (contact)	6	0.52 (2.87)	3	0.04 (0.21)	5	0.10 (0.44)
Social worker (contact)	12	0.58 (2.98)	15	0.42 (0.98)	17	0.44 (1.47)
Home care worker/care attendant (contact)	16	33.56 (107.73)	19	38.07 (95.60)	17	38.95 (110.10)
Chiropodist (contact)	35	0.88 (1.37)	20	0.53 (1.52)	32	1.11 (1.89)
Sitting scheme (contact)	0	0	5	1.23 (5.49)	4	0.76 (3.69)
Meals on wheels (contact)	2	0.63 (5.67)	2	3.77 (21.70)	2	3.14 (19.49)
Dentist (contact)	18	0.33 (0.96)	18	0.47 (1.25)	19	0.34 (0.81)
Dietician (contact)	0	0	0	0	1	0.01 (0.11)
Day services						
Day services (day)	16	5.57 (14.31)	18	7.26 (15.13)	16	5.17 (12.63)
Lunch club (visit)	1	0.31 (2.84)	1	0.38 (3.15)	3	0.83 (4.84)
Social club (visit)	2	0.62 (4.47)	3	0.57 (2.69)	1	0.33 (2.94)
Informal care						
Care giving (hours per week)	40	12.27 (21.24)	34	12.32 (24.07)	33	6.74 (11.82)

a Across full sample.

b Psychiatric and non-psychiatric inpatient bed-days.

c Practice nurse, district nurse health visitor, community psychiatric nurse, cardiac nurse and incontinence nurse.

TABLE 13 Health, social care and informal care costs and outcome

	Placebo		Sertraline		Mirtazapine		Bootstrapped mean difference (95% CI)		
Weeks	n	Mean (SD),	n	Mean (SD),	n	Mean (SD),	Sertraline placebo	Mirtazapine placebo	Mirtazapine sertraline
(a) Medication costs									
0 13	97	0	78	7 (5)	88	37 (22)	7 (6 to 8)	37 (32 to 41)	30 (25 to 34)
0 39	84	0	69	7 (5)	78	37 (22)	7 (6 to 8)	37 (32 to 41)	30 (25 to 34)
(b) Health and social care costs									
0 13	97	1438 (3339)	78	1434 (2326)	88	1094 (1871)	4 (900 to 798)	344 (1207 to 322)	340 (1049 to 283)
0 39	84	2146 (4402)	69	2832 (4111)	78	2513 (4290)	686 (630 to 1973)	367 (977 to 1596)	319 (1643 to 1023)
(c) Informal care cost									
0 13	97	2744 (4819)	78	3175 (5897)	88	2687 (6511)	431 (1000 to 2242)	57 (1686 to 1537)	488 (2380 to 1470)
0 39	84	3351 (5799)	69	3363 (6573)	78	1841 (3228)	12 (1940 to 2256)	1510 (3088 to 136)	1522 (3398 to 72)
Total costs excluding informal care inputs (a+ b)									
0 13	97	1438 (3339)	78	1441 (2327)	88	1131 (1869)	3 (893 to 806)	307 (1172 to 358)	310 (910 to 299)
0 39	84	2146 (4402)	69	2839 (4112)	78	2550 (4289)	693 (622 to 1980)	404 (972 to 1626)	289 (1545 to 1151)
Total costs including informal care inputs (a+ b + c)									
0 13	97	4182 (5821)	78	4616 (6488)	88	3818 (7060)	434 (1340 to 2356)	365 (2212 to 1560)	798 (2754 to 1498)
0 39	84	5497 (7922)	69	6202 (8241)	78	4391 (5285)	705 (1855 to 3234)	1106 (3137 to 970)	1811 (4048 to 543)
Depression score (CSDD)									
13	95	7.8 (4.1)	78	8.6 (4.9)	85	7.9 (5.0)	0.84 (0.60 to 2.14)	0.16 (1.53 to 1.11)	0.7 (0.57 to 2.52)
39	82	8.5 (5.5)	68	8.6 (5.5)	76	7.7 (6.2)	0.05 (1.83 to 1.67)	0.80 (2.55 to 1.21)	0.9 (1.10 to 2.73)
QALY 39 weeks (EQ-5D)	57	0.55 (0.17)	53	0.57 (0.14)	52	0.60 (0.13)	0.03 (0.09 to 0.03)	0.05 (0.10 to 0.10)	0.02 (0.03 to 0.07)

were no statistically signi cant differences between the groups in either of the time periods, either when health and social care service costs only were included, or when health and social care services and informal care costs are summed.

After adjustment for baseline costs, CSDD score at baseline and site, there were no statistically signi cant differences in health and social care costs or in health, social care and informal care costs in any pair-wise comparison in either time period.

In terms of observed mean differences, aggregated health and social care service costs per patient over 0 13 weeks were 3 between sertraline and placebo, 307 between placebo and mirtazapine and 310 between sertraline and mirtazapine. In each case, the rst named treatment was the more costly. In the 6 months leading up to 39 weeks, mean difference in health and social care costs was 693 between sertraline and placebo, 404 between mirtazapine and placebo, and 289 between sertraline and mirtazapine. Again, in each case the rst-named treatment was more costly.

Informal care costs exceeded health and social care costs by a factor of 1.2 1.7. Including informal care costs results in a change in the ranking of total costs, with mirtazapine being the least expensive of all treatments in both periods.

Cost-effectiveness

As noted earlier, the primary economic evaluation was a cost-effectiveness analysis with CSDD as the outcome over, rst, the period 0 13 weeks after randomisation and, second, the period 0 39 weeks after randomisation. A secondary analysis was a cost utility analysis using QALYs computed from the EQ-5D and societal weights over the same periods. Data used in the estimation of the ICERs are shown in Table 14. An ICER was calculated for each analysis comparing sertraline and mirtazapine against placebo and comparing mirtazapine against sertraline.

As reported previously, there were no signi cant differences in CSDD scores or QALYs in any of the pair-wise comparisons between sertraline, mirtazapine and placebo. There were also no signi cant pair-wise differences in costs from either perspective between the treatment groups.

Given uncertainty surrounding the choice of treatment when incremental costs are higher and incremental outcome better (or when incremental costs are lower and incremental outcome also lower), CEACs were used to aid decision-making. Probability estimates were plotted for a range of implicit monetary values attached to improvements in depression score and QALY gain. We are not aware of any studies that have attached monetary values to incremental changes in CSDD.

In Figure 5, we see that mirtazapine has a low probability (around 30%) of being more cost-effective than placebo if society was not willing to pay anything for a unit improvement in the CSDD depression score. The probability rose to 80% if society was willing to pay 5000 for a unit improvement in CSDD score, and stays at 80% over values of willingness to pay for an improvement in CSDD score up to 30,000. Sertraline had a < 20% chance of being cost-effective compared with placebo, with the probability increasing moderately to about 42% if society was willing to pay 5000 for each point improvement in CSDD score, and stayed below 50% for willingness-to-pay values greater than 5000 and up to 30,000 for a point improvement in CSDD score.

When both active treatments sertraline and mirtazapine were compared against each other the likelihood that treatment with mirtazapine would be seen as more cost-effective than sertraline would be over 60% from a health and social care perspective (and over 90% from a health, social care and informal care costs perspective).

TABLE 14 Differences in incremental cost, effect and cost-effectiveness

	Sertraline placebo		Mirtazapine placebo		Mirtazapine sertraline	
Comparison	0 13 weeks	0 39 weeks	0 13 weeks	0 39 weeks	0 13 weeks	0 39 weeks
Incremental cost (, 2009 10): mean (95% CI)						
Health and social care	3 (893 to 806)	693 (622 to 1980)	307 (1172 to 358)	404 (972 to 1626)	310 (910 to 299)	289 (1545 to 1151)
Health and social care and informal care	434 (1340 to 2356)	705 (1855 to 3234)	365 (2212 to 970)	1106 (3137 to 970)	798 (2754 to 1498)	1811 (4048 to 543)
Incremental effect: mean (95% CI)						
(a) CSDD score[a]	0.84 (0.60 to 2.14)	0.05 (1.83 to 1.67)	0.16 (1.53 to 1.11)	0.80 (2.55 to 1.21)	0.7 (0.57 to 2.52)	0.9 (1.10 to 2.73)
(b) QALY (EQ-5D); mean[b]		0.03 (0.09 to 0.03)		0.05 (0.10 to 0.10)		0.02 (0.03 to 0.07)
Incremental cost-effectiveness ( ) health and social care and:						
(a) CSDD score	4	13,860	1919	505	443	321
	(Dominated)	(Dominated)	(Lower costs; worse outcome)	(Higher costs; better outcome)	(Mirtazapine dominant)	(Mirtazapine dominant)
(b) QALY (EQ-5D)		23,100		8080		14,450
		(Higher costs; better outcome)		(Higher costs; better outcome)		(Mirtazapine dominant)
Incremental cost-effectiveness ( ) health and social care and informal care costs and:						
(a) CSDD score	517	14,100	2281	1382	1140	2012
	(Dominated)	(Dominated)	(Lower costs; worse outcome)	(Mirtazapine dominant)	(Mirtazapine dominant)	(Mirtazapine dominant)
(b) QALY (EQ-5D)[b]		23,500		22,120		90,550
		(Higher costs; better outcome)		(Mirtazapine dominant)		(Mirtazapine dominant)

a On CSDD higher scores = worse outcome; therefore, negative incremental CSDD scores indicate better outcome or active treatment. In case of the comparison between mirtazapine and sertraline, this is mirtazapine.

b Patient rated.

Note: 'dominant' = active treatment has lower costs and better outcome; 'dominated' = active treatment has higher costs and worse outcome.

Figures 5 and 6 show the CEACs from the secondary economic evaluation, where costs were considered alongside QALYs. Although we found no signi cant differences in QALY gain in any of the pair-wise comparisons between sertraline, mirtazapine and placebo, we see a trend towards marginally higher QALY gains (using the EQ-5D measured directly from patients) for the active treatments.

Figure 7 suggests that the probability that mirtazapine is more cost-effective than placebo was 89%, and increased to over 90% for a willingness to pay of 30,000 for a QALY. The likelihood of sertraline being more cost-effective than placebo was just over 50% and rose to just over 70% over higher values of willingness to pay for a QALY. Figure 8 shows that mirtazapine had a higher probability of being more

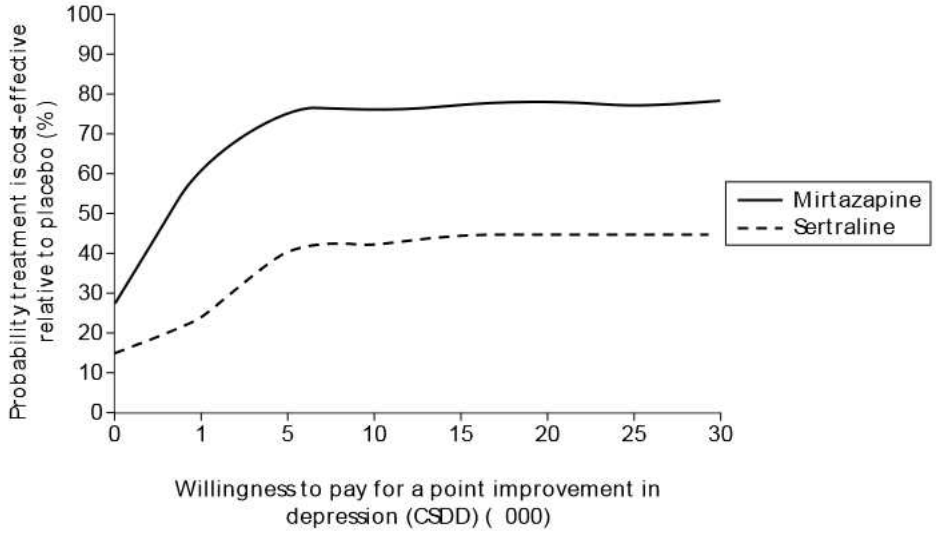

FIGURE 5 Probability that treatment is cost-effective at 0 39 weeks: health, social care costs and depression score (CSDD).

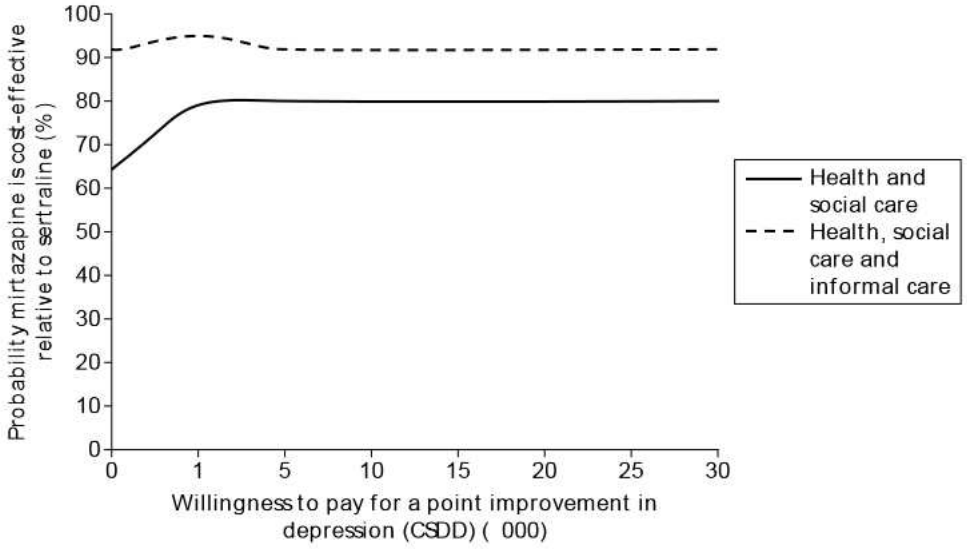

FIGURE 6 Probability that mirtazapine is cost-effective relative to sertraline at 0 39 weeks: costs and depression score (CSDD).

cost-effective than sertraline (over a range of willingness-to-pay values from 0 to 30,000) when health and social care costs are considered on their own, and also when considering health, social care and informal care costs.

In addition to assessing the uncertainty surrounding the cost-effectiveness of the antidepressants, we also assessed uncertainty around parameter estimates included in the cost analysis. For the main analyses, informal care costs were based on hourly cost of a home care worker. This hourly value for the care-giving inputs by friends and family was replaced in sensitivity analysis by an opportunity cost estimate, calculated as the gross hourly wage of a carer in paid employment and zero for a carer not in paid employment. Using alternative values of caregiver time inputs did not alter the ndings (Table 15).

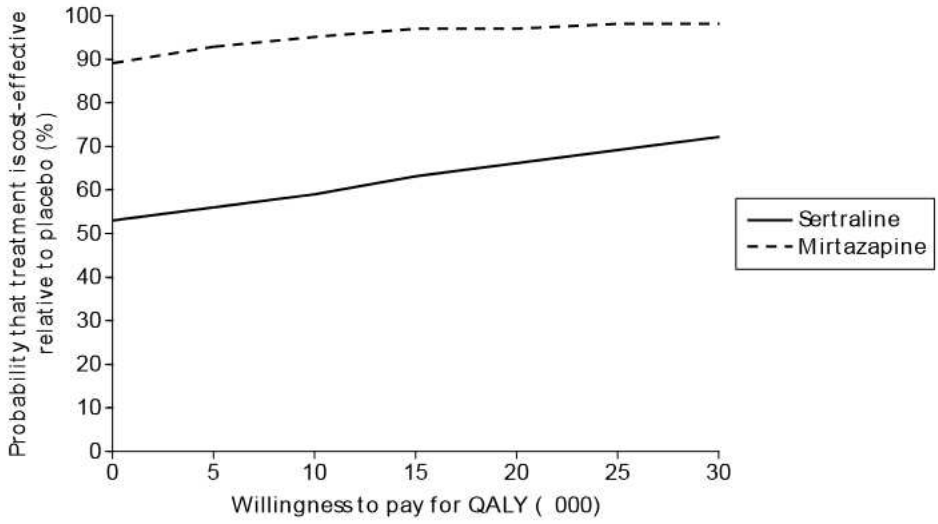

FIGURE 7 Probability that treatment is cost-effective relative to placebo: health, social care and informal care costs and QALYs.

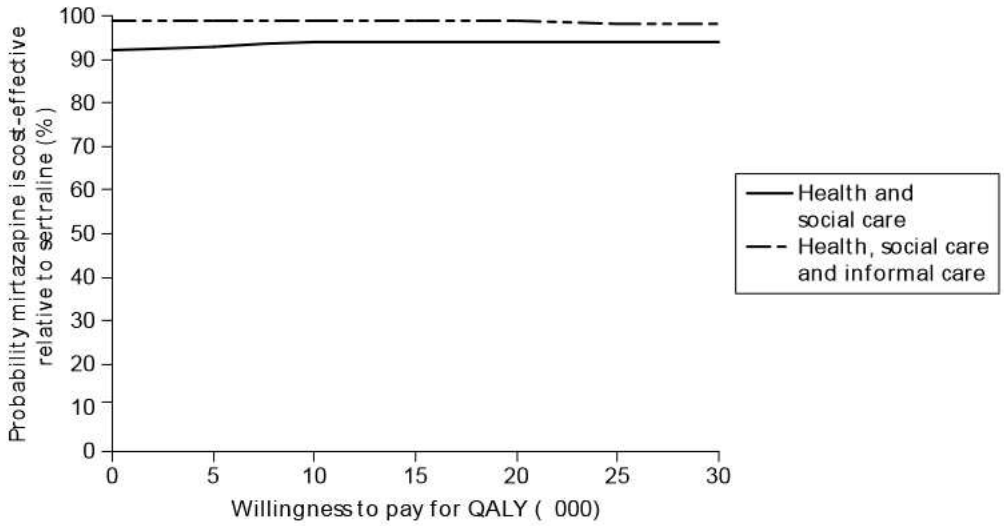

FIGURE 8 Probability that mirtazapine is cost-effective relative to sertraline: costs and QALYs.

TABLE 15 Sensitivity analysis

Analysis	Placebo: mean (SD)	Sertraline: mean (SD)	Mirtazapine: mean (SD)	Sertraline placebo: mean difference (95% CI)	Mirtazapine placebo: mean difference (95% CI)	Mirtazapine sertraline: mean difference (95% CI)
Main analysis 0–13 weeks (total cost including informal care)	4182 (5821)	4616 (6488)	3818 (7060)	434 (−1340 to 2356)	−365 (−2212 to 1560)	−798 (−2754 to 1498)
Applying gross wage for informal care inputs	3368 (4769)	3663 (5008)	3592 (5461)	322 (−1081 to 1797)	−353 (−1778 to 1087)	−71 (−1588 to 1588)
Main analysis 0–39 weeks (total cost including informal care)	5497 (7922)	6202 (8241)	4391 (5285)	705 (−1855 to 3234)	−1106 (−3137 to 970)	−1811 (−4048 to 543)
Applying gross wage for informal care inputs	4476 (6512)	5177 (6574)	3830 (4777)	702 (−1313 to 2751)	−645 (−2415 to 986)	−1347 (−3368 to 280)

Chapter 4 Discussion

This is a trial with negative findings but important clinical implications. The data suggest clearly that antidepressants, given with normal care, are not clinically effective when compared with placebo for the treatment of clinically significant depression in dementia. This implies a need to change the current clinical practice of prescribing antidepressants as the first-line treatment of depression in dementia due to AD.

Limitations

First, the dropout will have introduced bias if those dropping out had a different response to the trial interventions or placebo compared with those completing the trial. However, this was designed as a pragmatic trial, with few exclusions to mirror closely real clinical populations, and the levels of disengagement are similar to those experienced in clinical settings. Strenuous efforts were made to follow up and obtain outcome data on all those randomised but who defaulted from either the trial compound or clinical services.

A second putative limitation is the revision during the trial of the target sample size. Because of slower than forecast recruitment, we sought an extension and therefore further funding. The funder ordered interim analyses to determine the numbers needed using the data available on 75 cases followed up at 13 weeks. The new target set was 339. We recruited 326, falling short of the new target by 13. Nevertheless, this is the largest ever RCT of depression in dementia with unequivocal findings showing no effect of either antidepressant compared with placebo. Had the pattern of change seen in those recruited been continued, the extra precision in estimates that would have come from either another 13 cases, or even achieving the original trial target of 507, would not have generated a statistically significant positive result for either antidepressant.

Third, measurement error caused by the effect of cognitive impairment on domains such as memory, language and reasoning is a potential limitation. However, the study included only those measures best validated for use in dementia. Our primary outcome, the CSDD, is the most robust available measure of depression in dementia[57] incorporating data from the carer, the person with dementia, and the rater. Finally, we did not capture elements of intervention by the clinical teams other than the group to which they were randomised. Had we been able to characterise these non-drug elements of treatment then we might have been able to investigate their role in patient recovery. However, there is no suggestion that these would have varied across the three groups, so again the results would not have changed.

Finally, it might be considered a limitation that we did not adjust the results for the multiple comparisons made in the secondary analyses. The data are presented as they are so that the reader can interpret the actual findings as they find best. The work should be reviewed considering a 1% significance level for all secondaries.

Generalisability

This study was designed to reflect real clinical populations and interventions as closely as possible. To this end we minimised exclusions and had permissive inclusion criteria. However, the findings may not generalise to those too critically ill to risk randomisation (chiefly those with high suicide risk). Only three potential participants were excluded on this criterion but there will have been more not referred into the trial. Equally, outcomes of those with depression but a CSDD score of < 8 would not be covered by this study. In practice, however, very few people with a CSDD score at this level would be considered to have clinically significant depression, so the effect on generalisability will be limited.

One of the strengths of this study is its size and the broad nature of the study group, both by the range of depressive symptoms and the severity of dementia, neither of which appeared to in uence outcomes. We included not only those with narrowly de ned AD but also those with probable and possible AD. This is closer to the population encountered in clinical practice where there is often mixed dementia (i.e. those with a vascular component to their dementia). However, prudence would limit generalisability to AD and mixed dementia only and not to other subtypes, such as vascular dementia, dementia with Lewy bodies or frontotemporal dementia.

The one major limit to generalisability comes from all cases being drawn from referrals to old-age psychiatry services. Such services are designed to deal with complex clinical situations but there will be instances in which people with depression in dementia are not referred to specialist services but remain either treated or untreated in primary care. Possibly, such cases would respond differently to antidepressants. However, nding unrecognised and untreated cases in primary care is dif cult and referral of such cases to specialist services is good practice. Given the participants were not drawn from specialist research clinics or tertiary care but from nine geographically diverse areas and a large number of clinicians representative of services in general (see Acknowledgements), the external validity of the results reported here will be maximised.

The drugs used in this study represent the two most used classes of antidepressants but the extent to whether or not other classes [e.g. dual-acting antidepressants, such as venlafaxine (Effexor , P zer)] might have an effect is unclear; however, it would be reasonable to expect broadly similar responses in drugs of the same general class.

Interpretation

The main message from this study is that the drugs from the two classes of antidepressants most likely to be prescribed for depression in AD appear to be no more effective than placebo. This negative nding does not seem attributable to the type or the severity of depression in dementia included, or to the severity and vascularity of the dementia included. In this, our results are in line with those of the DIADS-II study.[26,27] It is, however, encouraging for people with depression in dementia that there was a strong consistent pattern of improvement in the depression at 3- and 9-month follow-up for this group of people referred to old age psychiatric services. This study gives strong evidence that this improvement is not attributable to antidepressants. What this study cannot tell us is if this improvement is a function of the non-drug `treatment as usual' by these old age psychiatric services, or due to artefact such as regression of the mean, the Hawthorne effect, or part of the natural history of depression in dementia. The last is perhaps made less likely by the nding that 221/326 (68%) had been depressed for > 6 months prior to randomisation.

In terms of harms from medication, there were more adverse reactions in those treated with antidepressants compared with placebo as in other studies.[26,27] It is important to be cautious about drawing conclusions from the analyses of secondary outcomes; the key message remains that there is no positive effect of the antidepressants on any of the pre-speci ed comparisons compared with placebo. There is, however, a signal in the data that is consistent with the pattern of adverse reactions observed. There were fewer neuropsychiatric symptoms, and there was higher carer-rated participant quality of life, and higher carer quality of life in those treated with mirtazapine compared with sertraline. Also, carers of those receiving placebo had higher quality of life themselves and better mental health compared with those caring for people on sertraline. Taken together, even though these differences did not persist at the 39-week follow-up, they may suggest that sertraline has more negative impacts than mirtazapine. This is of clinical importance since it is common clinical practice to use sertraline following the positive results of the rst DIADS study.[26]

One of the unique elements of this study is the simultaneous evaluation of cost-effectiveness as well as clinical effectiveness. As far as we are aware, this is the first RCT with an economic evaluation of the use of pharmacotherapy for older people with dementia and depression. Because of the lack of significant pair-wise differences in costs or outcomes (CSDD score) between sertraline, mirtazapine and placebo, the active treatments mirtazapine and sertraline have a low probability of being cost-effective compared with placebo. However, it is interesting that when both active treatments are compared against each other, treatment with mirtazapine has a high probability of being cost-effective compared with sertraline.

Care professionals, policy-makers and people with dementia and their families are primarily interested in quality of life, and so a secondary cost-effectiveness analysis examined pair-wise cost differences between the three treatments relative to the incremental difference in QALY gain. There were non-significant pair-wise differences in costs or outcomes (QALY gains) between sertraline, mirtazapine and placebo. Sertraline had a low probability of being cost-effective compared with placebo. However, treatment with mirtazapine had a high probability of being cost-effective compared with placebo or when compared against sertraline.

This seems counterintuitive given the lack of clinical effectiveness demonstrated in the primary analyses. We considered possible reasons for this finding: first, there was a trend towards lower incremental costs and higher incremental QALY gains for mirtazapine when compared with sertraline and placebo, in turn. The trends observed towards lower costs were due to the significantly lower informal care inputs when patients treated with mirtazapine were compared with those treated with placebo or sertraline. The differences in improvements in quality of life could perhaps be explained in part by the effects of treatment with mirtazapine, such as amelioration of sleep disturbances or anxiety state not explored in this study.[58,59] Improvements in sleep could potentially enhance mood not captured by the CSDD and mood has been shown to be correlated with patient-reported EQ-5D scores.[60] In this way mirtazapine might have a more general effect that was beneficial for both the patient and the carer.

When looking at our secondary outcomes (such as quality of life and NPI) it may well be that the amendments to protocol in terms of sample size resulted in a loss of power for secondary analyses. As discussed above, during the study, the protocol needed to be amended after slower than expected recruitment. An interim analysis was completed of the primary outcome and the sample size was recalculated based on the estimates from the interim analysis. The variance in these CSDD scores was smaller than previously expected. So under the new calculation (of a smaller sample size), there was enough power to show the potential differences in the CSDD but there were no such analyses for the secondary outcomes. The study may therefore not have been sufficiently powered to test the patterns of response observed in the secondary outcomes.

In any case it is striking that in the long run those randomised to mirtazapine appear to use half as much carer time as those randomised to sertraline or placebo. Likewise the pattern of dominance of mirtazapine over sertraline is maintained in these analyses. This all provides further evidence that sertraline may not be a good choice for the treatment of depression in dementia. The extent to which this is generalisable to other SSRIs is not clear from our study. The potential positive effects of mirtazapine seem more general than specific and may act more in the realm of general behavioural and psychological symptoms in dementia (BPSD) than depression per se. It is possible, for example, that a positive effect on sleep or agitation in the person with dementia may result in relief, not only for the person with dementia but also the carer in terms of hours of care needed.

The development of BPSD (e.g. agitation, aggression, wandering, shouting, repeated questioning, depression and sleep disturbance) is common in dementia occurring at some stage in up to 90% of cases. These symptoms cause problems in themselves, which complicate care, and they can occur at any stage of the illness. They are a legitimate object for intervention to decrease distress and harm and increase quality of life for the person with dementia and their carers. One area for concern is the reflexive use of

antipsychotic drugs to treat these symptoms. A ministerial enquiry into the use of antipsychotic drugs in dementia concluded that `... current systems appear to deliver a largely antipsychotic-based response'.[61] It is clear that these medications are being prescribed to deal with BPSD rather than just for psychosis.

The evidence includes gaps, contradictions and complexity but there is emerging consensus with respect to the level of use and risk of antipsychotic drugs for people with dementia. Reviewing the evidence, these drugs appear to have only a limited positive effect in treating these symptoms but can cause signi cant harm to people with dementia. On balance, it appears that around 180,000 people with dementia are treated with antipsychotic medication across the country per year. Of these, up to 36,000 may derive some bene t from the treatment. In terms of negative effects that are directly attributable to the use of antipsychotic medication, use at this level equates to an additional 1800 deaths, and an additional 1620 cerebrovascular adverse events, around half of which may be severe, per year.[61]

Despite the limited evidence base, the use of non-pharmacological interventions as the rst-line treatment for BPSD re ects `best practice' when taking into account safety considerations and the high rates of resolution of symptoms with placebo in pharmacological trials.[31] The main reason for the widespread use of antipsychotic drugs is the limited evidence for alternative treatments. Other pharmacological treatments used include anticonvulsants (carbamazepine and sodium valproate), and antidepressants (trazadone and citalopram). The best evidence is for carbamazepine, which has been shown to be better than placebo for agitation in several small placebo-controlled trials,[62] but there is limited information about long-term safety in people with dementia. A recent meta-analysis concluded that sodium valproate was effective only at high doses that were associated with unacceptable side effects.[63] The results of double-blind placebo-controlled trials of trazadone have been disappointing.[64]

In a double-blind placebo-controlled trial of people with AD that predominantly focused on depression, citalopram was also associated with improvement in a number of other behavioural and psychiatric symptoms, including irritability and restlessness.[65] However, as neuropsychiatric symptoms were not the main focus of the study, only a modest proportion of participants had clinically signi cant behavioural and psychiatric symptoms at baseline and so the results are dif cult to interpret. In a de nitive trial of a cholinesterase inhibitor for the treatment of clinically signi cant agitation in people with AD, donepezil showed no advantage over placebo.[66] One recent reanalysis of a placebo-controlled trial of memantine in people with moderate to severe AD suggested that patients with neuropsychiatric symptoms bene ted from treatment.[67]

The data presented here suggest that there may well be value in conducting a RCT of mirtazapine for the treatment of BPSD; no such trial has ever been completed. One small-scale open-label pilot study gives supportive evidence for the potential of a trial in this area (those on mirtazapine did better).[68] Given the paucity of alternatives and the priority of nding safe and effective treatments for BPSD, these data suggest that a placebo-controlled trial of mirtazapine would be of value.

Chapter 5 Conclusions

Implications for health care

So what can be concluded? This study finds no evidence to support the use of antidepressants as as a first-line treatment for people with depression in AD who are referred to old-age psychiatry services as many cases will resolve with usual care and without sertraline or mirtazapine. An important exclusion to this are the most critical of cases (by reason for example of self-harm or other risk) which were not included in this study.

Stepped care, with `watchful waiting', is advocated currently for the general treatment of depression (without dementia) in the community. The first step is provision of `low-intensity psychosocial interventions' with more complex psychosocial interventions an alternative to antidepressants at the next stage of severity.[69] Those recruited into the trial will have received non-drug `treatment as usual' provided by the community mental-health teams to whom they were referred. This will have included a broad range of supportive and problem-solving interventions, commonly delivered by a community psychiatric nurse, often in their own household. This will have focused on problems encountered by the person with dementia and the carer, covering aspects of dementia as well as depression, and ranging in intensity from low to high as needed. Identifying which components of `usual care' may be effective is an important area for future research. Compared with this personalised care the Hawthorne effect of the study assessments is likely to have had only a minor impact. These data suggest that having depression in dementia may be an appropriate trigger for referral to specialist services where non-drug treatments can be deployed, perhaps avoiding the use of medication with potential for adverse reactions.

In summary, the practical implications of this study are that we should reframe the way we think about the treatment of people with dementia who are depressed, as the evidence does not support the routine prescription of antidepressants for depression in dementia. As we find no evidence to support use of antidepressants, it suggests that potential cases might be more appropriately managed by specialist services that are able to offer non-drug interventions for depression and case management, which may not be available in primary care. Based on the data (a decrease at 13 weeks and this then maintained), except for those in whom medication is indicated by risk or extreme severity, and in the absence of evidence to the contrary, it might be appropriate to reconsider antidepressant prescribing for those who have not responded within a 3-month period (Figure 9).

Recommendations for research

1. The secondary analyses presented here suggest that there would be value in carrying out a placebo-controlled trial of the clinical effectiveness and cost-effectiveness of mirtazapine in the management of BPSD.
2. A conclusion from this study is that it remains both ethical and essential for trials of new medication for depression in dementia to have a placebo arm.
3. Further research is required to evaluate the impact that treatments for depression in people with dementia can have on their carers, not only in terms of any impacts on their quality of life, but also the time they spend care-giving.
4. There is a need for research into alternative biological and psychological therapies for depression in dementia. These could include evaluations of new classes of antidepressants (such as venlafaxine) or antidementia medication (e.g. cholinesterase inhibitors).
5. Research is needed to investigate the natural history of depression in dementia in the community when cases are not referred to secondary care services.

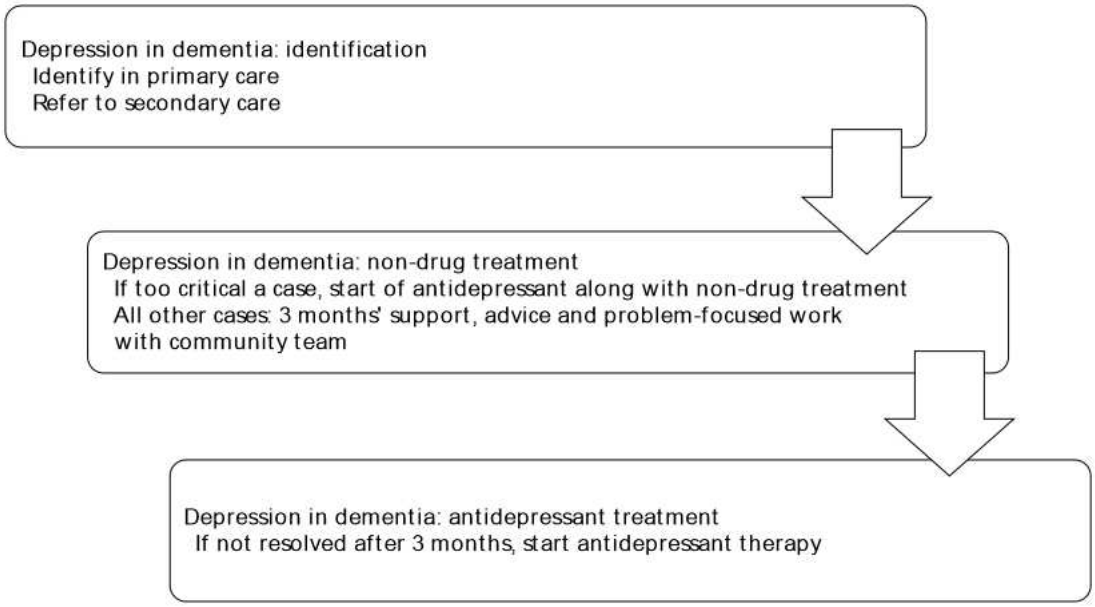

FIGURE 9 Management of depression in dementia.

6. Further work is needed to investigate the cost modelling results in this rich data set, investigating carer burden and possible moderators to the treatment effects.
7. There is scope for reanalysis of the primary outcome in terms of carer and participant CSDD results.

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SB was the chief investigator for the study, and designed and managed the study with input from the group. JH and MD undertook the statistical analyses. All authors participated in data interpretation. SB drafted the rst and subsequent versions of this report, with input and key revisions by all authors, who reviewed and approved the nal submitted report.

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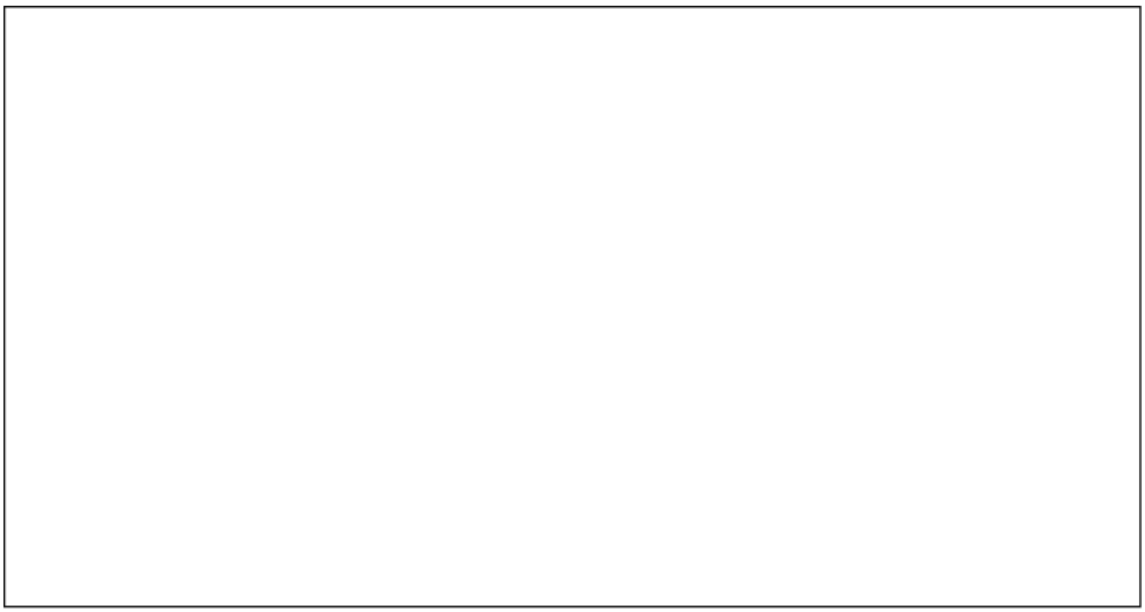
Appendix 1 Project protocol



1 GENERAL INFORMATION

1.1 Protocol Information

1.1.1 Compliance

The trial will be conducted in compliance with the protocol, the European Union Clinical Trials Directive (2001/20/EC), the associated UK Medicines for Human Use (Clinical Trials) Regulations (2004) and Medicines for Human Use (Clinical Trials) Amendment Regulations 2006, the Data Protection Act (1998), Ethics Committee and MHRA approvals, the principles of ICH Good Clinical Practice (GCP) guidelines (CPMP/ICH/135/95), the principles of the Declaration of Helsinki (1996) and other requirements as appropriate.

1.1.2 Name of person/s authorised to sign the final protocol and protocol amendments for the sponsor

The sponsor of the trial is the Kings College London and the nominated individual authorised to sign the protocol on behalf of the sponsor is Dr Gill Dale.

1.1.3 Peer-Review

This study has been subject to intensive independent anonymous peer review by the Health Technology Assessment Programme prior to their making their decision to fund this study.

Main Contacts

1.2.1 Sponsor

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1.2.4 Principal investigators

There will be 9 recruiting PI sites, where Research Workers will be employed. These 9 Recruiting PI sites are listed here. Each of these Recruiting PI's will have an Investigator Site File, managed by the Research Worker for that site. All participants will be registered as patients at the recruiting NHS Trust and that NHS Trust pharmacy will dispense study medication for that participant. The Recruiting PI will list all doctors, nurses, psychologists and other staff within that site on a `delegation of authority' form, which will clearly identify responsibilities within the study. Only authorised medical doctors within that site (i.e. those holding substantive or honorary contracts within that NHS Trust) may prescribe study medication.

There are also Referring Investigators, who will identify suitable potential participants and refer them to the Recruiting PI. Because the Referring Investigators will undertake assessments that will not be repeated by the Recruiting PI, all the Referring Investigators must be `part' of the study.

Therefore, each NHS Trust from which participants are referred to a Recruiting PI site will have an identi ed `Referring PI' who will be on the ethics application for that site and will hold a

`Referring Investigator Site File'. Any other clinician within that NHS Trust who is also willing to refer participants to the study must be listed on a `delegation of authority form' for that referring site. When the Research Worker receives a referral for the study from any authorised Referring Investigator within that site, he or she will copy the referral back into the `Referring Investigator Site File' for completeness of the NHS Trust records.

Copies of all delegation of authority forms for all sites must be sent to the Trial Manager, along with CVs for all those listed.

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Cornelius Katona
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Joanna Murray

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1.2.12 Study Medication Manufacture & Distribution

Manufacture of Mirtazapine

Genus Pharmaceuticals
As of 1st November 2009: Arrow Pharmaceuticals

Manufacture of Sertraline & Matching Placebo

P zer UK Limited

Manufacture of Mirtazapine Placebo, Central Packaging & Labelling & Distribution to Local Pharmacies

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Fax + 44 (0)1942 799799

1.3 Trial Committees

1.3.1 Trial Steering Committee (TSC)

The Trial Steering Committee (TSC) is responsible for the independent oversight of the progress of the trial, investigation of serious adverse events, and determining the future progress of the trial in light of regular reports from the DMC. The TSC has the power to prematurely close the trial. The TSC will meet annually or more often if the chair determines a reason for doing so and is composed of:

Professor Robin Jacoby, Professor of Old Age Psychiatry, University of Oxford (Chair)
Dr Cornelius Kelly, Consultant Old Age Psychiatrist, Central & North West Mental Health Trust
Dr Craig Ritchie, Clinical Research Fellow in Old Age Psychiatry, Imperial College London
Angela Clayton-Turner, Alzheimer's Society/Carer Representative
Professor Sube Banerjee (Chief Investigator)
Ms Rebecca Walwyn (Trial Statistician)
Niall McCrae (Trial Manager; Secretary to the TSC).

Invited observers include: NHS HTA, Sponsor, applicants.

Membership has been approved by the sponsor.

1.3.2 Data Monitoring Committee (DMC)

The Data Monitoring Committee (DMC) is independent and is responsible for monitoring progress of the trial and serious adverse events and reactions. The DMC will meet annually or more often

if the chair determines a reason for doing so. They will provide a con dential trial progress report at the end of each meeting which will be sent to the TSC. The DMC will agree their structure and organisation in an IDMC Charter (DAMOCLES Study Group, 2005) before randomisation commences. The DMC can

recommend premature closure of the trial to the TSC in accordance with the IDMC charter. The DMC is composed of:

Dr Peter Connolly, Consultant Old Age Psychiatrist, Murray Royal Hospital, Perth (Chair)
Dr Rowan Harwood, Medicine and Rehabilitation, Nottingham City Hospital
Dr Pat Shariatmadari, Alzheimer's Society/Carer Representative
Ed Juszczak, Senior Medical Statistician, Centre for Statistics in Medicine, Oxford.

1.3.3 Trial Management Group (TMG)

The Trial Management Group (TMG) is responsible for the day-to-day running and management of the trial. The full TMG will meet quarterly in the first year and biannually thereafter. It is composed of:

Professor Sube Banerjee (Chair)

All Investigators
Trial statisticians
Health economists User/Consumer representative Trial manager
Data manager (Secretary to the TMG)
Other HTA-SADD team members may attend as observers with the permission of the Chief Investigator.

Sub-committees may be formed from the full TMG for specific purposes (e.g. protocol development, writing papers, etc.). These committees will be appointed by the full TMG and will meet as necessary.

1.4 Staff Training Programme

All staff employed on the grant and all Investigators will be trained in:

- GCP
- Use of the assessment tools
- Trial standard operating procedures.

Up-to-date CVs of all staff working on the trial will be kept in the Trial Office along with a log of all trial training received by staff.

1.5 Declarations of Competing Interests

All Investigators have received support from pharmaceutical companies for example to attend conferences, for giving lectures, for the provision of consultancy, or for the conduct of research. No Investigator or member of staff employed on the grant has any shareholding in any company that might gain from the subject of this study.

2 ABBREVIATIONS

AE	Adverse Event	NASSA	Noradrenergic and Specific Serotonergic Antidepressant
AR	Adverse Reaction	NHS	National Health Service
ANCOVA	Analysis of Covariance	NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association
BADL	Bristol Activities of Daily Living (scale)	NPI	Neuro Psychiatric Inventory

CALM-AD	Cholinesterase Inhibitor in the Management of Agitation in Dementia	OCD	Obsessive Compulsive Disorder
CI	Chief Investigator	PI	Principal investigator
CIN	Carer Identification Number	PTSD	Post-Traumatic Stress Disorder
CIOMS	Council for International Organisation of Medical Sciences	QALY	Quality Adjusted Life Years
CSDD	Cornell Scale for Depression in Dementia	QRD	Quality Research in Dementia
CSRI	Client Service Receipt Inventory	R&D	Research & Development
CSO	Clinical Studies Officer	RCT	Randomised Controlled Trial
CTA	Clinical Trial Authorisation	REC	Research Ethics Committee
CTIMP	Clinical Trial of an Investigational Medicinal Product	RW	Research Worker
DEMQOL	Dementia Quality of Life	SADD	Study of Antidepressants in Dementia
DMC	Data Monitoring Committee	SAE	Serious Adverse Event
DSM-IV	Diagnostic & Statistical Manual, version 4	SAR	Serious Adverse Reaction
EC	European Community	SD	Standard Deviation
eCRF	Electronic Case Report Form	SES	Standardised Effect Size
EQ5D	EuroQol version 5D	SF-12	Short Form 12 version 2 (health survey)
GCP	Good Clinical Practice	SGOT	Serum Glutamic Oxaloacetic Transaminase
GHQ-12	General Health Questionnaire version	12	SGPT
GP	General Practitioner	SDW	Source Data Worksheet
HTA	Health & Technology Assessment	SmPC	Summary of Product Characteristics
IDMC	International Data Monitoring Committee (Charter)	SOP	Standard Operating Procedure
IMP	Investigational Medicinal Product	SNRI	Selective Noradrenergic Reuptake
LREC	Local Research Ethics Committee	SSRI	Selective Serotonin Reuptake Inhibitors
LSE	London School of Economics	SUSAR	Suspected Unexpected Serious Adverse Reaction
MH&N CTU	Mental Health & Neurology Clinical Trials Unit	TCA	TriCyclic Antidepressant
MHRA	Medicines & Health Care Products Regulatory Agency	TMF	Trial Master File
MHRN	Mental Health Research Network	TMG	Trial Management Group
MMSE	Mini-Mental State Examination	TSC	Trial Steering Committee
MRC	Medical Research Council	UK	United Kingdom

3 SUMMARY

3.1 Structured Synopsis

Primary Objective

1. To determine the clinical and cost effectiveness of two classes of antidepressants for depression in dementia (compared with placebo).
   i. To determine whether an SSRI (sertraline) is i) more clinically effective and ii) more cost effective than placebo in reducing Cornell depression score 13 weeks post randomisation.
   ii. To determine whether a NASSA (mirtazapine) is i) more clinically effective and ii) more cost effective than placebo in reducing Cornell Depression score 13 weeks post-randomisation.

Secondary Objectives

2. To investigate differences in the clinical and cost effectiveness, and, in terms of adverse events, withdrawals from treatment and adherence to treatment between mirtazapine and sertraline for depression in dementia at 13 and 39 weeks post-randomisation.
3. To investigate differences in the clinical and cost effectiveness of mirtazapine or sertraline compared with placebo on patient (e.g. quality of life, cognition) and family carer (e.g. carer burden, carer quality of life) outcomes at 13 and 39 weeks post-randomisation.
4. To investigate the influence on clinical and cost effectiveness of clinical characteristics including: dementia severity, dementia type, depression type, depression severity, care arrangements, neuropsychiatric symptoms, and physical illness.

Design

A multicentre double-blind placebo-controlled RCT of the clinical and cost effectiveness of two classes of antidepressants, and more specifically, mirtazapine and sertraline, from baseline to 3 months (13 weeks) and 9 months (39 weeks) enabling estimation of short and long-term impacts of these antidepressants on depression in dementia. Participants will remain on blinded study medication for a total of 10 months to allow time for data entry prior to routine unblinding.

Setting

Secondary care, referrals to old age psychiatric services and memory clinics in 9 regional sites each covering a catchment area of 100,000 older people (Birmingham, Cambridge, Leicester, Liverpool, Manchester, Newcastle, North London, Southampton and South London) aided by the Department of Health Mental Health Research Network (MHRN).

Target Population

People with probable and possible dementia of the Alzheimer type and co-existing depression.

Eligibility

This is a pragmatic trial. The criteria for inclusion are as close to clinical practice as possible. We will recruit those where a secondary care doctor makes a clinical diagnosis of mild to moderate probable or possible Alzheimer's Disease and a co-existing depressive illness of at least four weeks duration, likely to need treatment with antidepressants. The local research worker (RW) will then assess the patient's depression severity and those with a Cornell Scale for Depression in Dementia (CSDD) of 8+ will be eligible for entry into the trial. The other trial exclusions will be: the case being too critical to be randomised; absolute contra-indications to trial medications, being on another trial, and no family or professional carer to give collateral information.

Health Technologies Being Assessed

There will be three groups: 1. a Selective Serotonin Reuptake Inhibitor (SSRI), sertraline, with normal clinical care; 2. a Noradrenaline and Selective Serotonin Antidepressant (NASSA) mirtazapine, with normal clinical care; and 3. a control group, placebo, with normal clinical care. Interventions will be

presented in an identical double dummy form with all participants taking up to six capsules: up to three sertraline 50mgs or sertraline placebo; and up to three mirtazapine 15mgs or mirtazapine placebo.

Randomisation

Patients will be allocated to placebo, sertraline or mirtazapine (ratio 1:1:1) by the Mental Health & Neurology Clinical Trials Unit based at the Institute of Psychiatry. Allocation will be strati ed by centre by strati ed block randomisation with randomly varying block sizes. Allocation will be physically carried out during weekdays by phone, email or fax within 24 hours of a request.

Measurement Of Cost And Outcome

Cases identi ed will be assessed by a local research worker (G grade CPN or equivalent) who will collect baseline and follow-up data (0m, 3m, and 9m). The primary outcomes will be depression score - Cornell Scale for Depression in Dementia (CSDD) and cost - Client Service Receipt Inventory (CSRI). Secondary outcomes will include: adverse events, compliance, patient quality of life (disease-speci c DEMQOL, generic EQ5D), cognition (MMSE), behavioural and psychological symptoms (NPI), carer burden (Zarit), carer stress (GHQ12), and carer quality of life (SF12 v2). The analysis of the economic impact of the interventions is a central, fully integrated element of the proposed study. The comprehensive costs of care for all participants will be calculated (including the costs of formal care such as that provided by health and social services and also the costs of informal care) using data gathered using the CSRI completed by key workers or family carers at baseline, 13w and 39w. Unit costs will be best national estimates of the long-run marginal opportunity costs. Informal care will be costed.

Sample Size

An overall sample size of 507 patients will provide 90% power to detect a 2 point difference in CSDD (SD 5; SES 0.4) for the primary comparisons of mirtazapine vs placebo and sertraline vs placebo at 13 weeks and 86% power for the secondary analysis of these comparisons at 39 weeks. This allows for 10% loss to follow-up at 13 weeks and 20% loss to follow-up at 39 weeks, correlation between baseline and outcome CSDD> 0.6, and up to 12.5% of those randomized (per comparison) to be either drop-outs or drop-ins using an analysis of covariance with 2-sided 5% signi cance levels. Allowing for the same levels of loss to follow-up, an overall sample of 507 patients would also enable us to calculate 2-sided 95% con dence intervals for the difference in the proportion of pre-speci ed adverse events between the antidepressant arms of (a clinically signi cant) 10% (i.e. 5% vs 15%) 6% at 13 weeks and 7% at 39 weeks.

Statistical Analyses

Primary Analyses

CSDD score at 13 weeks will be analysed by ANCOVA adjusted for baseline CSDD and centre with contrasts for (a) sertraline vs placebo and (b) mirtazapine vs placebo.

Secondary Analyses

The ANCOVA of CSDD score at 13 weeks will further include a contrast for mirtazapine vs sertraline. CSDD score at 39 weeks will be analysed by ANCOVA adjusted for baseline CSDD and centre with contrasts for (a) sertraline vs placebo; (b) mirtazapine vs placebo, and (c) mirtazapine vs sertraline. Secondary outcomes will be compared using the same contrasts as above within a [longitudinal] generalised linear model framework adjusting for the respective baseline scores and centre. The signi cance level will be 5% (2-sided) for all speci ed analyses of the primary outcome variable and 1% (2-sided) for all speci ed analyses of secondary outcome variables.

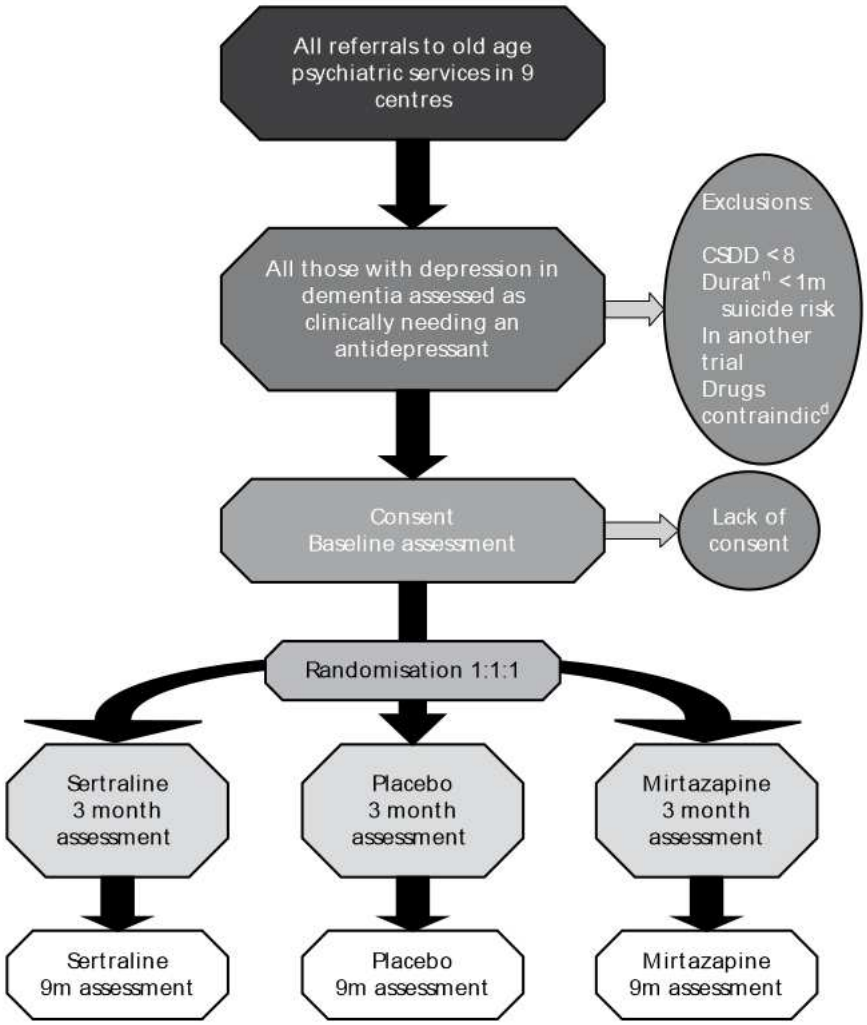
Economics

From the cost and the outcome data, we will compare total and component (by service or agency) costs, incremental cost-effectiveness ratios and net bene ts (using the primary outcome measure CSDD), cost utility ratios (using utility scores computed from the EQ-5D and societal weights) and cost-consequences results (using all non-cost outcomes measures). The primary evaluation will be the cost effectiveness analyses with CSDD change as the outcome. The evaluation will include the plotting of cost-effectiveness acceptability curves generated from bootstrap analyses. Sensitivity analyses will explore the impact of differences in key costs and outcome assumptions. Modelling will be conducted to predict costs and outcomes beyond the duration of the trial. The evaluation will be conducted from (a) societal, (b) public sector and (c) NHS perspectives.

Project Timetable

Month 6 to 0	development and nalisation of full protocol and CRFs, trial approvals sought;
Month 1 to 3	trial systems set up;
Month 1 to 3	manufacture and packaging of medications and placebo;
Month 3	training RWs, centres set up and priming;
Month 4 to 33	recruitment of patients, randomisation (30m);
Month 7 to 42	follow-up interviews (3m and 9m);
Month 43 to 45	nal analyses and study closeout.

3.2 Flowchart of Trial Design



4 BACKGROUND INFORMATION

4.1 Introduction including Relevant Studies

Depression occurs in at least 20% (Burns et al 1990; Ballard et al 1996a) of people with Alzheimer's disease (AD) in whom it causes considerable distress (Burns et al 1991), reduces quality of life (Burns 1991), exacerbates cognitive and functional impairment (Greenwald et al 1989), increases mortality (Burns et al 1991), and is associated with added carer stress and depression (Ballard et al 1996b). Treating depression is therefore a key clinical priority to improve the well-being, quality of life and level of function of people with Alzheimer's disease.

A Cochrane review completed in July 2002 Antidepressants for treating depression in dementia addresses directly the questions raised in the research brief (Bains et al. 2003); one of the applicants (TD) is an author of this review. The review identi ed six studies with 739 participants meeting inclusion criteria (all relatively unconfounded, double-blind, randomized trials comparing any antidepressant drug with placebo, for patients diagnosed as having dementia and diagnosed as having a depression according to established criteria). Only three studies, comprising 107 participants, had data that could be subject to a meta-analysis of ef cacy. Petracca et al (1996) studied 24 participants in a neurological out-patent clinic in Argentina in a double-blind placebo controlled crossover trial of clomipramine (a tricyclic antidepressant [TCA]) with two 6 week treatment periods with a 2 week washout period. There was a mean change of -10.7 on the Hamilton depression scale in the intervention group and 4.5 in the control group. Rei er et al (1989) selected 61 participants from two university outpatient clinics in an 8 week double-blind trial of imipramine (a TCA). The study showed no treatment effect. The third trial included was Lyketsos et al (2000), which is an interim analysis of data on 22 participants that subsequently were reported fully in Lyketsos et al (2003). These nal data were not available to the Cochrane review. In the nal study 44 participants were recruited from a single university out-patient clinic into a 12 week double-blind placebo controlled trial of sertraline (a speci c serotonin reuptake inhibitor [SSRI]). An effect size of 0.51 was reported with a mean change of -10.5 on the Hamilton depression scale in the intervention group and 4.5 in the control group and 9.9 and 3.2 in on the Cornell Scale for Depression in Dementia (CSDD; Alexopoulos et al 1988). Other than the further data on the additional 22 cases reported in Lyketsos et al (2003), we are not aware of any other studies published since that would have met the criteria for inclusion in the Cochrane review.

The main nding of the Cochrane review was that despite the clinical seriousness of the condition, there was only weak evidence available of the effectiveness of antidepressants in dementia. They noted that two of the studies used TCAs drugs not commonly used in this population , that only one used the most commonly used class of drugs, the SSRIs, and that there were no studies of the newer classes of antidepressants such as selective noradrenergic reuptake inhibitors. The review concluded that there was a need for further de nitive research of modern frequently used drugs . In addition they identi ed the need for trials to use instruments to measure outcome which have been validated for use in depression in dementia such as the CSDD.

It is clear that the participants recruited into all the trials discussed above were highly selected and so there may be limitations in the generalisability of the data derived from them. One element of this is the severity of depression recruited, with Lyketsos et al (2003) and Rei er et al (1989) requiring depression to meet DSM criteria for major depressive episode. Such disorders form only a small proportion of clinically signi cant depression requiring intervention in older adults in the community (Copeland et al 1990; Schaub et al 2003). Lyketsos et al (2003) acknowledged the need for research into the ef cacy of antidepressants in a wider range of depression type and severity, longer-term treatment, and the comparative ef cacy of different classes of antidepressants.

The Quality Standards Subcommittee of the American Academy of Neurology (Doody et al 2001) found that there was evidence of only moderate clinical certainty for antidepressants in the treatment of depression in dementia, concluding that SSRIs may offer some bene t with greater tolerability than

other antidepressants . They too reported the need for further research into the treatment of depression in dementia.

All of the studies to date are of short duration, and none tackle the crucial issue of whether there is longer term bene t associated with antidepressant treatment. It is unclear whether the differential ef cacy between the published studies relates to the choice of antidepressant, differences in study design and power or chance variation. Importantly, the literature does indicate that the successful resolution of depression is associated with cognitive and functional improvements (Greenwald et al 1989). There are however several cautions. For example, one study of the tricyclic antidepressant imipramine indicated that active treatment increased cognitive impairment and disability, whilst several studies of falls indicate that most antidepressants increase falls risk. In addition, there have been recent safety concerns relating to the SSRI sertraline and gastrointestinal bleeding (Anonymous 2004) and the SSRI paroxetine and withdrawal.

Depression is a major issue for the function and quality of life of people with dementia. A well- powered large randomised controlled trial (RCT) is crucial to determine the long-term clinical effectiveness, bene t to harm ratio and cost-effectiveness of antidepressant therapy in the treatment of depression in dementia, and to inform the optimal choice of antidepressant agent to enable best clinical practice and maximum bene t for people with dementia and their carers.

The HTA therefore prioritised this as an area for primary research and this protocol was successful in the competitive tendering process for a study that would ll these major gaps in the evidence base de nitively.

4.2 Consumer Involvement

This study has been developed in collaboration with the Alzheimer's Society. The consultations that have been conducted prior to the generation of this protocol are detailed below. The Alzheimer's Society is the leading care and research charity for people with Alzheimer's disease and other forms of dementia, their families and carers in the UK. It is a national membership organisation and works through nearly 250 branches and support groups. The Society is also a member of Alzheimer's Disease International and it works closely with dementia charities and organisations in other countries.

The Alzheimer's Society has an active research programme (Quality Research in Dementia - QRD), which is an active partnership between carers, people with dementia and the research community. The heart of Quality Research in Dementia is the QRD Advisory network of 150 carers, former carers and people with dementia who play a full role in all areas of setting priorities for research. They are involved in selecting and then commenting on grant applications and project monitoring.

The Alzheimer's Society, utilizing the QRD framework is therefore in an ideal position to act as an effective partner in the current project, having made an important contribution to our pre-trial consultation. One of the three co-PIs (Professor Clive Ballard) on this application is the Director of Research at the Alzheimer's Society and another (Professor Alistair Burns) is the chair of the Alzheimer's Society's Scienti c Advisory panel. One of the applicants is a nominee of the Alzheimer's Society (Mrs Shirley Nurock). All the centres have close and active links with their local Alzheimer's Society branches and consultation and collaboration on this project will take place on a local as well as a national level.

The QRD network has expressed enthusiasm and emphasised the importance of a strong consumer involvement in all key aspects of the study. QRD will be an integral part of the whole research process, from pre-trial design through project monitoring as a whole including the Trial Steering Committee, the Data Monitoring and Ethics Committee and the Trial Management Group with a remit for study monitoring and governance, concluding in the analyses, interpretation and dissemination of data generated. However, we will also look beyond QRD to also involve local user and carer groups in the study process and monitoring. This integration will enable broad and innovative dissemination of the

results to ensure that the important elements are communicated to people with dementia, carers and the general public as well as health care professionals, to enable effective implementation.

4.3 Choice of Trial Population

We have designed this study as a pragmatic trial of effectiveness in routine clinical practice. We wish to minimise exclusions from the study in order to maximise the generalisability of the data generated.

We are not intending to exclude participants on the basis of their taking concomitant psychotropic medication e.g. hypnotics, antipsychotics or cholinesterase inhibitors. These medications will be commonly prescribed in our study group and any such exclusions would limit the generalisability of the data generated, so compromising the pragmatic nature of the trial. Management of the participants in this study will therefore mimic true clinical practice with the sole exception of the trial medication.

4.4 Choice of Investigational Interventions

Inclusion of a TCA Arm

As discussed above and in the research brief, there are unanswered questions concerning what class of antidepressant to choose and how long to treat. We have designed this trial to attempt provide best-quality data on all these clinically important areas.

One possible area of contention is the appropriateness of including a tricyclic antidepressant (TCA) arm in the trial. This was referred to in the research brief. Prior to our initial submission we carried out a local consultation with people with dementia, family carers and clinicians in London, Manchester and within the Alzheimer's Society. The findings of this exercise were clear. Patients, carers and clinicians all believed that it would be unacceptable to randomise people with dementia to medication with a predictable set of negative (anticholinergic e.g. constipation, increased confusion, blurred vision, low blood pressure, drowsiness) side effects even given the fact that the competing classes of medication have their own profile of side effects. In addition clinicians reported to us that their clinical practice was not to use TCAs as a first line treatment for depression in dementia and that they believed people with dementia to be at a higher risk of harm from TCA side effects than people without dementia. They therefore raised questions of the clinical acceptability of a trial that included the possibility of randomisation to a TCA. To be successful we will need a large number of clinical teams to take part in case finding and if the trial is to generate real effectiveness data then these participants need to be an unbiased sample of all potential prescribers. On these grounds we therefore decided not to include a tricyclic antidepressant arm but instead to compare the clinical effectiveness and cost-effectiveness (including discontinuation and adverse events) of examples of the two classes of antidepressants most in use.

In the subsequent feedback from the HTA Commissioning Board we were invited to reconsider our decision not to include a TCA arm. We therefore consulted the Alzheimer's Society Quality Research in Dementia (QRD) Network. This is a panel made up of people with dementia and their carers that advises the UK Alzheimer's Society (AS) on research issues. The consultation was carried out by the AS Director of Research (Prof. Clive Ballard). He consulted regional co-ordinators of the Alzheimer Society's (QRD) and individual members of the network, representing the views of 45 QRD members; most with experience of caring for someone with dementia who has been treated with antidepressants. The purpose was to inform key aspects of the study, in particular whether it was appropriate to include TCAs as one of the treatments. All but one of the people responding strongly expressed the view that TCAs were an inappropriate treatment for people with dementia, describing a number of personal experiences where serious falls, increased confusion, urinary retention and other adverse events had resulted in a serious detrimental impact to the quality of life of the person with dementia.

We also consulted clinicians through the potential collaborating centres more widely and again there was a near unanimous view that it was not clinically supportable to initiate people with depression in dementia on a TCA. They also reported that the existence of such a possibility in randomisation would

discourage them from entering patients into the trial. At the very least it is therefore likely that there would be substantial selection bias (both in patient acceptability and clinician referral) introduced by the inclusion of a TCA arm. We therefore decided not to include a TCA arm.

Choice of Antidepressants

The selection of the best candidate antidepressants for this trial is not straightforward. Cost and power considerations dictate that an optimal design should include two active antidepressant treatments and a placebo. There are however several cautions. One previous small RCT has indicated bene t with the tricyclic antidepressant clomipramine (Petracca et al 1996), but other data indicate marked side effects and exacerbation of disability associated with TCA treatment. For example, one study of the tricyclic antidepressant imipramine, indicated that active treatment increased cognitive impairment and disability (Rei er et al 1989), whilst several studies of falls indicate that most antidepressants increase falls risk (e.g. Ensrud et al 2002). In addition, there have been recent safety concerns with SSRIs, particularly with respect to withdrawal effects and the potential risk of self harm (currently under review by the Committee for the Safety of Medicines).

Within this framework, the choice of speci c antidepressant agents requires careful consideration. For example, the best evidence of ef cacy in people with dementia is for the SSRI sertraline since that was the compound used in the Lyketsos et al (2003) RCT. But this was a very small trial and other SSRIs such as citalopram have also been reported to be effective in treating depression in later life including those with dementia but in less well designed studies (Nyth et al, 1992). Citalopram may have less interactions with other drugs than other SSRIs and people with dementia are usually recipients of polypharmacy. The most effective antidepressant in people without dementia is probably venlafaxine (Stahl et al 2002), but there are no RCTs in people with dementia and there are potential concerns regarding side effects in these individuals (Oslin et al 2003). A newer antidepressant, mirtazapine, has a good safety pro le and is widely used in clinical practice to treat depression in people with dementia, but has not been evaluated in a RCT for this indication.

In order to design and cost a trial of this sort there is a need to identify the compounds to be tested. We have therefore made the decision that our working trial design should include sertraline (the SSRI with the best evidence and which will be off licence by the end of the trial) and mirtazapine (the novel antidepressant with the least safety concerns). The doses chosen re ect common clinical practice for the treatment of depression in dementia and (in the case of sertraline) direct trial evidence (Lyketsos et al 2003), with higher doses than those suggested here (i.e. over 150mg of sertraline or 45mg of mirtazapine) being seen as less appropriate in people with dementia as well as depression.

Controls Use of Placebo

The research brief referred to comparison with standard care. Standard care for depression in dementia is generally the provision of antidepressants with SSRIs the most commonly used drugs (Doody et al, 2001). Standard secondary care is however much more than just medication. It involves a detailed multidisciplinary assessment of the person with dementia and their family carers with the generation of an individualised care package for each, often with continuing monitoring and follow-up (Banerjee 2001). We have therefore developed a study design whereby all participants receive full standard care with only the antidepressant element subject to investigation against placebo and between classes of compound.

Currently there is little convincing evidence that anti-depressant treatments are more effective than placebo in treating depression in dementia in real-world clinical practice. As discussed above, the data available are generally from small-scale studies of highly selected groups of patients with depression in dementia. The research brief requires a trial which can take the evidence base and clinical practice forward signi cantly. In these circumstances a placebo group is not just ethical, but probably essential. If antidepressants are indeed not effective, then the placebo group may do better as they should have fewer adverse events. The 1:1:1 randomisation results in a third of the participants receiving placebo. We

carried out a further consultation exercise on the acceptability of the inclusion of a placebo group with local people with dementia, family carers and clinicians. They were supportive of the strategy of using placebo in these circumstances as long as its use was minimised and that the information derived from the trial would yield a de nitive answer.

Run-in Period

One possible element of a trial such as this is the inclusion of a run in period. The potential value of this is to identify a group of people more likely to comply with subsequent data collection (i.e. to minimise loss to follow-up) and to identify a group of people with depression who are less likely to spontaneously recover (Ballard et al 1996c, Ballard et al 2001a,b). It is also possible that depression scores may be reduced by psychosocial interventions (Teri et al 2003), some of which may be provided as part of routine care. The result of these factors is a potentially high placebo response rate in clinical trials. The research brief was clear in its call for an evaluation of antidepressants in routine clinical practice and it is not routine clinical practice to precede the prescription of antidepressants for depression in dementia with a trial of a non-pharmacological treatment such as exercise. Instead we propose to include the clinically relevant inclusion criterion for the trial that the depression should have been present for at least 4 weeks.

The large sample size in this trial allows for the possibility of a high response in the placebo group. The placebo group also enables us to estimate the 13 and 39 week recovery rate with normal clinical care. We will be recruiting from a wide range of teams with heterogeneity in what constitutes normal clinical care . We will catch this variation by applying a typology of team intervention to identify those elements the team intervention offered and delivered as part of normal clinical care. We will then be able to complete secondary exploratory analyses to investigate the determinants of positive and negative outcome, controlling for the effect of antidepressants. Also we will have data from the Client Service Receipt Inventory (CSRI) on the services received by each patient so we can also include such input data into secondary analyses to test their in uences on the outcomes.

4.5 Choice of Primary Outcomes

The outcome measures have been chosen on the basis of their being the best-validated instruments available for the domains of function and activity of prime importance. We have balanced comprehensiveness with minimising respondent burden. The interview schedule is based on other successful trials in dementia (e.g. MRC CALM-AD) and designed to be completed in one session with the person with dementia and their carer lasting no more than 60 minutes.

4.6 Risks and Bene ts

4.6.1 Potential Risks

There are potential side effects of the medications but as these are being used within their licensing terms, the risks are well known.

Currently there is little convincing evidence that anti-depressant treatments are more effective than placebo in treating depression in dementia in real-world clinical practice. The data available are generally from small-scale studies of highly selected groups of patients with depression in dementia. The research brief required a trial which can take the evidence base and clinical practice forward signi cantly. In these circumstances a placebo group is not just ethical, but probably essential. If antidepressants are indeed not effective, then the placebo group may do better as they should have fewer adverse events. The 1:1:1 randomisation results in a third of the participants receiving placebo. We carried out a further consultation exercise on the acceptability of the inclusion of a placebo group with local people with dementia, family carers and clinicians. They were supportive of the strategy of using placebo in these circumstances as long as its use was minimised and that the information derived from the trial would yield a de nitive answer.

The research assessments can take a considerable amount of time, but will take place in the participants' homes to minimise inconvenience.

The placebo group will have untreated depression for the duration of the trial but this is justified in section 4.4 and all participants will be closely monitored and can withdraw at any time.

4.6.2 Potential Benefits

Participants will potentially benefit from an improvement in their symptoms.

5 TRIAL OBJECTIVES AND PURPOSE

5.1 Aims

To conduct a multicentre double-blind placebo-controlled RCT of the clinical and cost- effectiveness of two classes of antidepressants, and more specifically mirtazapine and sertraline, at 3 months (13 weeks) and 9 months (39 weeks) post randomisation. The primary outcome will be the 13 week outcome with assessment of long term outcome at 39 weeks.

5.2 Objectives

5.2.1 Primary Objectives

5.2.1.1

To determine the clinical and cost effectiveness of two classes of antidepressants for depression in dementia (compared with placebo).

(a) To determine whether a Selective Serotonin Reuptake Inhibitor (SSRI, sertraline) is (i) more clinically effective and (ii) more cost-effective than placebo in reducing Cornell depression score 13 weeks post randomisation.
(b) To determine whether a Noradrenaline and Selective Serotonin Antidepressant (NASSA, mirtazapine) is (i) more clinically effective and (ii) more cost-effective than placebo in reducing Cornell Depression score 13 weeks post-randomisation.

5.2.2 Secondary Objectives

5.2.2.1

To investigate differences in the clinical and cost effectiveness, and in terms of adverse events, withdrawals from treatment and adherence to treatment between mirtazapine and sertraline for depression in dementia at 13 and 39 weeks post-randomisation.

5.2.2.2

To investigate differences in the clinical and cost effectiveness of mirtazapine/sertraline and placebo on patient (e.g. quality of life, cognition) and family carer (e.g. carer burden, carer quality of life) outcomes at 13 and 39 weeks post-randomisation.

5.2.2.3

To determine the influence on clinical effectiveness and cost-effectiveness of clinical characteristics of importance including: dementia severity, dementia type, depression type, depression severity, care arrangements, neuropsychiatric symptoms, and physical illness.

(a) To investigate what baseline factors (other than randomised treatment) predict a reduction in Cornell Depression Score at i) 13 weeks and ii) 39 weeks.

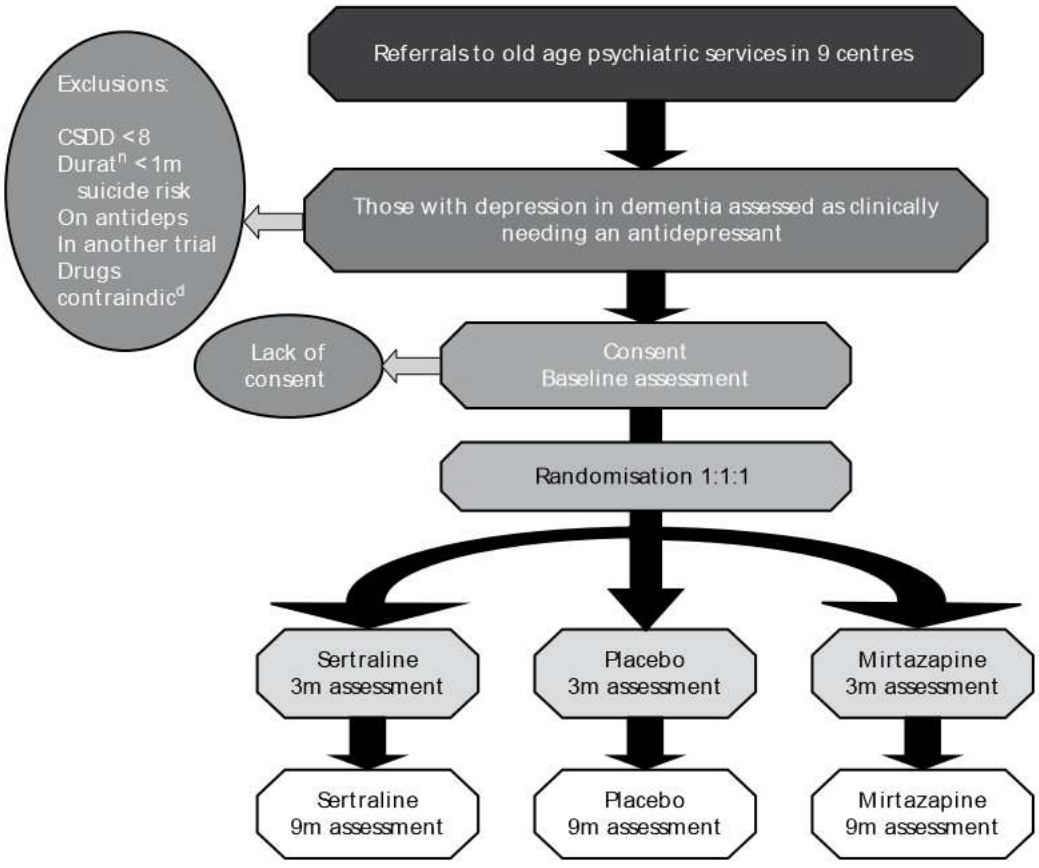
(b) To investigate whether there are any differential predictors of response to the antidepressants (both vs placebo) (i.e. treatment-covariate interactions).

6 TRIAL DESIGN

6.1 Description of Overall Trial Design and Plan

We propose to conduct a multicentre double-blind placebo-controlled RCT of the clinical effectiveness and cost-effectiveness of two classes of antidepressants, and more speci cally mirtazapine and sertraline, at 3 months (13 weeks) and 9 months (39 weeks) post randomisation. The primary outcome will be 13 week outcome with assessment of long term outcome at 39 weeks.

6.2 Schematic Trial Flow Diagram



6.3 Trial Duration

6.3.1 Duration of the treatment period

Ten months. Nine months de ned as 39 calendar weeks post randomisation to nal follow up plus one month further randomised treatment to allow for clinical transfer of care and database closure prior to routine unblinding.

6.3.2 Duration of the follow-up period

Short-term outcomes will be ascertained at 3 months (13 calendar weeks), long term outcomes will be ascertained at 9 months (39 calendar weeks) post randomisation. Safety outcomes will also be collected at 10 months, as participants come off the trial medications. Any ongoing serious adverse events will be tracked until closed.

TABLE 6.4.1 Research assessments by timepoint

	Informant	Screening	Baseline & randomisation	Wk 13	Wk 39	Treatment discontin^{n}	Trial drop out
Consent to pre-trial	Patient/ Carer	7					
Eligibility assessment	Doctor/RW	7					
Informed consent	Patient/ Carer	7					
NINCSD-ADRDA (for dementia)	Doctor	7					
Modi ed Hachinski Ischemic Scale (MHIS, vascularity)	Carer		7				
DSM-IV (for Depression)	Carer		7	7	7		
Olin (Depression in Dementia)	Carer		7	7	7		
Cornell Scale for Depression in Dementia (CSDD)	Patient/ Carer		7	7	7	7	7
Demographics participant	Carer		7				
Demographics carer	Carer		7				
Client Service Receipt Inventory (CSRI)	Carer		7	7	7		
DEMQOL	Patient		7	7	7		
DEMQOL-Proxy	Carer		7	7	7		
EQ5D (Patient)	Patient		7	7	7		
EQ5D (Proxy)	Carer		7	7	7		
SF-12 v2 (Carer)	Carer		7	7	7		
Mini-Mental State Examination (MMSE)	Patient		7	7	7		
GHQ-12 (Carer)	Carer		7	7	7		
Zarit Carer Burden Scale (ZCBS)	Carer		7	7	7		
Neuropsychiatric Inventory (NPI)	Carer		7	7	7		
Bristol Activities of Daily Living (BADL)	Carer		7	7	7		
Carer global impression of change	Carer			7	7		
Medical history	Carer		7				
Adverse Events Checklist	Carer			7	7	7	7
Adverse Events Log	Carer			7	7	7	7

continued

TABLE 6.4.1 Research assessments by timepoint (continued)

	Informant	Screening	Baseline & randomisation	Wk 13	Wk 39	Treatment discontinn	Trial drop out
Pill Count	RW			7	7	7	7
Medication Preference	Carer		7				
Treatment Guess	Carer/RW			7	7	7	7
Concomitant Medications	Carer		7	7	7	7	7
Concomitant Treatments	Carer		7	7	7	7	7
Trial Treatment Log	Carer			7	7	7	7

TABLE 6.4.2 Other trial forms by timepoint

	Informant	Screening	Baseline & randomisation	Wk 13	Wk 39	Treatment discontinn	Trial drop out
Registration form	RW	7					
Exclusion Form	RW	7					
Randomisation Request Form	RW		7				
Serious Adverse Event Report Form	RW/Doctor			7	7	7	7
Withdrawal Form	RW/PI			7	7	7	7
Unblinding Request Form	RW/PI			7	7	7	7

6.3.3 De nition of completion of the trial for an individual participant

Completion of 10 months on the trial medication or withdrawal from follow-up for any cause before. Participants may withdraw from the trial medication but remain in follow-up. Participants may not formally withdraw from follow-up and remain on the trial medication.

6.3.4 De nition of the end of the trial

In ethics and regulatory terms, the end of the trial is de ned as the end of data collection i.e. 10 months after the randomisation of the last patient into the trial (to allow for the collection of adverse events and concomitant medications until all patients have stopped taking the trial medication). In terms of the funder, the end of the trial is de ned as the provision of the nal report to the HTA.

6.4 Overview of Data Recording and Case Report Forms

An overview of data recording and the content of case report forms is given below in table 6.4.1 (research assessments by timepoint) and table 6.4.2 (other trial forms by timepoint).

6.5 Research Setting

Participants will be drawn from secondary care as stipulated in the research brief. These will be referrals to and other contacts with old age psychiatric services and memory clinics in 9 regional sites each covering a catchment area of at least 100,000 older people each (Birmingham, Cambridge, Leicester, Liverpool, Manchester, Newcastle, North London, Southampton, South London/Kent).

The applicants are at the centre of networks of old age psychiatric and memory services in their regions. The study has been adopted by the DH-funded Mental Health Research Network (MHRN) and will bene t from its resources in facilitating trial approvals and recruitment in the study sites. Support will also be sought from the emergent Dementia and Neurodegenerative Disease Research Network (DeNDRoN).

7 SELECTION AND WITHDRAWAL OF PARTICIPANTS

7.1 Number and Source of Participants

General Issues

In order to succeed this trial needs to recruit a large number of people with depression in dementia in a relatively short period of time (one year) and then follow them up over 9 months. Also, given that this is an effectiveness trial, these participants need to be representative of all people with depression in dementia presenting to secondary care (as stipulated in the research brief). The need to recruit quickly and broadly requires a multicentre approach. However, both criteria also require that our participants are not simply drawn from highly specialist research centres rst because of the need to maximise generalisability but also because the number needed could not be generated to time by existing research facilities (e.g. university memory clinics).

A nal cardinal design issue consequent to this is that the recruitment of participants will require the active and prolonged collaboration of numerous old age psychiatrists and their teams. For this to work requires as little a burden on these teams as possible. After considerable consultation, drawing on the experience of other successful trials in dementia (e.g. MRC CALM-AD) and the comments of reviewers and the Commissioning Board, we have designed a robust multicentre recruitment and follow-up strategy which will interfere as little possible with routine clinical care.

Establishing the Multi-Site Recruitment Frame

Our participants will be drawn from referrals to and other contacts with old age psychiatric services in England; these will include community mental-health teams and their associated memory clinics. Each centre has well developed successful research links with a network of such local service providers. The local PIs in each university centres will establish and co-ordinate a local network of service providers in their area participating in this trial. Old age psychiatric services are provided on catchment area basis with individual consultants and their teams responsible for a geographically de ned area. These catchment areas are typically described in terms of the numbers of older people (i.e. over 65) falling within the area and so the responsibility of the consultant and team. The size of these catchment area varies from 7,000 to 20,000 older people per full time consultant.

Each local PI will establish a local network for the trial covering at least 100,000 older people. Depending on local con guration of teams and trusts this will represent the catchment areas of 7-14 community mental health for older adults teams provided by 2 to 6 NHS Trusts. This creates exactly equivalent areas for recruitment in each centre, enabling equal recruitment from each site and so requiring equal resource for recruitment in each area. In addition to this a further reserve list of potential local teams will be identi ed covering a further 50,000 older adults to enable substitution or addition of teams if services withdraw from the study or if recruitment fails to meet target levels.

Planned Recruitment Rate and Feasibility

There are nine centres each expected to recruit 57 patients. One RW is employed at each site, who will assess patients referred to the trial from clinical old age psychiatric services.

Recruitment will be pursued through all psychiatric services, particularly focusing on new referrals to outpatient clinics, community teams and memory clinics, but also screening other secondary contacts

including care homes. It was originally anticipated that a catchment area of 100,000 would yield at least 100 referrals of people with dementia per month, and that on a conservative estimate 20% of these would have depression, equating to 240 potential cases per centre per year.

Initially the recruitment period was 12 months, but as the target transpired as rather more dif cult to achieve than anticipated, partly because many patients have already been prescribed anti-depressants by GPs prior to referral, an extension to the recruitment period was sought. The HTA agreed to this request on 15th May 2008. The recruitment period is 30 months. The HTA have agreed to a minimum recruitment target of 1.3 per site per month, although sites will continue to aim for 2 recruits per month. Recruitment rates of 1.3 and 1.5 per site per month would generate 351 and 405 participants respectively. Recruitment will be monitored formally on a monthly basis centrally and if any site fails to achieve its minimum recruitment target, extension funding may be transferred to another site. Sites have been allocated extension funding beyond the original period to employ a RW on a half-time basis. Note that the Leicester site will not receive extension funding, the allocation has gone to Birmingham which has recently expanded to trusts across the West Midlands.

7.2 Recruitment Strategies

We will employ a single local RW in each site to carry out all study-related work. This will include publicising the trial and maintaining awareness, but the major role of the local RW will be to carry out recruitment and follow-up interviews.

Referring Investigators will identify cases meeting study criteria and will document in their medical notes that they have obtained verbal consent for the RW to contact cases to discuss the study and obtain written consent to the trial. We will recruit those in whom a secondary care doctor makes a clinical diagnosis of mild to moderate probable or possible Alzheimer's Disease (MMSE> 8) and a co-existing depressive illness likely to need treatment with antidepressants with a duration over 4 weeks as detailed below. The RW will actively promote the study with the participating Referring Investigators to help maximise referrals into the study.

When a case is identi ed the RW will then assess the patient within one week at a place of the patient and carer's choosing. Our experience suggests that this will most commonly be the person with dementia's household rather than a clinic or GP surgery. This is a function of the age and frailty of the population under study. This accords with normal old age psychiatric practice where home assessment and delivery of care is the norm. The RW will extract data from the participants' NHS notes in order to minimise duplication. The assessment interview will ascertain type of dementia and depression according to set diagnostic criteria: NINCDS-ADRDA [McKhann et al 1984] for dementia; DSM-IV for depression (American Psychiatric Association 1994); the Olin criteria speci cally designed for depression in dementia (Olin et al 2002); and depression severity (CSDD). The purpose of this diagnostic work is not to exclude further individuals from the study (this would limit the generalisability of the ndings) but instead to closely characterise the cases on the basis of diagnoses and severity to enable us to be able to describe the study group in detail and to be able to investigate as secondary analyses the effect of diagnostic group and severity on subsequent outcome.

The local RW will complete a semi-structured interview with the person with dementia and their main carer. This interview will include the primary and secondary outcome measures (please see below) and possible moderating variables including behavioural and psychological disturbance (Neuropsychiatric Inventory, NPI, Cummings et al, 1994]), physical illness, and severity of cognitive impairment (MMSE Folstein et al 1975).

In industry ef cacy studies recruitment is often managed by the use of payment by case recruited. In this existing resource (often the highly selected participating consultant or worker in a specialised clinic) is used to carry out the trial assessments. This is not possible within this trial since there are no local research resources that could be used in this way to carry out the detailed and systematic assessments

required at baseline and follow-up. It would not be feasible to expect the wide range of local consultants needed in this effectiveness study to complete these assessments and it would be very difficult to control and assure data quality.

We will work closely with the MHRN as a local and national partner. We have discussed their possible role. They will play a vital role in expediting local R&D approvals and ethical approvals. They will promote the study within the mental health trusts they cover and will help with recruitment monitoring and problem-solving if needed. What they are unable to provide is direct help with recruitment or individuals to carry our assessments and recruit to the study. This is not their role. The DeNDRoN will be setting up through the life of the trial but will also have no resource to help directly recruit to the study.

If payment by case is not possible then specific resource needs to be made available in each recruiting site. We estimate that the minimum level of staffing needed to complete these tasks is 1.0WTE (whole time equivalent) RW in each site. The rationale for the equality of provision over the nine sites is that the work demanded is equal over the nine sites.

Monitoring and Ensuring Recruitment to the Trial

Recruitment will be monitored by the TMG, the TSC and the DMC as well as the MHRN. The intention will be to identify problems early and problem solve to bring recruitment back on track. We propose that centres are given 6 months funding for a full time RW in the first instance with continuation of funding depending on satisfactory recruitment. If recruitment is low then only 0.5WTE will be continued in that site and the resource freed (i.e. funding rather than a person) will be used to extend or bolster a centre with effective recruitment although we hope that this will not be necessary.

The local recruitment frames are the same size and there will be careful monitoring and support to maximise recruitment. We believe that all these factors will minimise the likelihood of failure to recruit in individual centres and overall.

7.3 Consent Procedures

The main potential ethical issue in this study is that dementia itself may interfere with an individual's ability to give their informed consent, especially in more severe stages of the illness. Carers and people with dementia have contributed to finalising the information sheets and consent forms. We estimate on the basis of previous experience that less than 20% of potential participants will lack capacity to give informed consent.

The issue of informed consent in people with Alzheimer's disease is complex. Full informed consent will be obtained where possible. If the person with dementia does not have the capacity to consent, then the next of kin or primary carer of the patient will be asked to act as the personal legal representative to the person being enrolled in the trial. This person would also be expected to act as caregiver informant on the study. We will rely on them to use their previous knowledge of the individual in terms of any stated preference for research, to assess whether they would have agreed to take part if they had capacity.

The study RWs will be trained in issues of obtaining consent by the local Recruiting PI and will only be delegated to undertake this task if their skills in this area are satisfactory. The Referring Investigator will obtain verbal consent for the potential participant to be approached by the RW and will document this in their medical notes. The RW will telephone the potential participant and their caregiver to confirm their agreement to be approached and to arrange a screening visit appointment. The RW will send them each a pack containing all of the following documents to read and consider prior to the screening visit:

- `Information and Consent Form for Patient (full version)'
- `Information and Assent Form for Patient (shortened version)'
- `Information Sheet and Consent Forms for Carer'.

At the screening visit, if the patient has capacity to consent, they will be asked to read and sign an `Information and Consent Form for Patient (full version)'. If they lack capacity, they will be given an `Information and Assent Form for Patient (shortened version)' and if possible they will sign the form to indicate their assent. If this is not possible and they can only give verbal assent, the caregiver will be asked to sign the form to witness the patient's verbal assent.

The caregiver will be asked to read the `Information and Consent Forms for Carer'. Within this document there are two consent forms. As data will be collected directly from carers about their experiences and health status, a separate consent form will be signed by the carer to cover this data. Therefore if the patient has capacity to consent, the caregiver will be asked to sign the `Carer Consent for Carer Participation' form only. However, if the participant lacks capacity and has only given been able to give their assent to participate, the carer must also sign the `Carer Consent for Patient Participation' form.

In practical terms, when the participant is approached to be interviewed or to take the study medication, that individual will be able to indicate whether he or she wishes to be interviewed or take the medication. The interviews and recruitment will be completed only if there is no sign of distress in the person with dementia. This is an approach that has been used successfully in trials and other descriptive and evaluative studies.

The study RW will discuss the study in detail with participants and carers and will obtain consent as described above. Participants will be given as long as they wish to consider participating before the end of the recruitment phase, but a minimum of 24 hours. It is expected that it will normally take at least a week between the initial approach by the Referring Investigator and the taking of consent by the RW.

7.4 Eligibility Criteria

7.4.1 Inclusion Criteria

We have designed this study as a pragmatic trial of effectiveness in routine clinical practice. We wish to minimise exclusions from the study in order to maximise the generalisability of the data generated.

The criteria for inclusion are set to be as close to clinical practice as possible. For this reason we do not specify the use of anything other than clinical diagnoses of dementia and depression since standardised instruments (other than the MMSE as a measure of severity) are not used in routine practice. A detailed characterisation of cases using standardised tools will be completed at the research assessment. We will recruit those in whom a secondary care doctor makes at the point of referral to the RW:

- a clinical diagnosis of mild to moderate probable or possible Alzheimer's Disease,
- a co-existing depressive illness likely to need treatment with antidepressants, and
- that depression should have a duration of more than four weeks.

7.4.2 Exclusion Criteria

Again we wish to minimise exclusions. We will exclude from the trial those in whom a secondary care doctor nds at the point of referral to the RW are:

- currently taking antidepressants;
- those with severe dementia (de ned as the participant being unable to contribute to theCSDD);
- the case is considered as being too critical to be randomised (e.g. because of suicide risk);
- displays absolute contraindications to one or more of the trial treatments;
- they are on another trial; and
- those where there is no identi able family carer or other informant (e.g. a formal/professional carer who spends suf cient time with the person with dementia to be able to give an informed opinion) to give collateral information.

We will further exclude from the trial those in whom the RW nds have:

- a Cornell score < 8 at the point of randomisation.

The impact of these exclusions is likely to be small with our estimate that around 10% would be excluded by reason of severity and 10% by reason of lack of identi ed carer. The carer exclusion is needed because our primary outcome measure, the Cornell, is a carer report instrument. However, we will not require carers to be co-resident or to be providing hands-on care (many will see themselves as supporters or simply family members rather than carers per se), also information can be obtained by friends and neighbours or professional carers who take on a caring or support role.

Given our intention to ensure that the trial follows routine clinical practice as closely as possible, we would seek to recruit patients for whom switching of anti-depressants has been deemed necessary by their referring clinicians, after allowing an existing therapy a reasonable chance to work. Timing of trial initiation would be determined by normal clinical practice for the initiation of sertraline or mirtazapine. An existing regimen may continue up to the point of referral, depending on the drug and prescribing guidelines. Patients must not be taking another anti- depressant while participating in the trial.

We are not intending to exclude participants on the basis of their taking concomitant psychotropic medication e.g. hypnotics, antipsychotics or cholinesterase inhibitors. These medications will be commonly prescribed in our study group and any such exclusions would limit the generalisability of the data generated, so compromising the pragmatic nature of the trial. Management of the participants in this study will therefore mimic true clinical practice with the sole exception of the trial medication.

The Referring Investigator will refer potentially eligible patients to the Recruiting PI for eligibility assessment. The RW will review the case notes for eligibility criteria. The RW will contact the patient and carer by phone to ask if they would like an appointment to be considered for the trial and if the carer is, in principle, willing to participate as the participant's informant. An `Information and Consent Form for Patient (Full version)', an `Information and Assent Form for Patient (Shortened version)' and an `Information and Consent Forms for Carer' should then be posted to both the potential participant and the carer. Patients cannot participate in the trial without a carer informant to complete the assessments. After screening, the RW will review the patient according to the eligibility criteria above and will then discuss and review the eligibility criteria and case notes for each participant that appears to meet eligibility criteria with the Recruiting PI. This discussion will be documented and signed by the Recruiting PI prior to randomisation.

7.5 Screening/Baseline Procedures

7.5.1 Time Periods

Referrals to the trial will be randomised within a maximum of 28 days of having been seen by the Referring Investigator, although it is expected that they will be randomised within 14 days of having been seen by the Referring Investigator.

In order to ensure study medication availability and to ensure statistical credibility, follow-up interviews must be completed within strict timelines.

The week 4 phone contact must be completed between 21 and 28 days from treatment start date in order to decide whether to dose increase at Day 28. The week 8 contact, if needed, should be completed between 49 and 56 days from treatment start date.

The 13 week (3 calendar month) and 39 week (9 calendar month) assessments must be completed at those timepoints + /- 7 days from randomisation

7.5.2 Informed Consent for Eligibility/Baseline Assessment

A log will be kept by the RWs of everyone referred to them and their path through the trial for the purposes of the CONSORT diagram (see Appendix 5). Research workers will be assisted by MHRN clinical study of cers (CSOs) in identifying and recruiting participants to the study. RWs and CSOs will work together to decide how trial related activities are shared within their area. Where RW is speci ed in this section, both the RW and CSO are included.

Referring Investigators will identify cases meeting study criteria and will obtain verbal consent to refer to the Recruiting PI. The referral letter will be copied to the RW. The Recruiting PI and the RW will work together to recruit the patient to the trial. We will recruit those who meet the eligibility criteria as de ned in Section 7.4 above. The RW will actively promote the study with the Referring Investigators to help maximise referrals into the study.

Once a referral is received, the RW will then telephone the potential participant and their carer to arrange an appointment and to inform them that a long patient information sheet, a short patient information sheet and a carer information sheet will be posted to the potential participant and participant's carer in advance of the appointment so that they have time to read them through and consider whether they wish to participate. The RW should explain that there is a long and a short patient information sheet so that on a case by case basis the patient and/or carer can decide which is more appropriate for each patient.

The RW will assess the patient within 28 days of receiving the referral letter at a place of the patient and carer's choosing. Our experience suggests that this will most commonly be the person with dementia's household rather than a clinic or GP surgery. The assessment interview will ascertain type of dementia and depression according to set diagnostic criteria: NINCDS- ADRDA [McKhann et al 1984] for dementia; DSM-IV for depression (American Psychiatric Association 1994); the Olin criteria speci cally designed for depression in dementia (Olin et al 2002); and depression severity (CSDD).

The local RW will complete a semi-structured interview with the person with dementia and their main carer. This interview will include the primary and secondary outcome measures (please see sections 10.3.1.1 and 10.3.1.2) and possible moderating variables including behavioural and psychological disturbance (Neuropsychiatric Inventory, NPI, Cummings et al, 1994]), physical illness, and severity of cognitive impairment (MMSE Folstein et al, 1975).

7.6 Randomisation and Enrolment Procedure

7.6.1 Method of Identi cation of Participants and Carers

The local RWs will assign Participant Identi cation Numbers (PINs) and Carer Identi cation Numbers (CINs) to each patient carer dyad once they receive a referral letter from the Referring Investigator. The PIN will start with a P (to indicate that it refers to a patient), will be followed by a two-digit number to indicate the centre (Birmingham = 01; Cambridge = 02; Leicester = 03; Liverpool = 04; Manchester = 05; Newcastle = 06; North London = 07; Southampton = 08; and South London/ Kent = 09) and then a three-digit number indicating the number within the centre. The CIN will be formatted in the same manner except that it will start with a C (to indicate that it refers to a carer) and it will end with an 'A' to indicate that they are the original carer. These identi cation numbers will be unique to an individual and will remain with the patients and carers throughout the trial. New carers who may join during the trial (if, for example, the original carer becomes incapacitated) will be assigned their own unique CIN, which will be the same as the original carers CIN but with the nal character of the CIN changing (A, B or C). Using this system, data management can see when a new informant carer has become involved. This is very important as it may have a signi cant impact on the assessments.

7.6.2 Method of Randomisation (inc. Allocation Concealment)

Patients will be allocated to placebo, mirtazapine or sertraline (ratio 1:1:1) by the Mental Health & Neurology Clinical Trials Unit (MH&N CTU) based at the Institute of Psychiatry. Allocation will be strati ed by centre (Birmingham, Cambridge, Leicester, Liverpool, Manchester, Newcastle, North London, Southampton, South London/Kent) by strati ed block randomisation with randomly varying block sizes.

7.6.3 Implementation Procedures

The medication will be sent to an independent company (Catalent, Bolton) for manufacture of placebo to mirtazapine and this company will handle the pre-packaging and labelling of all the study medications. The MH&N CTU (while keeping the Trial Statistician blind) will communicate the randomisation sequence to this company so that they can package the study medications accordingly. The study medications will then be sent to the relevant pharmacies (ensuring that the pharmacies remain blind). Once an eligible patient carer dyad has completed the baseline assessment and provided written informed consent, a member of the local trial team will complete a Randomisation Request Form and contact the MH&N CTU via email, phone or fax to register the request. Once the MH&N CTU are happy that the patient is eligible and that minimal baseline data is available, they will notify the local pharmacy, the Recruiting PI and the RW within 24 hours of the request (Mondays to Fridays, 9am to 5pm, except bank holidays) which treatment pack number to dispense to the patient and copy this communication to the Trial Managers Of ce. The local pharmacy will then acknowledge to the MH&N CTU that they have received this information. The RW will ensure that this number is entered correctly on the trial speci c prescription and signed by the Recruiting PI. When pharmacy receives the prescription they will cross check the prescription with the fax from the MH&N CTU to ensure there has been no error.

7.7 Withdrawal of Participants from the Trial

It is the aim of the trial to minimise withdrawal of participants from treatment and follow-up. Withdrawal may be initiated by the participant, their carer, the Recruiting PI or their Referring Investigator. Withdrawal from treatment is separated from withdrawal from follow-up assessments.

7.8 Loss to Follow-Up

We estimate a loss to follow up of 10% at 13 weeks and 20% at 39 weeks. One of the features of the natural history of dementia is that this is a substantial mortality associated with the disorder. We estimate there will be a 3% mortality at 13 weeks and a 9% mortality at 39 weeks with the rest of the loss to follow up contributed by refusal, loss of carer, or death of carer.

Loss of data by to follow up other than by death will be minimised by all means including the following: carrying out assessments at the subject's home; prioritising order of collection of follow-up data to safeguard primary endpoints; and using telephone interviewing of carers if necessary.

Loss to follow-up will be monitored locally and centrally. If a participant or carer is identi ed as potentially lost to follow-up, procedures will be put in place to avoid loss to follow-up and to obtain data. They will only be regarded as lost to follow-up following agreement with the Recruiting PI and the Trial Manager. The Patient and Carer Information Sheets will state explicitly that participants contact details and GP details will be collected centrally by the Trial Manager. In the event of loss to follow-up the Trial Manager will use this information to track participants via the NHS system.

8 TREATMENT OF PARTICIPANTS

8.1 Description of Randomised Treatments

8.1.1 Placebo

Matching placebo tablets will be manufactured for both the 15mg mirtazapine and the 50mg sertraline tablets. These will be identical to the active tablets in all respects.

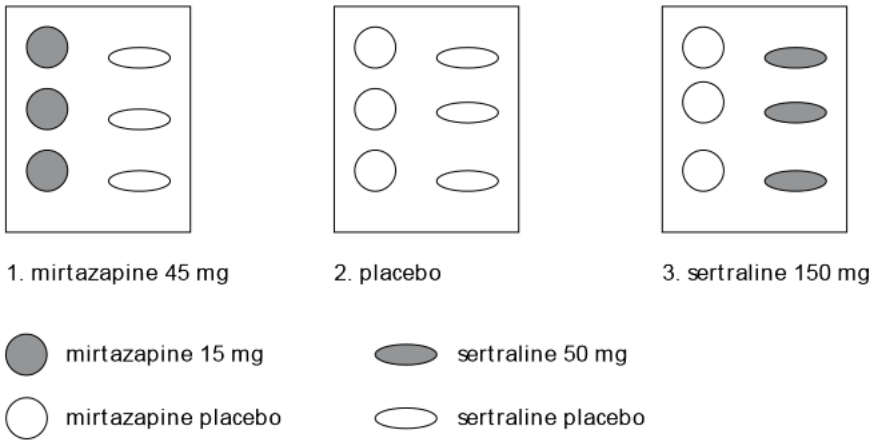
8.1.2 Mirtazapine and Sertraline

The experimental interventions are:

5. mirtazapine (a NASSA) with normal clinical care
6. sertraline (an SSRI) with normal clinical care.

Interventions will be available in 15mg tablets for mirtazapine and 50mg tablets for sertraline.

8.1.3 Double-Dummy Design



8.2 Selection of Doses for the Trial

These study medications are being used within their recommended doses for their licensed indication.

8.3 Selection & Timing of Dose for Each Participant

Interventions will be available in 15mg tablets for mirtazapine and 50mg tablets for sertraline. The design will be a double dummy with each participant taking:

1. sertraline plus placebo of mirtazapine, or
2. mirtazapine plus placebo of sertraline, or
3. placebo of mirtazapine plus placebo of sertraline.

For the first two weeks of treatment, participants will receive:

- sertraline 50mg plus a placebo mirtazapine tablet
- mirtazapine 15mg plus a placebo sertraline tablet
- a placebo sertraline tablet and a placebo mirtazapine tablet.

For the second two weeks, participants will receive:

- sertraline 100mg (2 tablets) plus two placebo mirtazapine tablets
- mirtazapine 30mg (2 tablets) plus two placebo sertraline tablets

- two placebo sertraline tablets and two placebo mirtazapine tablets.

At week 4 (indexed on treatment start date) carers will be contacted by telephone and the CSDD completed. Those who score less than 4 will remain on the above dose and those scoring 4 or more will move to the higher dose below. The carers of those who remain on the middle dose will be contacted by telephone and the CSDD completed in the same way after 8 weeks (de ned as day 49 to 56) and if CSDD is 4 or more at this time they will be placed on the higher dose.

With the above exceptions, from week 4 until the end of the trial (nine months in total), participants will receive:

- sertraline 150mg (3 tablets) plus three placebo mirtazapine tablets
- mirtazapine 45mg (3 tablets) plus three placebo sertraline tablets
- three placebo sertraline tablets and three placebo mirtazapine tablets.

Dose adjustments can be made by reducing back to 2 of each tablet daily or to 1 of each tablet daily in participants experiencing troublesome side effects.

8.4 Blinding of Investigational Medicinal Products

Active study medications and placebos for each will be identical.

Mirtazapine and matching placebo will be different to sertraline and matching placebo.

8.5 Identity & Supply of Investigational Medicinal Products

Mirtazapine Genus Pharmaceuticals (from 1st November 2009 : Arrow Pharmaceuticals) Sertraline P zer UK Ltd.

8.6 Packaging & Labelling of Investigational Medicinal Products

Active study medications and placebo will be bottled in pots of 100 tablets. One months supply will be one pot of each allocated treatment. Packaging and labelling will be completed in accordance with Good Manufacturing Practice (GMP) and GCP by Catalent in Bolton.

8.7 Prescription of Investigational Medicinal Products

A trial speci c prescription will be designed for use by all centres. This will be completed by Recruiting PIs or other medically quali ed doctors with a substantive or honorary contract with the recruiting NHS Trust and who have signed the `Recruiting Investigator site delegation of authority form'. If prescriptions are faxed to pharmacy in advance of collection by the RW, the original prescription with the Recruiting PIs signature (or another authorised doctor within the site) must be given to the pharmacist before study medication is dispensed.

RWs will fax the site delegation of authority forms to the Trial Manager whenever it is updated. From these delegation forms, the Trial Manager will create a list of authorised prescribers for the trial in that site. This list will be provided to the site pharmacy and the pharmacist will be instructed to only dispense if the medication is prescribed by an authorised person.

8.8 Dispensing & Distribution of Investigational Medicinal Products

Study medication will be distributed to the nine study site pharmacies by Catalent. Study medication receipt will be recorded in the study pharmacy le. A study medication dispensing and return log will be maintained by the site pharmacies. RWs will deliver the study medications to the participants.

Supplies of the study medications will be dispensed to the patient on a three monthly basis up to the nine month assessment, when they will be given a nal one month supply of trial medication.

8.9 Administration of Investigational Medicinal Products

These will be taken by participants using their normal methods for medicines management in a single dose at night. They and their carers will be provided with written information from the RW detailing the dose to be taken.

8.10 Unused Study Medication & Study Medication Accountability

Used treatment packs will be obtained from the patient by visit. Pharmacy departments in each site will maintain a study medication dispensing and returns log, including date dispensed, batch number, expiry date, number of tablets dispensed, study medication return date and amount of study medication returned. In addition, the study speci c prescriptions will be maintained in the pharmacy le for audit purposes. Study medications supplies will not be destroyed until the end of the trial analysis, they will be sent back to Catalent. The RW will count the medication returns and enter the information on the eCRF. The Trial Manager will cross check this information with the pharmacy records during site visits and re-count pill bottles where there is any discrepancy. The pharmacist or RW will then be asked to amend whichever record was incorrect.

8.11 Prior & Concomitant Interventions

All concomitant drug and non-drug interventions received will be recorded at baseline and follow-up assessment.

8.12 Departures from Randomised Treatment

8.12.1 Treatment Compliance/Adherence

This trial is a pragmatic trial and non-compliance and attempts to promote compliance are part of routine clinical practice. Our approach will essentially be to observe this and to compare compliance between the three study groups.

The treatment packs dispensed during the previous visit will be collected, inspected, and stored for inspection by the Trial Manager. Tablet counts will be completed with the number of capsules returned per bottle recorded in the case report forms. Reasons for signi cant instances of non- compliance with the dosing regimen will be recorded in the electronic case report form and source le. Details on how individuals receive their medication (e.g. self managing, prompted by carer, or given by carer) will also be noted at each interview. Carers will be asked to make a note of the dates of any occasions when patients missed their medication and the reason for missing it. The research worker will note this information during each visit.

8.12.2 Treatment Preference/Guess

The primary effectiveness outcome (CSDD) is a subjective outcome completed by the RW after an interview with the participant and the participant's carer. While the trial is double-blind, and therefore the participant, carer and RW are blind to treatment status, the success of this blinding will be evaluated by collecting data on medication preferences and guesses. The participant and the Recruiting PI must be in equipoise regarding the three trial interventions for the participant to be randomised into the trial. Carers will be asked at baseline to rate their preference for antidepressants versus nothing and mirtazapine versus sertraline. Carers and RWs will be asked at 13 and 39 weeks post randomisation to guess whether the participant was randomly prescribed an antidepressant versus placebo and mirtazapine versus sertraline.

8.12.3 Emergency Unblinding

Emergency code break envelopes will be distributed by Catalent to Guy's Toxicology Unit, where an emergency unblinding service will be available 24 hours a day. The pharmacy site les will contain an emergency unblinding SOP. In of ce hours site pharmacists will direct requests for unblinding to the Recruiting PI, who will contact the unblinding service if needed. Out of hours Guy's Toxicology Unit will be responsible for requests for emergency unblinding. Each participant or their carer will be given an

emergency card to carry for the participant for the duration of the trial. Depending on the participants circumstances, the RW will work with the participant and carer to decide who the most appropriate person to carry the card is, or whether it should be kept in a specific location where carers can access it if needed (e.g. with the medication). In addition, the emergency unblinding number will be printed on the boxes of study medication.

The toxicology unit must notify the Trial Manager on the next working day of any requests for unblinding, whether they were unblinded or not. Only requests to unblind from a medical doctor will be accepted (e.g. A&E doctor, GP). The Trial Manager will inform the Recruiting PI of an unblinding where appropriate. If the participant has been unblinded, the Recruiting PI may not be informed of the treatment allocation unless that information is needed for the participant's medical care. The decision on whether to inform the Recruiting PI will be made by the CI in conjunction with the Trial Statistician.

Where possible participants will be advised to omit the study medication rather than unblind. Code break envelopes will be collected and reconciled by the Trial Manager at the end of the trial.

8.13 Modification of Trial Treatment

The design allows for modification of the dose of medication where there are concerns about side effects that have not remitted. Under these circumstances the dose can be decreased (to mirtazapine 30mg, sertraline 100mg or placebo or, in exceptional circumstances, to mirtazapine 15mg, sertraline 50mg or placebo).

8.14 Treatment at the End of the Trial

The arrangements for continued provision of the trial medication at the end of the trial will be made on an individual basis by the Referring Investigator or other clinician responsible for the patients care at the end of the trial. At the 39 week assessment participants will be given a further four weeks supply of their medication. Further prescriptions will be the responsibility of the Referring Investigator or any other clinician who has taken over the participants care during the study. That person will be informed of the treatment group to which the participant was randomised.

The Recruiting PI must inform the Referring Investigator or other clinician taking over the participant's ongoing care of their treatment allocation between month 9 and month 10, as no further blinded study medication will be available to the participant. Since the clinician will need time to review the patient clinically, make a decision on ongoing treatment for depression and have a prescription issued, it is vital that the system of data entry, review and database lock on a participant by participant basis happens promptly after their week 39 assessment, so that their treatment allocation can be revealed (see section 12.5).

Routine unblinding will be requested by the Trial Manager once the data has been monitored, using the `Unblinding Request Form'. This will be sent to the MH&N CTU who will then inform the Trial Manager of the treatment allocation.

9 ADVERSE EVENTS

9.1 Adverse Events

9.1.1 Adverse Events and Adverse Reactions

Adverse Event (AE)

An adverse event is any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

Note: An adverse event can therefore be any unfavourable and unintended sign (including abnormal lab results), symptom or disease temporally associated with the use of the medicinal product, whether or not considered to be related to the medicinal product.

Adverse Reaction (AR)

An adverse reaction is any untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant.

Note: Any adverse event judged by either the reporting Investigator or the sponsor as having a reasonable causal relationship to an IMP qualifies as an AR; there is evidence or argument to suggest a causal relationship.

All adverse reactions are adverse events.

Unexpected Adverse Reaction

An unexpected adverse reaction is an adverse reaction, the nature and severity of which is not consistent with the applicable product information:

(a) the summary of product characteristics for that product (for an approved investigational medicinal product) or
(b) the Investigator's brochure (for an unapproved investigational product).

Note: Reports which add significant information on specificity or severity of a known, already documented serious adverse reaction constitute unexpected events. For example, when the outcome of an expected adverse reaction is not consistent with the relevant product information, the event may be considered unexpected.

9.1.2 Serious Adverse Events (SAEs)

An adverse event or adverse reaction is defined as serious if it:

(a) results in death
(b) is life-threatening[1]
(c) requires hospitalisation
(d) prolongs a current hospitalisation
(e) results in persistent or significant disability or incapacity
(f) consists of a congenital anomaly or birth defect
(g) deliberate self harm
(h) other (please specify).[2]

[1] Life threatening in the definition of an SAE or SAR refers to an event in which the participant was at risk of death at the time of the event; not an event that hypothetically might have caused death if it were more severe.

[2] Medical judgement should be exercised in deciding whether other AEs may be considered serious because they jeopardize the patient or may require intervention to prevent one of the other outcomes. Examples include blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or cancer.

9.1.3 Serious Adverse Reactions (SARs)

A suspected serious adverse reaction, the nature and severity of which is consistent with information about the IMP in question presented in either:

(a) the summary of product characteristics for that product (in the case of a product with a marketing authorisation)
or

(b) the Investigator's brochure relating to the IMP in question (in the case of any other IMP).

9.1.4 Suspected Unexpected Serious Adverse Reactions (SUSARs)

A Suspected Unexpected Serious Adverse Reaction (SUSAR)

All adverse events that are suspected to be related to an investigational medicinal product and that are both unexpected and serious are considered to be SUSARs.

Not all adverse events are adverse reactions but all adverse reactions (including those that are unexpected) are adverse events.

9.1.5 Assessment of Severity and Causality

Each AE should be evaluated for seriousness, causality, expectedness and intensity. This evaluation may be performed by both the Recruiting PI and the Sponsor (or CI acting on behalf of the Sponsor). In this trial, the Recruiting PI will assess an event for seriousness, causality and intensity and the CI will assess for expectedness.

Intensity (severity)

The assessment of intensity will be based on the Investigator's clinical judgement using the following de nitions:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is suf ciently discomforting to interfere with normal everyday activities.
- Severe: An event that prevents normal everyday activities.

Note: Severity is often used to describe the intensity of a speci c event. This is not the same as `seriousness', which is based on participant/event outcome or action criteria.

Seriousness

An adverse event, adverse reaction or is de ned as serious if it:

(a) results in death
(b) is life-threatening[1]
(c) requires hospitalisation
(d) prolongs a current hospitalisation
(e) results in persistent or signi cant disability or incapacity
(f) consists of a congenital anomaly or birth defect
(g) deliberate self harm
(h) other (please specify).[2]

[1]Life threatening in the de nition of an SAE or SAR refers to an event in which the participant was at risk of death at the time of the event; not an event that hypothetically might have caused death if it were more severe.

[2]Medical judgement should be exercised in deciding whether other AEs may be considered serious because they jeopardize the patient or may require intervention to prevent one of the other outcomes. Examples include blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or cancer.

Causality

The relationship between the study medication and the occurrence of each adverse event will be assessed and categorised (as detailed below). The Investigator will use clinical judgement to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors etc. will also be considered. The Investigator will also consult the SmPC or other product information.

- Not related Temporal relationship of the onset of the event, relative to administration of the product, is not reasonable or another cause can by itself explain the occurrence of the event.
- Remote Temporal relationship of the onset of the event, relative to administration of the product, is likely to have another cause which can by itself explain the occurrence of the event.
- *Possibly related Temporal relationship of the onset of the event, relative to administration of the product, is reasonable but the event could have been due to another, equally likely cause.
- *Probably related Temporal relationship of the onset of the event, relative to administration of the product, is reasonable and the event is more likely explained by the product than any other cause.
- *De nitely related Temporal relationship of the onset of the event, relative to administration of the product, is reasonable and there is no other cause to explain the event, or a re-challenge (if feasible) is positive.

*Where an event is assessed as possibly, probably, or de nitely related, the event is an adverse reaction.

Expectedness

The expectedness of an adverse reaction shall be determined according to the summary of product characteristics (SmPC).

- Expected Reaction previously identi ed and described in protocol and/or reference documents, e.g. SmPC.
- Unexpected Reaction not previously described in the protocol or reference documents.

NB Adverse reactions must also be considered as unexpected if they add signi cant information on the speci city or severity of an expected adverse reaction.

It is most appropriate for the Recruiting PI at each centre to evaluate each event before reporting it to the Sponsor (or CI acting on behalf of the Sponsor). The Recruiting PI's causality assessment should not be downgraded by the Sponsor (or CI acting on behalf of the Sponsor).

If a Sponsor (or CI acting on behalf of the Sponsor) disagrees with the Recruiting PI's assessment, further clari cation and discussion should take place to reach a consensus. If a consensus cannot be reached, both the opinion of the Recruiting PI and the Sponsor (or CI acting on behalf of the Sponsor) should be provided if the report requires expedited reporting to the MHRA and REC.

9.1.6 Reporting Adverse Events

All adverse events occurring in the trial will be recorded in the participant's source data worksheet and led in their medical records at the end of the trial. They will also be transcribed onto the electronic Case Record Form (eCRF). Data on adverse events will be collected by the RW from participants and their carers at weeks 4, 13 and 39. Any events reported by participants or their clinical teams will also be reported and followed up between visits. The RW will then review the adverse events immediately to ascertain whether they meet the criteria for `serious' (see section 9.1.2). If the event is assessed as being an SAE, see section 9.1.7. For events that are not de ned as serious, the RW will review the events for each participant with the Recruiting PI, prior to completing the eCRF, in order to assess and record intensity and causality of the event. The intensity, causality and seriousness of each event will be recorded on the eCRF and can be amended if new information about the event later emerges. All

adverse events will be monitored until resolution or until month 10. At month 10, the Recruiting PI should formally write to the clinician assuming responsibility for the participants' ongoing clinical management, informing him or her of any ongoing unresolved adverse events.

Please note, when the RW meets with the Recruiting PI to review the non-serious adverse events, the Recruiting PI may decide at this point that an event should have been considered an SAE, based on their clinical judgement and the event would at that point be reported as an SAE.

It is expected that the RW would only be expected to assess events as being serious if they result in death, are immediately life threatening, require hospitalisation or a prolonged hospitalisation. Medical judgement should be exercised in deciding whether other AEs may be considered serious because they jeopardize the patient or may require intervention to prevent one of the other outcomes. Examples include blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or cancer.

9.1.7 Reporting SAEs and SARs

King's College London (Institute of Psychiatry), as sponsor, have delegated the delivery of the sponsor's responsibility for pharmacovigilance, as de ned in Regulation 5 of the Medicines for Human Use (Clinical Trials) Regulations 2004 to the Joint Clinical Trials Of ce (JCTO).

If an event is assessed as `serious' (see 9.1.2), the RW and Recruiting PI will complete an SAE form and enter it onto the eCRF within 24 hours of becoming aware of the event. The SAE report form should be signed electronically by the Recruiting PI or a doctor within the research team delegated to undertake this task. In the absence of the Recruiting PI or another trial doctor being available to assess an adverse event that quali es as an SAE, the RW should complete the eCRF form with as much information as possible. The Recruiting PI should then review the event at the earliest opportunity, make changes to the assessments as appropriate on the eCRF. It will then enter the pharmacovigilance system as a follow-up report. The RW should assess causality to the best of their ability but should seek assistance from the Trial Manager if necessary, in order that the medical advisor to the trial can assist if the Recruiting PI is unavailable. Any SAE received by the CI will be assumed to be de nitely study medication related if no causality assessment is completed and may then enter the SUSAR reporting system.

The Trial Manager will enter a unique number on the eCRF to identify each SAE and will issue queries on the eCRF to collect follow up information until event resolution

Every event (new and follow up) received by the CI on the eCRF must be reviewed within 24 hours. The eCRF will trigger an email to the Recruiting PI, the CI and the Trial Manager informing them that an SAE has been entered or altered on the eCRF.

The CI (or a doctor nominated by the CI) must review every event within 1 working day of it being received. The review will consist of a review of the seriousness, causality and intensity. If there is disagreement about the assessments, there should be a discussion between the Recruiting PI and the CI to resolve the discrepancy and any changes sent added to the eCRF and signed off by the Recruiting PI. The CI, acting on behalf of the sponsor, is at liberty to upgrade the intensity or causality of an event without the Recruiting PIs agreement, but may not downgrade that assessment. Only the Recruiting PI can downgrade the event based on further follow up information. The CI, acting on behalf of the Sponsor, must assess and document the expectedness of the event (see 9.1.5).

Once the event has been signed off by the CI, a report will be generated from the eCRF and forwarded by fax from the Trial Manager to the JCTO and the pharmacovigilance department at P zer UK Ltd. They will issue queries about the event to the Trial Manager, who will relay them to sites via the eCRF.

Serious Adverse Reactions will be extracted from the eCRF for the annual MHRA safety report.

In the event that the RW is away and another member of site staff without access to the eCRF needs to report an SAE, the paper form should be faxed to the Trial Manager. It is a legal requirement that the site informs the CI within 24 hours of becoming aware of the event.

9.1.8 Reporting SUSARs

The JCTO will report SUSARs and other SARs to the regulatory authority (MHRA). The Chief Investigator will report to the relevant ethics committees. Reporting timelines are as follows:

- SUSARs that are fatal or life-threatening must be reported not later than 7 days after the sponsor is first aware of the reaction. Any additional relevant information must be reported within a further 8 days.
- SUSARs that are not fatal or life-threatening must be reported within 15 days of the sponsor first becoming ware of the reaction.
- The Chief Investigator will provide an annual report of all SARs (expected and unexpected) and SAEs, which will be distributed to the sponsor (JCTO, MHRA and ethics committee)

Reporting Other Safety Issues

In addition, other safety issues also qualify for expedited reporting (15 day timeframe) where they might alter the current risk-benefit assessment of the IMP or would be sufficient to consider changes in the IMP administration or overall conduct of the trial, for example:

(a) single case reports of an expected serious adverse reaction with an unexpected outcome (e.g. death);
(b) an increase in the rate of occurrence of an expected serious adverse reaction, which is judged to be clinically important;
(c) post-study SUSARs that occur after the participant has completed a trial;
(d) a new event, related to the conduct of the trial or the development of the investigational medicinal product (IMP), that is likely to affect the safety of participant;
(e) a serious adverse event which could be associated with the trial;
(f) procedures and which could modify the conduct of the trial; a significant hazard to the participant population such as lack of efficacy of an IMP used for the treatment of a life-threatening disease;
(g) a major safety finding (e.g. carcinogenicity) from a newly completed animal study.

These safety issues must be reported to the MHRA and the main REC in the format of a letter titled Safety Report .

The CI, acting on behalf of the sponsor, should retain a copy of the expedited report and associated documentation in the TMF

The sponsor (via the DMC) will perform an integrated safety analysis of all adverse event information reported and ensure discussions are held and actions undertaken to secure the safety of all participants. Discussions may result in the expedited reports being submitted and/or the discontinuation of the trial.

9.2 Expected Adverse Reactions to the Trial Medications

As per Summary of Product Characteristics (SmPC):

MIRTAZAPINE

Depressed patients display a number of signs and symptoms associated with the illness itself. It is therefore sometimes difficult to ascertain which symptoms are a result of the illness itself and which are a result of mirtazapine treatment.

Blood and the Lymphatic System Disorders

Rare > 1/10000, < 1/1000

Acute bone marrow depression (eosinophilia, granulocytopenia, agranulocytosis, aplastic anaemia, thrombocytopenia).

Metabolism and Nutrition Disorders
Common > 1/100, < 1/10.
Increased appetite and weight gain

Psychiatric Disorders
Rare > 1/10000, < 1/1000.

Mania, confusion, hallucinations, anxiety*, insomnia*, nightmares/ vivid dreams. (*Anxiety and insomnia, which may be symptoms of depression, can develop and become aggravated - under treatment with mirtazapine, development or aggravation of anxiety and insomnia has been reported very rarely).

Nervous System Disorders
Common > 1/100, < 1/10.
Somnolence (which may impair alertness), usually occurring during the first few weeks of therapy (NB. dose reduction does not generally lead to less sedation but can jeopardize antidepressant efficacy); dizziness, headache.
Rare > 1/10000, < 1/1000.
Convulsions (seizures), tremor, myoclonus, paraesthesia, restless legs.

Cardiac Disorders
Rare > 1/10000, < 1/1000 (Orthostatic) hypotension, syncope.

Gastrointestinal Disorders
Uncommon > 1/1000, < 1/100.
Nausea.
Rare > 1/10000, < 1/1000.
Dry mouth, diarrhoea.

Hepato-biliary Disorders
Rare > 1/10000, < 1/1000.
Elevations of hepatic transaminase levels.

Skin and Subcutaneous Tissue Disorders
Rare > 1/10000, < 1/1000.
Exanthema.

Musculoskeletal, Connective Tissue and Bone Disorders
Rare > 1/10000, < 1/1000.
Arthralgia, myalgia.

General Disorders
Common > 1/100, < 1/10.
Generalized or local oedema and accompanying weight gain, fatigue.

Although mirtazapine does not cause dependence, post-marketing experience shows that abrupt termination of treatment after long-term administration may sometimes result in withdrawal symptoms. The majority of withdrawal reactions are mild and self-limiting. Among the various reported withdrawal symptoms, nausea, anxiety and agitation are the most frequently reported. Treatment with mirtazapine should be discontinued gradually.

SERTRALINE

Side-effects which occurred signi cantly more frequently with sertraline than placebo in multiple dose studies were: nausea, diarrhoea/loose stools, anorexia, dyspepsia, tremor, dizziness, insomnia, somnolence, increased sweating, dry mouth and sexual dysfunction (principally ejaculatory delay in males). The side-effect pro le commonly observed in double-blind, placebo-controlled studies in patients with obsessive compulsive disorder (OCD) and post-traumatic stress disorder (PTSD) was similar to that observed in patients with depression. In paediatric OCD patients, side-effects which occurred signi cantly more frequently with sertraline than placebo were: headache, insomnia, agitation, anorexia, tremor. Most were of mild to moderate severity. Post-marketing spontaneous reports include the following:

Cardiovascular

Blood pressure disturbances including postural hypotension, tachycardia.

Eye Disorders

Abnormal vision.

Gastro-intestinal

Vomiting, abdominal pain.

Nervous System

Amnesia, headache, drowsiness, movement disorders, paraesthesia, hypoaesthesia, depressive symptoms, hallucinations, aggressive reaction, agitation, anxiety, psychosis, depersonalisation, nervousness, panic reaction and signs and symptoms associated with serotonin syndrome which include fever, rigidity, confusion, agitation, diaphoresis, tachycardia, hypertension and diarrhoea. There have also been reports of manic reaction, although this phenomenon may be part of the underlying disease.

Convulsions (Seizures)

Sertraline should be discontinued in any patient who develops seizures (See `Special warnings and special precautions for use').

Musculoskeletal

Arthralgia, myalgia.

Hepatic/Pancreatic

Rarely, pancreatitis and serious liver events (including hepatitis, jaundice and liver failure). Asymptomatic elevations in serum transaminases (SGOT and SGPT) have been reported in association with sertraline administration (0.8 1.3%), with an increased risk associated with the 200mg daily dose. The abnormalities usually occurred within the rst 1 to 9 weeks of study medication treatment and promptly diminished upon study medication discontinuation.

Renal & Urinary Disorders

Urinary retention.

Reproductive

Hyperprolactinemia, galactorrhoea, menstrual irregularities, anorgasmy.

Skin and Allergic Reactions

Rash (including rare reports of erythema multiforme, photosensitivity), angioedema, ecchymoses, pruritus and anaphylactoid reactions.

Metabolic

Rare cases of hyponatremia have been reported and appeared to be reversible when sertraline was discontinued. Some cases were possibly due to the syndrome of inappropriate antidiuretic hormone

secretion. The majority of reports were associated with older patients, and patients taking diuretics or other medications.

Haematologic
There have been rare reports of altered platelet function and/or abnormal clinical laboratory results in patients taking sertraline. While there have been reports of thrombocytopenia, abnormal bleeding or purpura in several patients taking sertraline, it is unclear whether sertraline had a causative role. See also `Special warnings and special precautions for use'.

General
Malaise.

Other
Withdrawal reactions have been reported with sertraline. Common symptoms include dizziness, paraesthesia, headache, anxiety and nausea. Abrupt discontinuation of treatment with sertraline should be avoided. The majority of symptoms experienced on withdrawal of sertraline are non-serious and self- limiting.

Suicidal thoughts and suicide attempts were mainly observed in clinical trials with Major Depressive Disorder.

9.3 Emergency Unblinding Procedure
Please see 8.12.3.

9.4 Study ID Cards
Due to the participants having dementia, it may be considered impractical to expect participants to carry cards during the study, with emergency unblinding procedures detailed on them. A card will be provided with the contact details of the research team and out of hours emergency procedures, to show medical staff in the event of an emergency, as they may need to contact Guy's Toxicology Unit for unblinding.

It is anticipated that the RW will decide on a case by case basis with the participants and carers who needs to have this information for that particular participant. In addition, the emergency unblinding telephone number will be printed on the study medication boxes to ensure that in an emergency where the carer may not be present, a health care professional would have access to that information.

10 VISIT ASSESSMENTS

10.1 Assessments and Procedures

10.1.1 Assessment Schedule
The main trial assessments will be completed at baseline, 13 weeks and 39 weeks. Data on adverse events will also be collected by the RW from participants and their carers monthly for the first three months (when medication is dispensed), and three monthly thereafter. There will be a final phone call at 10 months to the participant/carer to review any new or outstanding adverse events and to record concomitant medication for safety monitoring.

10.1.2 Flexibility of Visit Assessments
The baseline assessment will take place within 28 days of the patient having been referred by the Referring Investigator. It is intended that the follow up assessments will be completed within +/ 7 days of the 13 and 39 calendar weeks from randomisation. Baseline assessments will take place prior to randomisation. Follow-up assessments will take place after randomisation.

10.1.3 Unscheduled Assessments

These will be sought at treatment discontinuation or if loss to follow-up is anticipated. Please see table 6.5.1. Patients can be seen by the Recruiting PI at any time if they experience troublesome adverse events that require assessment.

10.1.4 Details of Assessments

Please see table 6.5.1.

Participants will be visited in their own homes and they and their carer will be interviewed by a research worker who will complete the assessments due at that time. The assessments are a mixture of direct assessment of the person with dementia (e.g. MMSE, DEMQOL); proxy report by the carer of the person with dementia (e.g. CSRI, NPI, DEMQOL-Proxy, EQ5D, adverse events, adherence); and self-report from the carer (e.g. GHQ, SF-12, Zarit). Instruments completed will be interview administered. The full set of assessments will be completed at baseline and at 13 and 39 week follow-up onto Source Data Worksheets (SDWs). During the trial these will be kept in the participants medical notes or similar files as arranged by the Recruiting PI. At the end of the trial they will be stored in the participants medical records as source data in case of future audit.

10.1.5 Premature Trial Closure

The trial may be stopped by the Trial Steering Committee. The Data Monitoring Committee in accordance with the IDMC charter, may recommend to the Trial Steering Committee that the trial be stopped.

10.2 Visit Procedures

10.2.1 Baseline Visit

The RW will arrange a meeting with the person with dementia and their carer. The RW will describe the trial and attempt to obtain consent as per the trial consent procedure (see Section 7.3). This will include the person with dementia and their carer. Where this is forthcoming the baseline assessment will be completed.

The assessment interview will ascertain type of dementia and depression according to set diagnostic criteria: NINCDS-ADRDA [McKhann et al 1984] for dementia; DSM-IV for depression (American Psychiatric Association 1994); the Olin criteria specifically designed for depression in dementia (Olin et al 2002); depression severity (CSDD); and vascularity (MHIS). The purpose of this diagnostic work is not to exclude further individuals from the trial (this would limit the generalisability of the findings) but instead to closely characterise the cases on the basis of diagnoses and severity to enable us to be able to describe the trial group in detail and to be able to investigate as secondary analyses the effect of diagnostic group and severity on subsequent outcome.

The local RW will complete a semi-structured interview with the person with dementia and their carer. This interview will include the measures used during follow-up as primary and secondary outcome measures and possible moderating variables including behavioural and psychological disturbance (Neuropsychiatric Inventory, NPI, Cummings et al, 1994]), physical illness, and severity of cognitive impairment (MMSE Folstein et al 1975).

10.2.2 Week 4 Follow-Up Visit

At week 4 (indexed on treatment start date) carers will be contacted by telephone and the CSDD completed. Those who score less than 4 will remain on the middle dose (2 mirtazapine/placebo and 2 sertraline/placebo) and those scoring 4 or more will move to the higher dose.

10.2.3 Week 8 Follow-Up Visit

The carers of those who remain on the middle dose will be contacted by telephone and the CSDD completed in the same way after 8 weeks (indexed on treatment start date) and if CSDD is 4 or more at this time they will be placed on the higher dose.

10.2.4 Week 13 Follow-Up Visit

Please see Table 6.5.1. The interview will include the primary and secondary outcome measures and AEs will be assessed using the aide memoire.

10.2.5 Week 39 Follow-Up Visit

Please see Table 6.5.1. The interview will include the longer-term outcome measures and AEs will be assessed using the aide memoire.

10.3 Measures

10.3.1 Baseline measures

The outcome measures have been chosen on the basis of their being the best-validated instruments available for the domains of function and activity of prime importance. We have balanced comprehensiveness with minimising respondent burden. The interview schedule is designed to be completed in one session with the person with dementia and their carer lasting no more than 60 minutes.

10.3.1.1 Participant measures

Primary Outcomes:

Depression in dementia CSDD (Alexopoulos et al 1988) The CSDD was designed speci cally for the measurement of depression in dementia. It is widely used and well validated with acceptable reliability and feasibility. It has been shown to be responsive to change in previous trials.

Costs:

Client Service Receipt Inventory (CSRI; Beecham et al 2001) This schedule measures service use and informal care input. It allows for the comprehensive costs of care for all participants to be calculated (including the costs of formal care such as that provided by health and social services and also the costs of informal care) using data gathered from carers.

Secondary Outcomes:

- Disease speci c quality of life DEMQOL and DEMQOL-Proxy (Smith et al 2005).
- Generic measure of quality of life interview administered to carer (Coucill et al 2001) EQ-5D (EuroQoL Group 1990).
- Withdrawal from treatment arm.
- Cognitive impairment MMSE (Folstein et al 1975) Medication adherence.
- Adverse events.

10.3.1.2 Carer measures

Secondary Outcomes:

- Carer mental health General Health Questionnaire 12 (GHQ-12; Goldberg et al 1988) Carer quality of life -- SF-12 v2 (Ware et al 1996).
- Carer burden Zarit Carer Burden Scale (Zarit 1980).

10.4 Safety Monitoring

All adverse events occurring in the trial will be recorded in the participants' source data worksheets and led in their medical records at the end of the trial. They will also be transcribed onto the eCRF. Data on adverse events will be collected by the RW from participants and their carers monthly for the rst three months (when medication is dispensed), and three monthly thereafter. Any events reported by participants or their clinical teams will also be reported and followed up between visits.

Reports of serious adverse events will be forwarded to the DMEC members as requested. Any recommendations or additional information required by the DMEC will be actioned. Non-serious unexpected adverse events will be collated and sent to DMEC members in advance of scheduled meetings.

11 STATISTICS

11.1 Sample Size

11.1.1 Assumptions

Based on a review of previous studies (e.g. Alexopoulos et al, 1988; Katona et al, 1998; Lyketsos et al, 2003; Teri et al, 2003), the sample sizes used in estimation, and the broad eligibility criteria of the proposed trial we assume that the common standard deviation (SD) of the CSDD scores at baseline and follow-up will be approximately 5 points. We propose that a clinically important difference between the antidepressant and placebo groups would be 2 points on the CSDD observable at 13 weeks, and maintained at 39 weeks. This equates to a moderate standardised effect size (SES) of 0.4. We have further assumed that loss to follow-up (including by death of participant or carer) will be 10% at 13 weeks increasing to 20% at 39 weeks. We believe these estimates are realistic based on the existing literature and given the measures we will take to minimise loss to follow-up (e.g. active follow-up in the home, minimising the burden of data collection) in the trial design.

11.1.2 Power Analyses

Our primary intention to treat analyses will compare i) sertraline against placebo and ii) mirtazapine against placebo at 13 weeks post-randomisation. Allowing for 10% loss to follow-up at 13 weeks, an overall sample of 444 patients (randomised 1:1:1 to placebo: sertraline: mirtazapine) would provide 90% power to detect a 2 point difference in CSDD (SD 5; SES 0.4) for the sertraline vs placebo and the mirtazapine vs placebo comparisons using independent sample t-tests with 2-sided 5% signi cance levels. This is equivalent to assuming a zero correlation between baseline and outcome CSDD in an analysis of covariance adjusting for baseline CSDD (Machin et al, 1997). Machin et al (1997) suggest that correlations of 0.6 to 0.75 between baseline and outcome measurements are common. Assuming a conservative correlation of at least 0.6, the overall sample size required based on an analysis of covariance with 2-sided 5% signi cance levels reduces to 285 patients (using a multiplying factor of 0.64; Machin et al, 1997) but making no particular adjustment for drop-outs (patients allocated to sertraline or mirtazapine withdrawing from treatment and effectively shifting to placebo) or drop-ins (patients allocated to placebo withdrawing from placebo and effectively shifting to sertraline or mirtazapine). It is important to adjust the power calculation for such drop-outs and drop-ins. Therefore, additionally allowing up to 12.5% of those randomized (per comparison) to be either drop-outs or drop-ins (e.g. 10% drop-outs and 15% drop-ins) the overall sample size required becomes 507 patients (i.e. 169 patients in each arm) (using a multiplying factor of 1.78; Friedman et al 1998).

An overall sample size of 507 patients will therefore provide 90% power to detect a 2 point difference in CSDD (SD 5; SES 0.4) for the sertraline vs placebo and the mirtazapine vs placebo comparisons at 13 weeks and an 86% power at 39 weeks. This allows for 20% loss to follow-up, correlation between baseline and outcome CSDD 0.6, and up to 12.5% of those randomized (per comparison) to be either drop-outs or drop-ins using an analysis of covariance with 2-sided 5% signi cance levels.

Allowing for the same levels of loss to follow-up, an overall sample of 507 patients would also enable us to calculate 2-sided 95% con dence intervals for the difference in the proportion of pre-speci ed adverse events between the antidepressant arms of (a clinically signi cant) 10% (i.e. 5% vs 15%) 6% at 12 weeks and 7% at 39 weeks.

11.2 Data Monitoring & Interim Analyses

We have no planned interim analyses. One analysis of the data will be conducted once the trial database has closed. We have not planned an interim analysis of the data primarily because the rst 39 week outcome data will only become available as recruitment into the trial is coming to an end (i.e. after 39 weeks with only 13 weeks of recruitment to follow). The Data Monitoring Committee will wish to collate effectiveness and safety data during the trial to inform their recommendations to the Trial Steering Committee but we do not anticipate a formal analysis of the data mid-trial at this stage.

11.3 Brief Analysis Plan

11.3.1 General Considerations

The analyses of effectiveness will be pragmatic, based on intention to treat, and will utilise all available follow-up data from all randomised patients. A full Analysis Strategy will be developed, independently of looking at the trial data, and before undertaking any analysis, about 6 months after the start of randomisation. This will be approved by the TMG and the TSC before any analysis is undertaken. The Trial Statistician will remain blind wherever possible until the main analyses are complete.

11.3.2 Analyses of Effectiveness

Primary Effectiveness Analyses

The primary outcome of symptoms of depression on the CSDD (CSDD, continuous score) at 13 weeks post randomisation will be analysed by ANCOVA adjusted for baseline CSDD and centre with contrasts for (a) sertraline vs placebo and (b) mirtazapine vs placebo.

Secondary Effectiveness Analyses

Change in CSDD score from baseline to 13 weeks will further include a contrast for mirtazapine vs sertraline. CSDD score at 39 weeks will be analysed by ANCOVA adjusted for baseline CSDD and centre with contrasts for (a) sertraline vs placebo; (b) mirtazapine vs placebo and (c) mirtazapine vs sertraline. Secondary outcomes will be compared using the same contrasts as above within a longitudinal generalised linear model framework adjusting for the respective baseline scores and centre. Results will be summarised as mean differences together with 95% con dence limits.

The signi cance level will be 5% (2-sided) for speci ed analyses of the primary outcome variable and 1% (2-sided) for speci ed analyses of secondary outcome variables. Sensitivity analyses will be used to assess the robustness of conclusions to missing outcome data and to departures from randomised treatment. Loss to follow-up, departures from randomised treatment and the prevalence of serious adverse events will be reported at 13 and 39 weeks post randomisation.

Missing Data

Missing data will be considered according to type in the analyses. It is anticipated that there will be no missing scale covariate data for the primary analyses as copies of the relevant data (e.g. CSDD) collected at baseline will be required at the point of randomisation. Missing covariate item data will be imputed using mean imputation per patient (pro-rating) if no more than 5% of items are missing across all of the data collected and using multiple imputation (Schafer 1999) if more than 5% of items are missing on at least some of the data collected. Missing primary outcome data is anticipated from three sources: missing items; missing scale due to loss to follow-up; and missing scale due to death. As the primary analysis is of CSDD at 3 months there will only be one assessment of CSDD post-randomisation to include in this analysis. To guard against missing post randomisation CSDD data for patients withdrawing from

treatment before 3 months, the CSDD will also be collected at the point of withdrawal if consent for this is available. Missing outcome item and scale data will be imputed using multiple imputation.

Three month outcome data will not be imputed, however, if the patient has died between randomisation and 3 months. In addition, sensitivity analyses will be constructed using methods to assess the robustness of the conclusions to the method used (Little & Rubin 2002). The secondary analysis of CSDD at 39 weeks will utilise pattern mixture models (Little & Wang 1996; Hedeker & Gibbons 1997) to handle any missing 13 or 39 week outcome scale data and multiple imputation to handle any 13 or 39 week outcome item data. Thirty nine week outcome data will not be imputed if the patient has died between the 13 and 39 week assessments. Again several sensitivity analyses will be conducted using a range of methods.

Non-Compliance/Non-Adherence

The primary `intention to treat' analysis is intended to provide inferences regarding the effectiveness of the three interventions overall. It is not primarily intended to provide inferences regarding the causal effect of the interventions themselves, but on the interventions as deployed in as `real life' a setting as possible. As such, compliance information is not necessary to ensure that the `intention to treat' analysis is valid. The implications of treatment non-compliance for the `intention to treat' analysis were handled within the power calculation by adjusting the sample size for drop-outs and drop-ins, effectively reducing the expected effect size to allow for a degree of non-compliance.

Our secondary analyses will include an assessment of the causal effect of the trial interventions and will be detailed in the full analysis strategy. Two aspects of treatment compliance will be considered: the proportion of the intended dose actually taken per patient; and the impact of non-randomised concomitant medications and treatments received. The expected magnitude of the placebo effect in this trial makes the methods described by Nagelkerke et al (2000) inappropriate. We will therefore draw on the methods described by Dunn et al (2003), White et al (2003), Kenna & Sheiner (2004) and Levy et al (2004).

11.3.3 Analyses of cost-effectiveness

The economic evaluation will be led by Professor Martin Knapp and his group at the Institute of Psychiatry with input from the London School of Economics (LSE) (linking to long term care nancing projections work and social care studies for older people) and Dr Linda Davis at Manchester. The analysis of the economic impact of the interventions is a central, fully integrated element of the proposed study. The study design as presented in the proposal overall has been constructed to meet the needs of economic and well as clinical evaluations of the interventions to be studied. In an earlier draft of this proposal the economic funding was mistakenly included as `consultancy', this has been corrected.

Costs of formal and informal care

The comprehensive costs of care for all participants will be calculated (including the costs of formal care such as that provided by health and social services and also the costs of informal care) using data gathered using the CSRI completed by key workers or family carers at baseline, 13 weeks and 39 weeks. Unit costs will be best national estimates of the long-run marginal opportunity costs, built up from both national unit costs compendia (Curtis et al 2004), NHS specialty costs and speci c care homes (costs or charges, depending on availability).

Informal care will be costed (Netten 1993). We will collect information on the volume and nature of informal care inputs, mindful of the dif culties of measuring such dimensions and of their interpretation as inputs to the care process. We will attach costs to informal care inputs using two or three approaches (opportunity cost of lost work/leisure; replacement cost with a (paid) home carer or similar; zero value; and possibly some blending of these approaches to re ect different informal care tasks and circumstances, along the lines of Brouwer's approach [van den Berg et al 2004]) and examine the

cost-effectiveness consequences of these different approaches (one dimension of sensitivity analysis). Aggregate and agency-speci c costs will be reported.

Analyses

From these costs and the outcomes data, we will compare total and component (by service or agency) costs, incremental cost-effectiveness ratios and net bene ts (using the primary outcome measure CSDD), cost utility ratios (using utility scores computed from the EQ-5D and societal weights) and cost-consequences results (using all non-cost outcomes measures). The primary evaluation will be the cost-effectiveness analysis using CSDD change as the outcome. Missing data will be addressed using multiple imputation. The evaluation will include the plotting of cost- effectiveness acceptability curves generated from bootstrap analyses. Sensitivity analyses will explore the impact of differences in key costs and outcome assumptions. Given the nature of the study aims and the data to be generated we are unlikely to use probabilistic sensitivity analysis. Evaluation will be conducted from (a) societal, (b) public sector and (c) NHS perspectives, and comparisons made between the results.

Quality Adjusted Life Years (QALYs)

We will calculate QALYs from the EQ5D, though recognizing that there remains uncertainty about the validity of this measure with a population of older people with dementia and depression. Societal weights will be employed. The QALYs will not include `carer quality of life (QOL) issues', as described by one of the reviewers, but will focus exclusively on the patient. Technically it would be complex and speculative to merge patient and carer QOL measures into a composite QALY representation especially in dementia where there are so few relevant comparative data available. The study will however assess a number of aspects of carer QOL and experience (directly using the SF-12; and indirectly via the GHQ 12 [carer mental health] and Zarit [carer burden]). This will enable a full evaluation of the impact of the intervention on carers of people with dementia. Dementia studies have a good track record of assessing carer impacts including economic impacts, and we as individual researchers have similarly given this attention and emphasis over many years and studies (Murray et al 1999; Schneider et al 1999, 2001, 2002; Banerjee et al 2003).

Beyond Trial Modelling

We will seek alternate funding for this further economic exploitation of data from this study.

11.3.4 Analyses of Safety

All cause withdrawal from randomised treatment will be reported at 13 and 39 weeks post randomisation. Withdrawal rates will be compared at 13 and 39 weeks across the three trial arms (as randomised) using Chi square tests. The prevalence of speci c adverse events will be reported descriptively at 13 and 39 weeks post randomisation. The prevalence of patients experiencing one or more serious adverse events will be compared at 13 and 39 weeks post randomisation across the three trial arms (as randomised) using Chi Square tests. We will calculate 2-sided 95% con dence intervals for the difference in the proportion of pre-speci ed adverse events between the antidepressant arms.

11.3.5 Other Exploratory Analyses

Associations between post-treatment outcomes and baseline predictor variables (including dementia severity, dementia type, depression type, depression severity, care arrangements; type of normal clinical care received; behavioural and psychological symptoms in dementia, and physical illness) will be examined using multiple linear and logistic regression modelling techniques, including a limited examination of rst order interactions. We will also explore the baseline predictors of costs measured for the rst 13 weeks and the full 39 weeks post randomisation.

11.4 Changes to the Analysis Plan

Any signi cant changes made to the Statistical Analysis Strategy (see Appendix 6) after approval by the TMG and the TSC will be taken back to the TMG and the TSC for their approval before the changes are put into effect.

12 DATA MANAGEMENT & MONITORING PROCEDURES

12.1 Direct Access to Trial Data & Documents

The principal investigators, carers and participants will permit trial-related monitoring, audits, ethics committee review and regulatory inspections by providing direct access to source data/documents.

During the course of the trial, only the principal investigators, their staff and the coordinating research team will have access to data generated by the trial. Other researchers may submit an application to the Trial Management Group at a later date for access to the anonymised master database.

12.2 Con dentiality

The con dentiality of participant and carer identi cation details will be protected according to the Data Protection Act. Participants will be identi ed by their PIN, initials and date-of-birth only. The one exception will be a separate list, held by the Trial Manager at the South London & Kent Centre only, of name, postal address, email address and telephone numbers of participant/carer, date of birth, PIN/CIN, medication pack number, date of randomisation, GP contact details and NHS number (to enable the trial team to track the participant for follow-up assessments). Participant names, addresses, and other contact details will be written in the CRF for identi cation and contact purposes. The CRFs will be regarded as con dential, and kept in locked ling cabinets in the local centre and the coordinating centre (South London & Kent).

12.3 Record Keeping

12.3.1 Custodian of the Data

The Chief Investigator will have control of and act as custodian for the data generated by the trial (i.e. the source data and the Trial Master Database) on behalf of the Trial Management Group.

The Trial Statisticians and Health Economists will be responsible for all analyses covered by the Statistical Analysis Strategy (see Appendix 7). Any further analyses will be conducted by researchers with the approval of the Trial Management Group (and the Trial Steering Committee prior to the publication of the main papers).

12.3.2 Format of Records

The majority of the source data will be collected on the paper source data worksheets (SDW). These will be entered at each centre encrypted via the internet using the InferMed Macro electronic data capture and stored on a dedicated secure server within the MH&N Clinical Trials Unit at King's College London. The system ensures con dentiality.

A proportion of the assessment interviews with the participants and carers may be audiotaped in order to assess the interrater reliability of the RWs in their ratings of the primary outcome.

These will be collected using audio devices and will be stored centrally.

12.3.3 Duration & Location

The eCRF will be archived in accordance with the EU Directive by Recruiting PIs on behalf of the Trial Management Group. The MH&N CTU will provide each site with a disk containing their data at the end of the trial.

The electronic Trial Master Database will be stored on a dedicated server within the MH&N CTU, King's College London inde nitely so that it is available should the Trial Management Group wish to access it for further analysis.

Copies of the Trial Master Database will be kept securely on university computers and/or laptop computers.

12.4 Trial Data Management System

12.4.1 eCRF

An eCRF will be created using the InferMed Macro system. This system is regulatory compliant (GCP, 21CRF11, EC Clinical Trial Directive). The eCRF will be created in collaboration with the Trial Manager, the Trial Statisticians and the Health Economists and maintained by the MH&N Clinical Trials Unit. It will be hosted on a dedicated secure server within KCL.

12.4.2 Training and User Support

The Trial Manager will be trained in the data entry and data query modules of the MACRO system by the MH&N CTU. He will then train the RWs and Recruiting PIs on the data entry and data query modules during site initiation.

Sites will seek support with the eCRF from the Trial Manager in the first instance and problems that cannot be resolved at that level will be passed by the Trial Manager to the MH&N CTU. There will be only one point of contact between the Trial Team and the MH&N CTU (Trial Manager to Database Programmer).

12.5 Entry of Data by Local Research Assistants

RWs will complete participant data using source data worksheets provided to the sites at site initiation. Data will be entered onto the eCRF from these source data worksheets. The source data will be filed in the participants clinical records (or within the Recruiting PIs department if this is not possible) at the end of the trial.

Each RW and Recruiting PI will have a unique username and password for the eCRF provided by the MH&N CTU. Passwords must not be shared and if new researchers join the study, a personalised username and password should be requested via the Trial Manager. Data, once entered, can subsequently be changed. The system will maintain a clear audit trail of when and who entered the original data, what that data was, what it was changed to, by whom, when and why. It is a legal requirement that passwords to the eCRF are not shared and that only those authorised to access the system are allowed to do so. It is the responsibility of each individual issued with a password to keep it secret and ensure nobody else uses it.

RWs will transcribe data from the SDWs at their own centre (which will act as the source data for the trial) onto the eCRF. This should be done within one working week of a participant assessment. A proportion of these will be checked by the Trial Manager during on-site monitoring visits. Queries will be resolved on the eCRF by referring back to the SDWs.

After the week 39 assessment, the RW must enter the participant data as soon as possible, in order to allow time for the Trial Manager and Trial Statistician to review the data and issue any queries promptly. These queries must then be answered by the RW before the participant's data is locked within the database. After that time, changes cannot be made to the database by sites. The participant's treatment allocation cannot be revealed until this process has been completed. The Recruiting PI must inform the Referring Investigator or other clinician taking over the participant's ongoing care of their treatment allocation between month 9 and month 10, as no further blinded study medication will be available to the participant. Since the clinician will need time to review the patient clinically, make a decision on ongoing treatment for depression and have a prescription issued, it is vital that the system of data entry, review and database lock on a participant by participant basis happens promptly after their week 39 assessment, so that their treatment allocation can be revealed.

At the end of the trial, the Recruiting PI will review all the data for each participant and provide and electronic signoff to verify that all the data is complete and correct. The electronic signoff is the legal equivalent to a paper signature.

At the end of the trial each centre will be supplied with a CD-ROM containing the eCRF data for their centre which must be led in the Recruiting PI site le in case of future regulatory or internal audits.

12.6 Trial Monitoring Procedures

12.6.1 Quality Assurance

12.6.1.1 Selection of Centres/Sites

The nine trial centres/Recruiting PIs were selected because of their track record and experience in other large multicentre dementia trials.

12.6.1.2 Training of Trial Personnel

All staff employed on the grant and all Investigators will be trained in:

- GCP
- Use of the assessment tools
- Trial standard operating procedures.

Interrater reliability of the CSDD will be assessed prior to the start of data collection and reassessed during the course of the trial.

12.6.1.3 On-Site Monitoring

The Trial Manager will conduct a minimum of three on-site monitoring visits to each site and will complete a Site Monitoring Report for each site at each visit.

During monitoring visits he will check and update the Investigator Site Files and will visit pharmacies to check the Pharmacy Files.

He will examine the consent forms for 100% of the participants during site monitoring visits.

He will examine the source data worksheets on a pre-de ned subset of participants (to be detailed in the monitoring SOP) to check for accuracy and completeness against the eCRF. He will check all reported SAE data and discuss any follow-up data needed with the site and he will also talk through with the RW the progress of each participant, double checking that there have been no unreported SAEs.

He will meet with the RW and Recruiting PI at regular intervals to discuss the progress of the trial on the site to check if there are any signi cant problems.

He will check the study medication dispensing and returns data for all participants against the eCRF data. The current stock held in pharmacy should be checked in order to ensure the study medication distribution system is working. He will re-count all the medications returned to pharmacy, check his pill count against the pharmacists' pill count and the pill count recorded in the eCRF by the RW and resolve any discrepancies. He will then complete a study medication returns inventory, package up the study medication returns and notify Catalent that they are ready for collection from site. Once they are received back at Catalent, a warehouse number will be issued for that shipment and this must be retained with the details of the study medication returns shipped, in order that they can be identi ed and retrieved if this is ever required during the trial.

12.6.1.4 Essential Documentation

The Trial Manager will maintain a Trial Master File containing the essential trial documents in accordance with GCP and the EC Clinical Trial Directive. In addition, he will supply each site with an Investigator Site File and a Pharmacy File, which will contain the some of the essential documents.

12.6.2 Quality Control

12.6.2.1 Data Checking & Verification Procedures

Where possible, the eCRF system will generate automatic queries to the RW if data fields are being completed with illogical data. These will appear as pop up boxes as the data is entered.

The Trial Manager will monitor the data electronically for completeness and will generate queries back to the site, via the eCRF, if there is data that looks as if it may be erroneous or is unclear.

The RW will respond to the queries and the Trial Manager will review the response. The query will then be closed by the Trial Manager, though it can be re-issued if the matter is not resolved satisfactorily. All queries raised and their responses will be retained as an audit trail.

The Trial Manager or Statistician may also identify data fields that should be checked against the source data during site monitoring visits. These can then be listed per site while the Trial Manager is there and `signed off' electronically as they are checked. Likewise, if any source data is missing or incorrect, this will be noted in the eCRF.

Detailed standard operating procedures will be established for data checking once the eCRF has been created.

12.7 Data Locking Procedures

Trial data will be locked in stages. Once a participant has completed the 39 week follow-up assessments, or these have formally been lost to follow-up, all outstanding queries on their eCRF will be resolved before their data is locked. A period of one month following participants 39 week assessment has been allowed for this. The Recruiting PI will sign off each participant's eCRF prior to unblinding. Once all data collection to the trial has been completed any further outstanding queries will be resolved and the entire database will be locked prior to its transfer to the Trial Statisticians and Health Economists. The Trial Statisticians and Health Economists will conduct the final checking of the data and any queries generated will be resolved at site by the Trial Manager and RWs before the Master Trial Database is frozen for analysis.

13 ETHICAL CONSIDERATIONS

The main potential ethical issue in this study is that dementia itself may interfere with an individual's ability to give their informed consent, especially in more severe stages of the illness. Given that this is an effectiveness study it is very desirable that all potential participants with depression in dementia are included if the overall impact of the medications are to be ascertained. This is an important issue in this study's design since compromised capacity and lack of insight may be a source of significant variation (e.g. via compliance).

The trial group has considerable experience in the ethical issues raised by obtaining consent for treatment trials in dementia, including severe dementia. One strength of the study is the level and integral nature of consumer involvement at all stages which means that carers and people with dementia will contribute to finalising information sheets and consent forms. The methods of obtaining consent for the study proposed here follow COREC guidance for information sheets and consent forms and specific guidance for incapacitated adults in CTIMPs to ensure that they are compliant with

the Medicines for Human Use (Clinical Trial) 2004 Regulations. However, for the purposes of this trial our design minimises the likely impact of lack of capacity by having an informant caregiver involved throughout who will act as the participant's personal legal representative.

Full informed consent will be obtained where possible. If the person with dementia does not have the capacity to consent, then their assent will be sought, the consent of an appropriate caregiver will be sought and the interviews and recruitment will be completed only if there is no sign of distress in the person with dementia. This is an approach that has been used successfully in trials and other descriptive and evaluative studies.

That said, the giving and discussion of information to people with dementia to enable them to make an informed decision with respect to consent is more complex and time consuming than for people without cognitive impairment. The study RWs will be trained in issues in obtaining consent and will only be deployed if their skills in this area are satisfactory. Also for this reason, the Referring Investigator will obtain verbal consent, not for entry into the study, but only for the potential participant to be approached by the RW. The study RW will then discuss the study with participants and carers, providing information, and will obtain consent or assent as described in section 7.3. Participants will be given a 7 day period to consider the information given and their willingness to participate.

14 REGULATORY AND ETHICS APPROVAL

14.1 Research Ethics Approval

We have submitted the protocol for consideration by the Manchester Research Ethics Committee (REC) which is a Type 3 ethics committee and therefore has the authority to approve a multiple domain CTIMP (clinical trial of an investigational medicinal product).

Ethics Reference: 06/Q1407/66.

See also sections 17, 18 and 19.

14.2 Local Research Ethics Approvals (LREC)

Site specific assessments (SSAs) will be undertaken by local ethics committees, the submission of which are being coordinated by the Mental Health Research Network.

Within each of the 9 recruiting sites, the Recruiting PI will be named on the local ethics SSA.

For each NHS Trust with Referring Investigators, one lead `Principal Referring Investigator' will be identified and named on the SSA. Other Referring Investigators within that site will be listed on a delegation of authority form which is filed in the `Referring Investigator Site File' that is held by the Principal Referring Investigator. The RW, in collaboration with the Trial Manager, will be responsible for ensuring the site files for the Recruiting PI and all the Principal Referring PIs contain all essential documents.

See also sections 17, 18 and 19.

14.3 Medicines and Healthcare Products Regulatory Agency Approval (MHRA; CTA)

CTA application has been submitted by the Chief Investigator on behalf of the sponsor and has been approved. The Qualified Person (QP) is Dr Ian Scully at Catalent.

See also sections 17, 18 and 19.

14.4 R&D Approvals and Research Governance

The study will be approved by all local NHS Trust R&D Departments involved prior to recruitment at each site or referral by a Referring Investigator. This will be facilitated by the Mental Health Research Network.

15 FINANCIAL AND INSURANCE MATTERS

15.1 Funding Arrangements

15.1.1 Contact Details of Funding Bodies

Liz Dunn
Commissioning Manager
NHS Health Technology Assessment
University of Southampton
Biomedical Sciences Building (Mailpoint 728) Bassett Crescent East
Southampton SO16 7PX
Email hta@soton.ac.uk
Tel + 44 (0)23 80 595770
Fax + 44 (0)23 80 595639.

Sertraline and sertraline placebo are being donated by Pfizer UK Ltd. (Total value c. £25,000).

15.1.2 Duration of Grant

Twenty-seven months, from 1st August 2006 to 31st October 2008.

15.1.3 Grant Summary

Total grant: £1.6 million
Funders reference number: 04/11/02

15.2 Indemnity/Compensation/Insurance Arrangements

The Chief Investigator is covered under the Kings College London no-fault liability insurance for clinical trials. Catalent, Pfizer UK, Genus Pharmaceuticals and Arrow Pharmaceuticals are covered by their own appropriate insurances and contracts will be agreed between them and KCL.

The study site staff will be covered by NHS indemnity from the principal investigators' employers for negligent harm.

15.3 Site Agreements

These have been drawn up by sub-contracts between KCL and the participating sites.

16 PUBLICATION POLICY

It is intended that the trial results will be disseminated in peer-reviewed scientific journals, an internal report to the HTA, conference presentations, written feedback to trial participants and carers, and presentations to relevant community groups.

A publication policy will be developed by the TMG and all data from the study will only be disseminated with the prior agreement of the TMG.

The results will be made available by a newsletter to the research participants. If any news comes to light during the trial itself about the treatments involved, these will be conveyed to the research participant, their GP and their family and carer.

17 ETHICS SUBMISSIONS

Ethics application submitted 24.03.06	Approved 12.07.06
Substantial amendment 1 submitted 23.08.06	Approved 14.09.06
Substantial amendment 2 submitted 04.10.06	Approved 20.10.06
Non-substantial amendment 1 submitted 20.12.06	Noted 17.01.07
Non-substantial amendment 2 submitted 02.05.07	Noted 10.05.07
Non-substantial amendment 3 submitted 08.06.07	Noted 27.06.07
Substantial amendment 3 submitted 14.09.07	Approved 2.10.07
Substantial amendment 4 submitted 5.12.08	Approved 9.01.09
Substantial amendment 5 14th September 2009	Approved 2.11.09.

18 MHRA SUBMISSIONS

CTA application submitted 21.06.06	Approved 04.08.06
Substantial amendment 1 submitted 23.08.06	Approval not required
Substantial amendment 2 submitted 04.10.06	Approval not required
Substantial amendment 3 submitted 14.09.07	Approval not required
Substantial amendment 4 submitted 5.12.08	Approval not required
Substantial amendment 5 14th September 2009	Approved October 2009.

19 AMENDMENTS

19.1 Non substantial amendments

Non-substantial amendment 1 was a protocol amendment (protocol 2.1)
Minor changes made to sections 1.1.1, 1.1.2, 1.2.4, 6.2 and 15.2.

Non-substantial amendment 2 was not a protocol amendment

Non-substantial amendment 3 was a protocol amendment (protocol 2.2)
Minor changes made to sections 3.1 and 7.4.2.

19.2 Substantial amendments

Substantial amendment 1 (ethics) was not a protocol amendment

Key changes:

1. Original ethics application stated incorrect CI. Ethics application revised. Lock code AB/88518/1.

Substantial amendment 2 (ethics & MHRA) was a protocol amendment (v2.3)

Key changes:

1. Principal investigator in Cambridge changed from Tom Dening to Claire Lawton (MHRA also informed) (section 1.2.4. (02))
2. Addition of Appendix 3: Source Data Worksheets (data entered on eCRF)
3. Clarification of study medication dispensing regimen (sections 8.7. 8.10.)
4. Participant & Carer Information & Consents revised to provide additional information to participants and carers and protocol amended to make clearer the situation for consent of incapacitated adults in CTIMPs, as required by the Sponsor (sections 7.3. and 7.5.2.)

5. Clari cation on the roles & responsibilities of Referring Investigators and Recruiting Investigators (section 1.2.4.)
6. Con rmation that Referring Investigators will document that the patient has given verbal consent to be referred to the Recruiting Investigator, rather than written consent (sections 7.2., 7.3. and 7.5.2.)
7. List of abbreviations added (section 2.)
8. Update of contact details to the study including DMC members and minor administrative changes to improve readability of protocol (section 1.3.2 and throughout protocol)
9. P zer UK Ltd. pharmacovigilance department to have access to anonymised SAE data for information only, as they are now donating sertraline and matching placebo tablets in bulk for the study (sections 9.1.7. and 15.1.1.)
10. Protocol amended to re ect the addition of week 4 and week 8 data collection
11. points as agreed in the original ethics approval (sections 7.5.1, 8.3, 10.2.2 10.2.3)
12. Protocol amended to re ect alterations to the system of adverse event data collection (sections 9.1.1. 9.1.8.)
13. Addition of information regarding 24 hour emergency unblinding service via
14. Guy's Toxicology Unit (section 8.12.3)
15. More detailed procedure for data management prior to routine unblinding at end of study added to protocol, to ensure both continuity of prescribing and integrity of trial data (sections 8.1.4. and 12.5.)
16. Addition of section in protocol to document all substantial and non-substantial amendments to the study, for administrative purposes (sections 17, 18 and 19.)

Substantial amendment 3 (ethics & MHRA) was a protocol amendment

Key changes:

1. Change of sponsor (sections 1.1.2 and 1.2.1)
2. Change of sponsor representative (section 1.2.1)
3. Update of section on submissions to ethics committee and regulatory authority.

Substantial amendment 4 (ethics & MHRA) was a protocol amendment (v2.4)

Key changes:

1. Extension of recruitment period (sections 7.1 and 7.2)
2. Change of address of Manchester PI, change of telephone and fax numbers for
3. Birmingham PI (1.2.4)
4. Change of role title for health economist Renee Romeo (1.2.10)
5. Change of name of drug supplier (1.2.12)
6. Changes in membership of Trial Steering Committee (1.3.1)
7. Addition of Clare Rutterford as statistician (1.2.9)
8. Week 4 and 8 assessments indexed on treatment start date rather than randomisation (7.5.1, 8.3, 10.2.2, 10.2.3)
9. Adverse events checklist replaced by aide memoire (Appendix 3).

Substantial amendment 5 (ethics & MHRA) was a protocol amendment (v2.5)

Key changes:

1. Supplier of mirtazapine changed from Genus to Arrow (pages 15, 43, 72)
2. Section on reporting procedure for SAEs, SARs and SUSARs (9.1.8, p52) revised to describe new arrangements

3. Line stating that consent forms are sent to the Chief Investigator deleted.

20 ANCILLARY STUDIES

These will be agreed by the TMG and the TSC.

21 REFERENCES

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22 APPENDICES

22.1 Appendix 1 Participant and Carer Information

Ethics approved 12 July 2006		
Participant information sheet	Version 1 (shortened version)	29.03.06
Participant information sheet: Patient	Version 2	28.06.06
Participant information sheet: Carer	Version 2	28.06.06

Ethics submitted 28 September 2006		
Information and consent form for patient (full version)	Version 3	28.09.06
Information and assent form for patient (shortened version)	Version 2	28.09.06
Information and consent forms for carer	Version 3	28.09.06

22.2 Appendix 2 Letters

Standard letters will be contained within the Trial SOPs. These will include:

- letter of referral from Referring Investigator to Recruiting Investigator
- letter from Research Worker to GP informing them of Participants inclusion.

22.3 Appendix 3 Source Data Worksheets and Electronic Case Report Forms)

	_____		
	_____		
	_____		

A3.1 Additional Diagnostic Questions
A3.2 Adverse Events Aide Memoire

Adverse Events

Adverse events will be recorded throughout the trial, with information systematically collected at weeks 4, 13 and 39. Adverse events should be recorded if they have prevented the participant from continuing with his / her normal activities, or if they have signi cantly affected the participant's well being. Any adverse events should be discussed with the principal recruiting investigator, to consider causality and seriousness. Adverse events are recorded in the eCRF on the basis of these discussions.

The following list is an aide memoire only. All adverse events should be recorded, whether or not they appear here.

- abnormal vision
- aggression
- anaemia
- high or low blood pressure
- confusion
- ts (seizures)
- diarrhoea / loose stools
- dizziness
- dry mouth
- quickened heart rate
- falls
- fatigue
- sleepiness
- fever
- headache
- indigestion
- itching
- malaise
- muscle jerks
- muscle rigidity
- nightmares/vivid dreams
- numbness/tingling
- pain abdominal
- pain joints
- pain muscle
- rash
- restless legs
- sexual dysfunction
- sweating
- tremor
- urinary retention
- vomiting.

Adverse events will be classed as serious if any of the following apply:

- life-threatening
- necessitates hospitalisation
- prolongs hospitalisation
- causes persistent and / or signi cant disability or incapacity
- deliberate self-harm.

A3.3 Bristol Activities of Daily Living Scale

A3.4 Carer Demographic Information

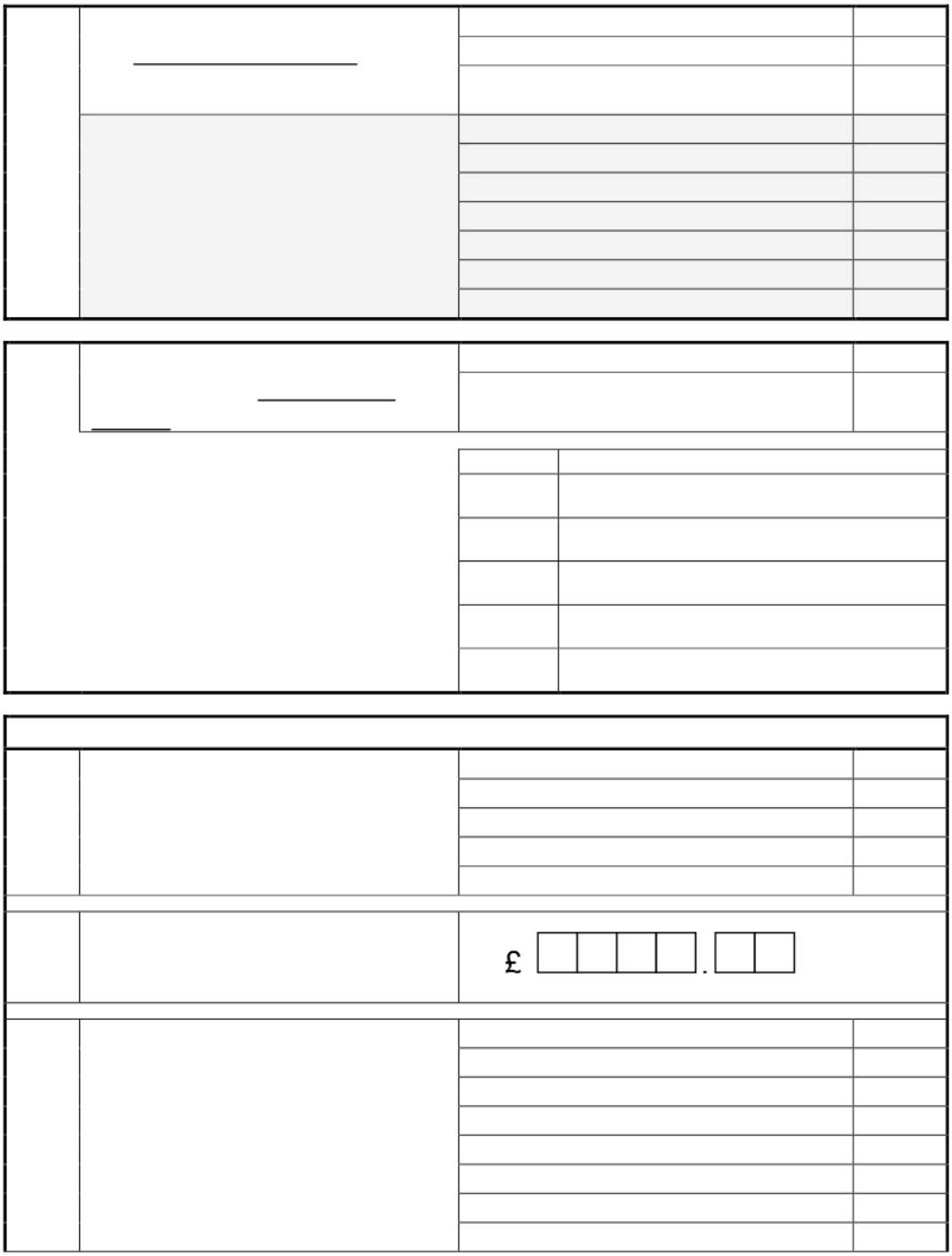
		Day Month Year	

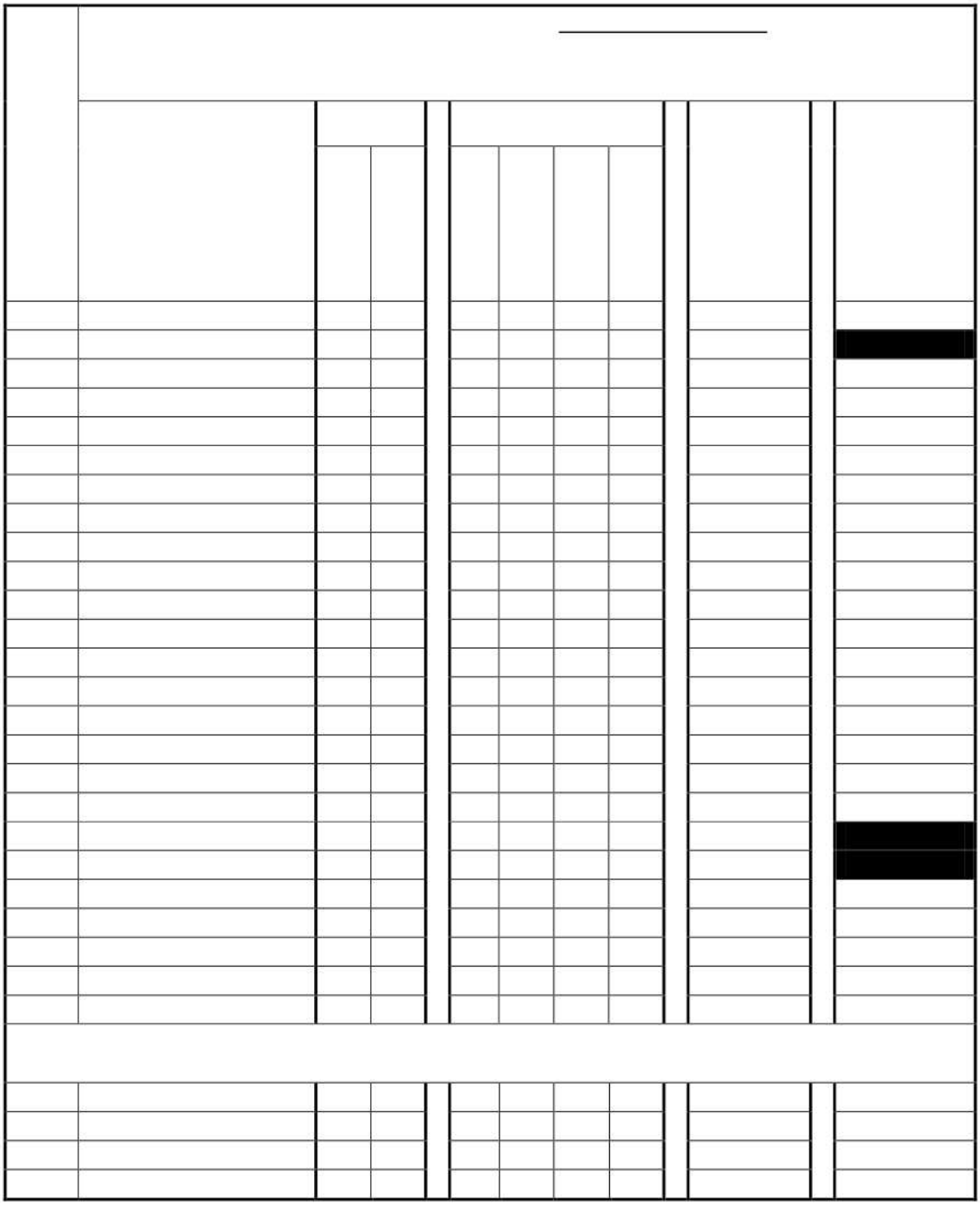
A3.5 Carer Global Impression

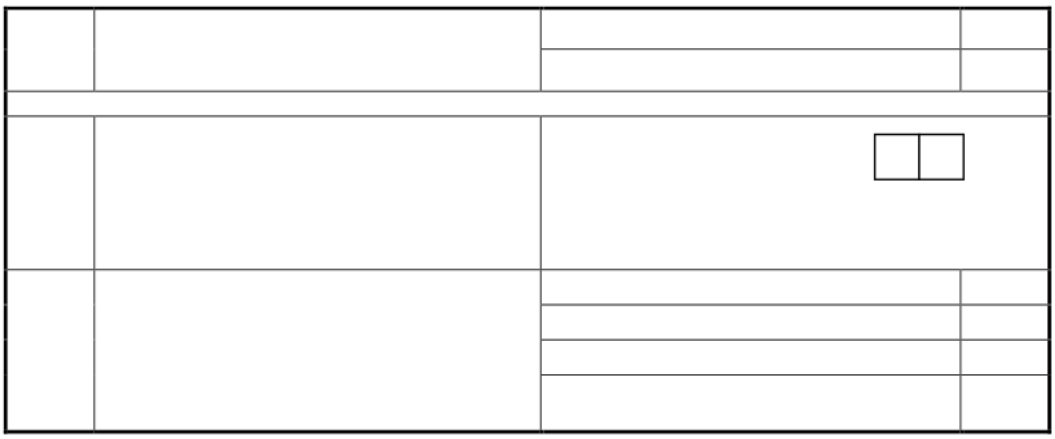
A3.6 Carer Registration # 1

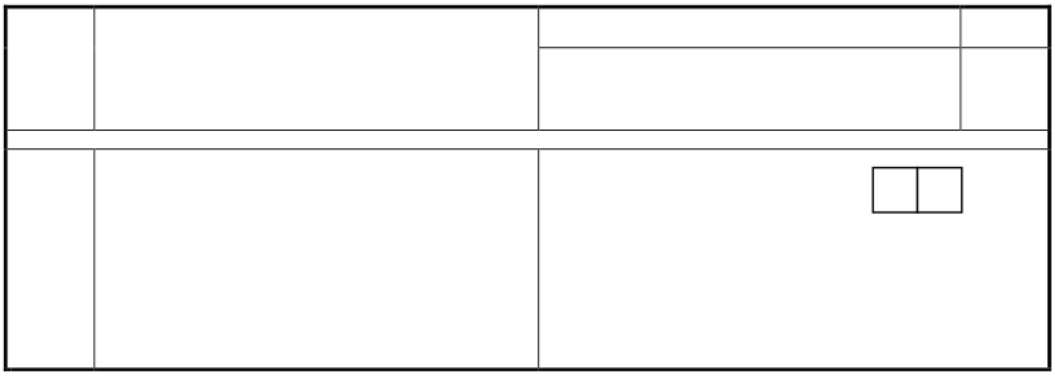
		C ☐☐ ☐☐☐ A	
		Centre Number Same as PIN First Carer	
		☐☐☐☐	
		☐☐ ☐☐ ☐☐☐☐	
		Day Month Year	
		☐☐☐☐	

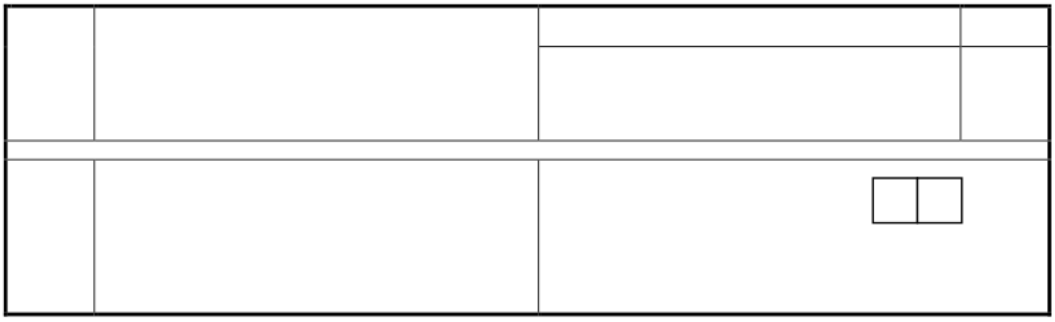
A3.7 Client Service Receipt Inventory (CSRI)





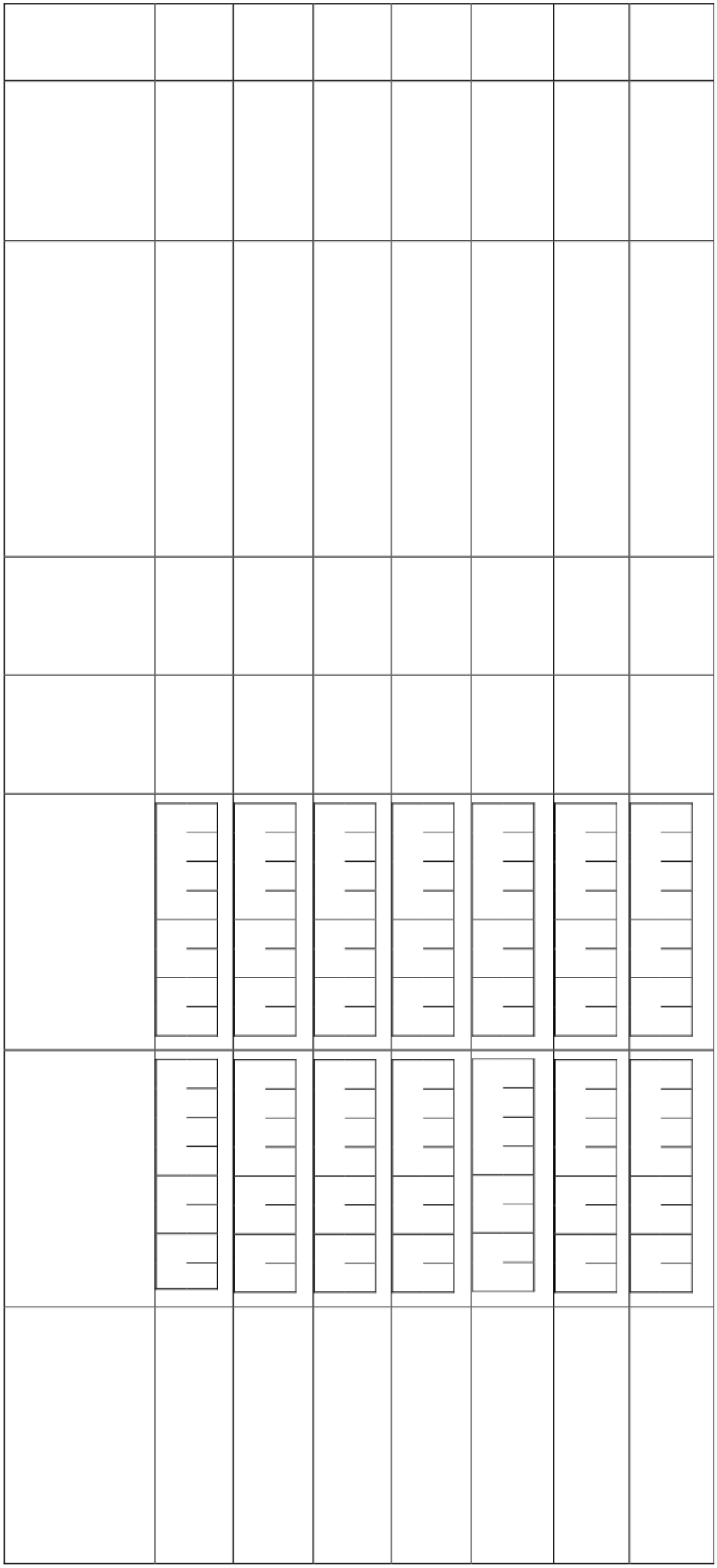


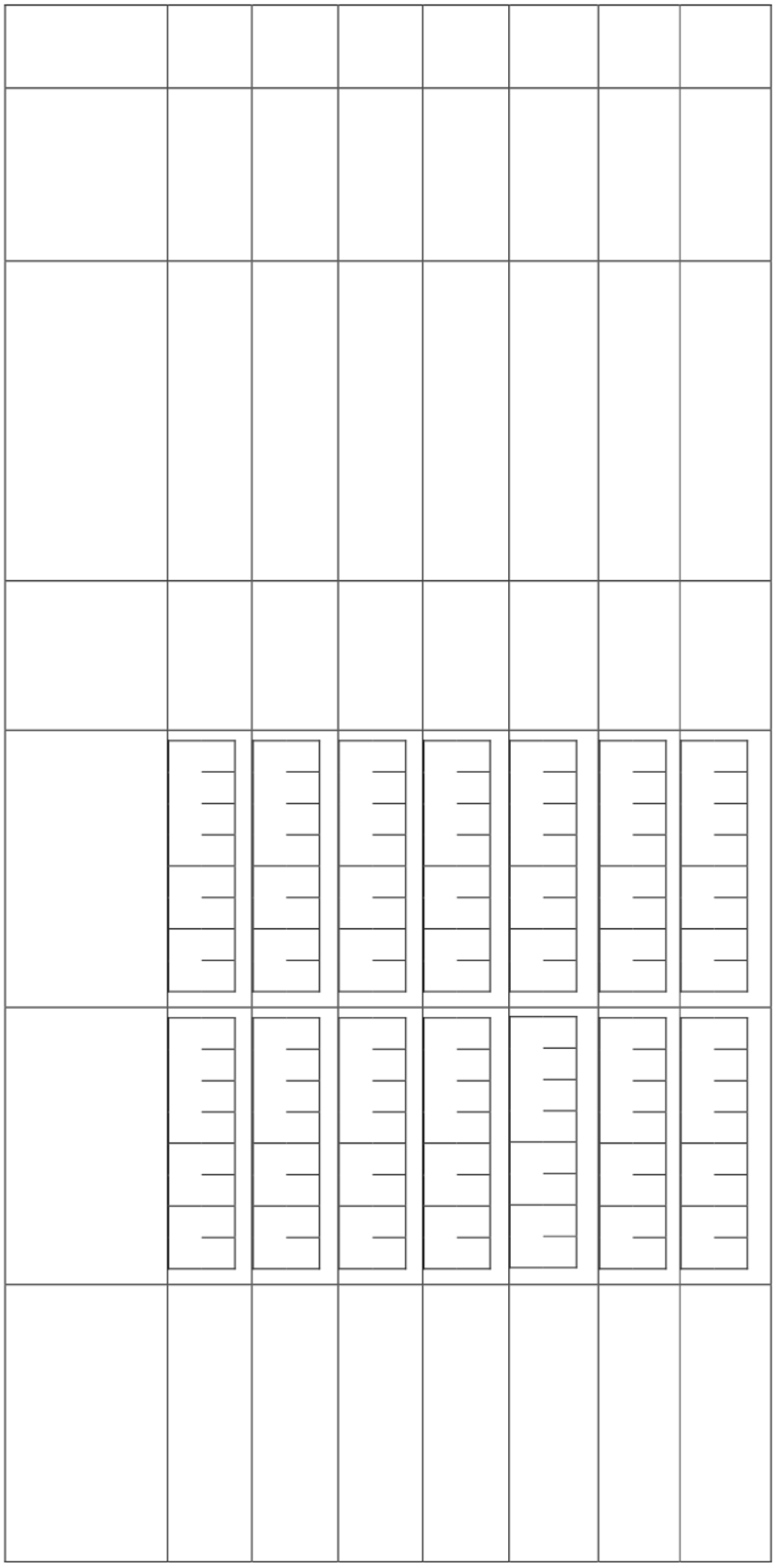




A3.8 Cornell Scale for Depression in Dementia (CSDD)

A3.9 Concomitant medications/DRUGS (Page one)





A3.10 Concomitant treatments/Non Drugs

A3.11 DEMQOL

A3.12 DEMQOL Proxy

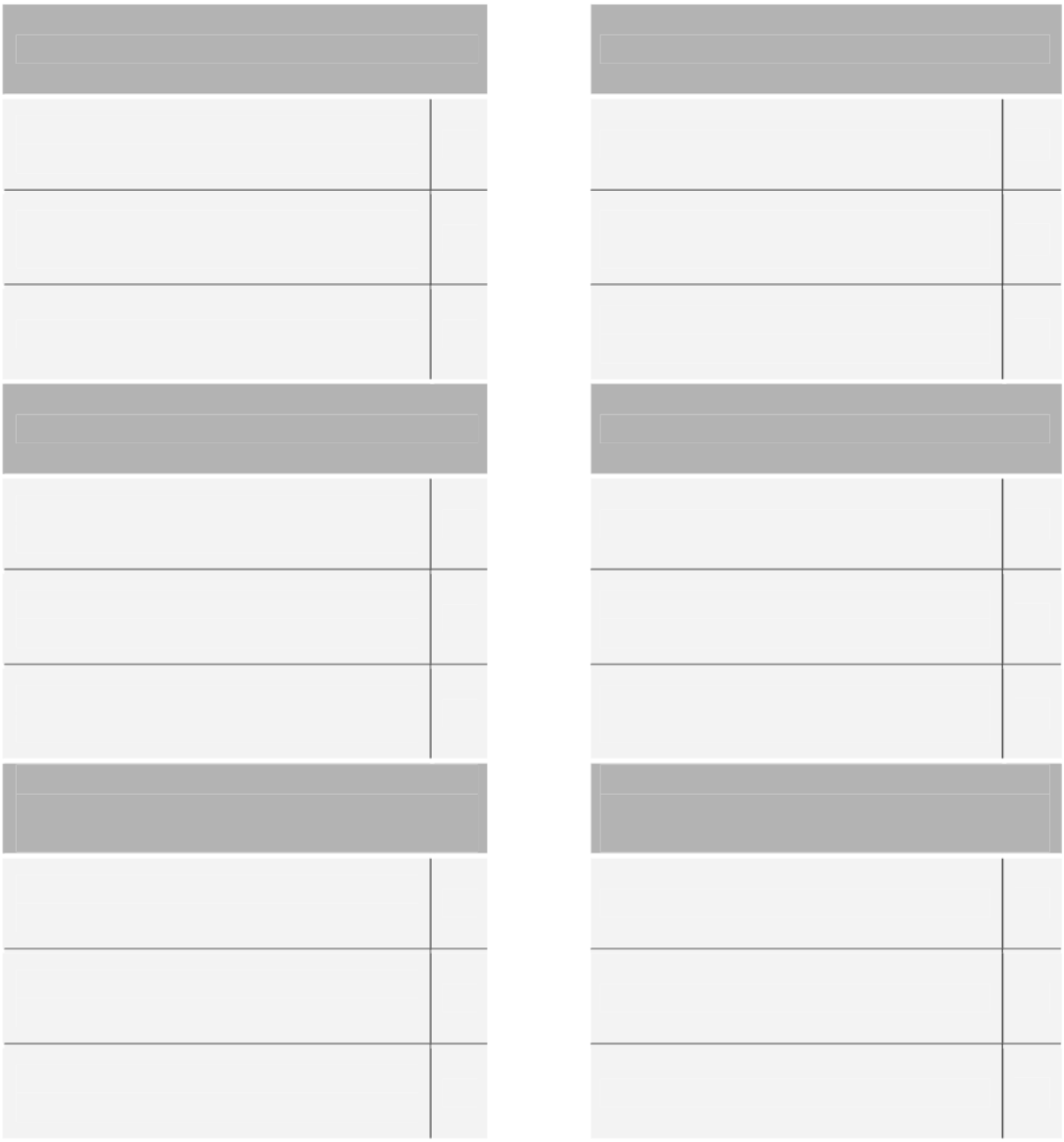
A3.13 End of Trial (Routine) Request for Unblinding

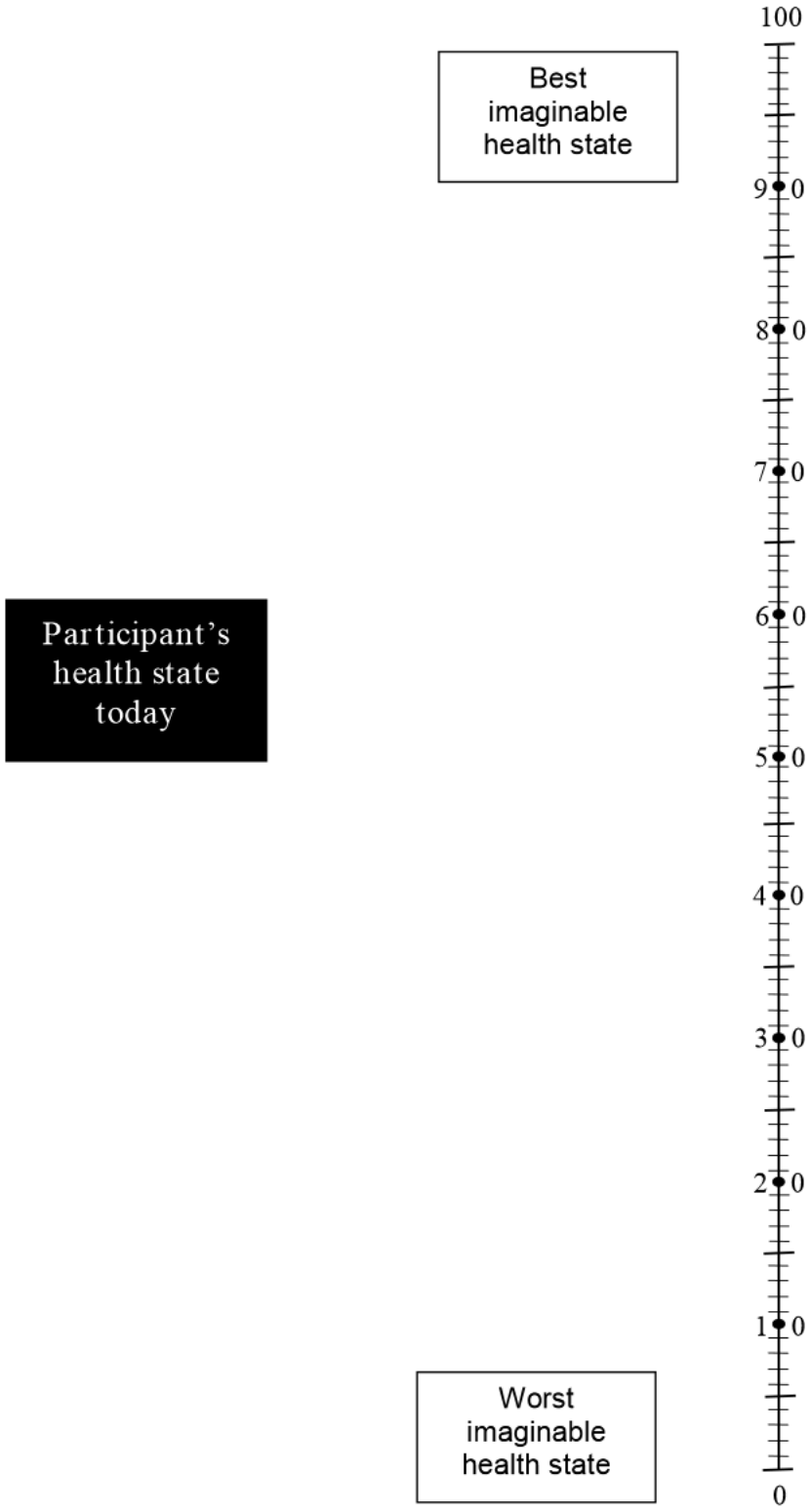
1.	Person Requesting Codebreak	Name:	_____
		Position:	_____
2.	Date of Request	☐☐ ☐☐ ☐☐☐☐ Day Month Year	
3	Type of Request		
4a	Data Entry Complete		
4b	Data Cleaning Complete		
5			

FOR OFFICE USE ONLY

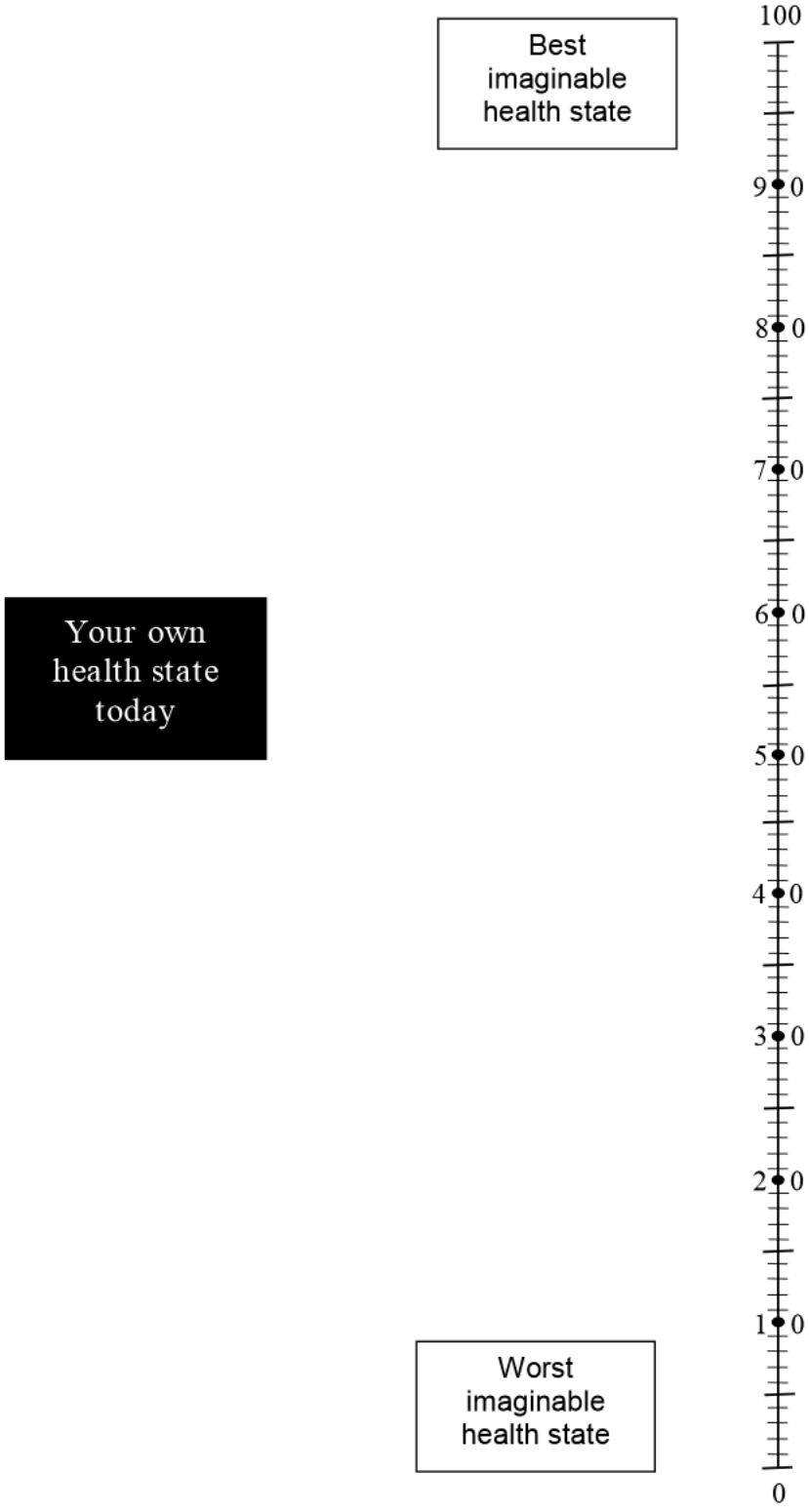
6	Person Authorising Codebreak	Name:	_____
		Position:	_____
7	Date of Codebreak	☐☐ ☐☐ ☐☐☐☐ Day Month Year	
8	Further Notes		

A3.14 EuroQol (EQ-5D) Carer




Best imaginable health state
100
90
80
70
60
50
40
30
20
10
0
Participant's health state today
Worst imaginable health state

A3.15 EuroQol (EQ-5D) Participant


Best imaginable health state
100
90
80
70
60
50
40
30
20
10
0
Your own health state today
Worst imaginable health state

A3.16 Exclusions from Randomisation

A3.17 General Health Questionnaire (GHQ12)

A3.18 Medical History (Page One)

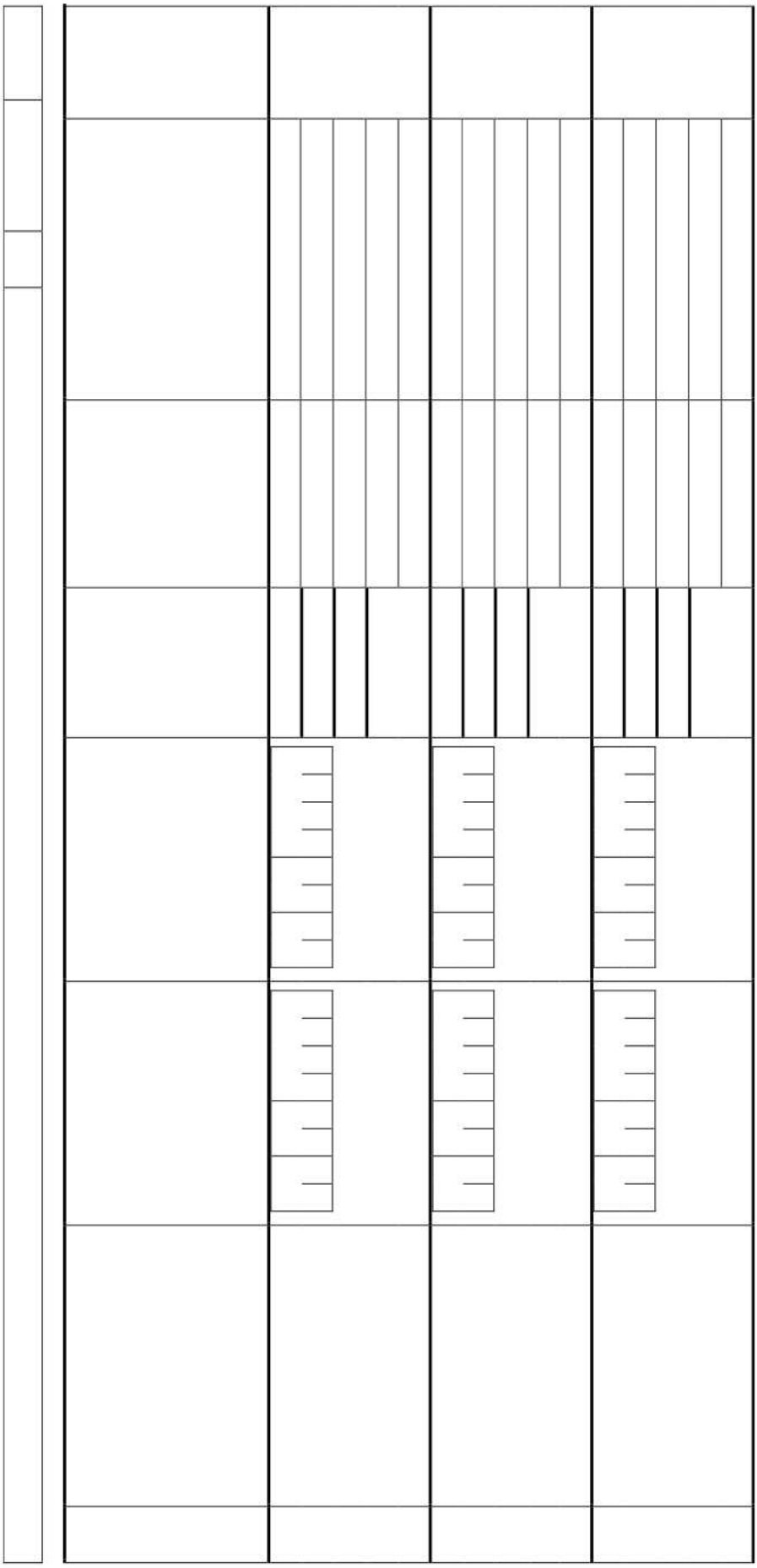
Code	System	*Yes	No	Code	System	*Yes	No

A3.19 Medication Guess

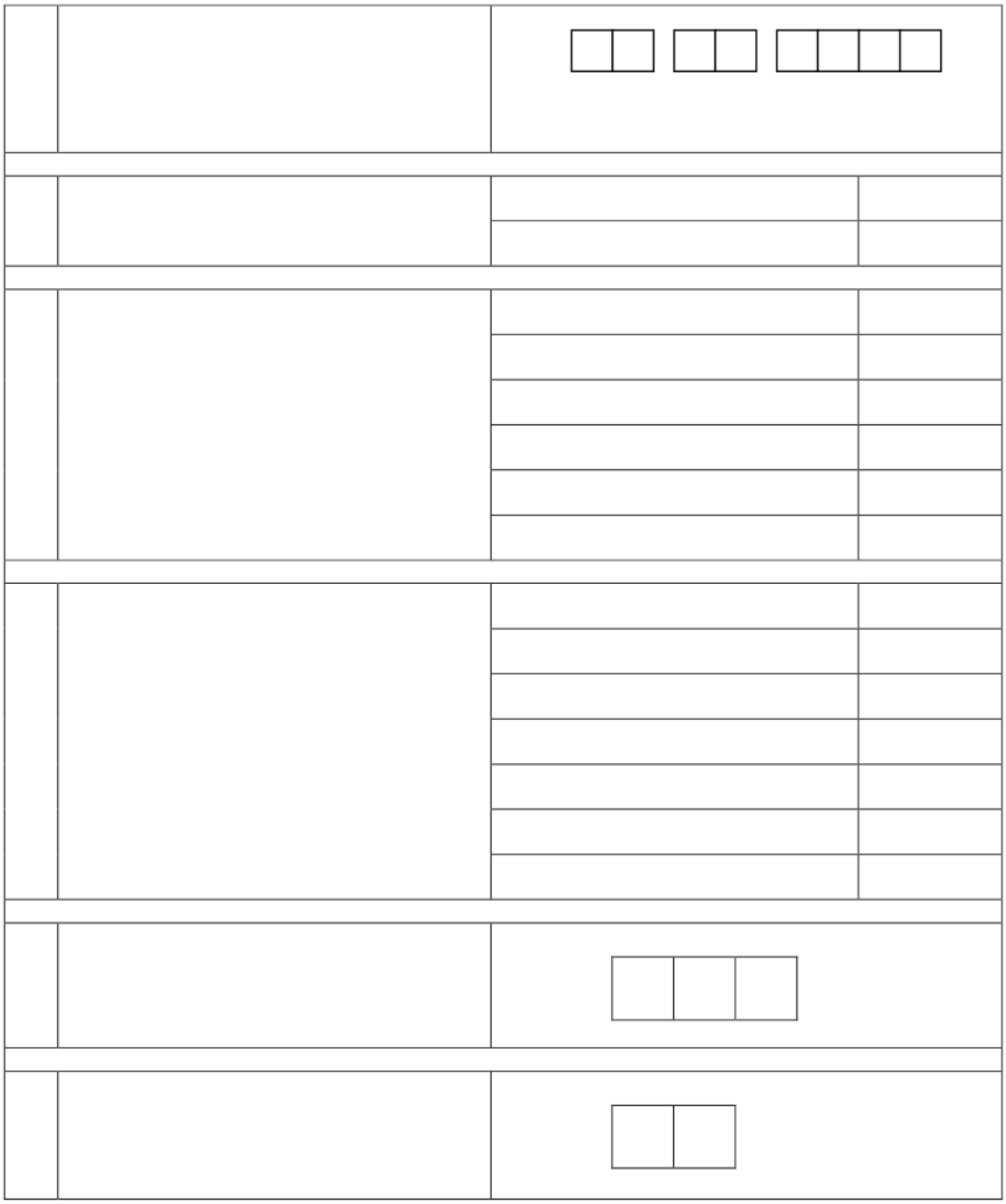
A3.20 Medication Preference

A3.21 Neuropsychiatric Inventory (NPI)

A3.22 Non-serious Adverse Events Log (Page One)



A3.23 Participant Demographic Information



A3.24 Participant Registration

A3.25 Pill Count

A3.26 Randomisation Request Form: HTA-SADD trial

A3.27 Serious Adverse Event (SAE) Form

1.	Seriousness (Circle all that apply)	Death	1
		Life-threatening	2
		Requires inpatient hospitalisation	3
		Prolongs current inpatient hospitalisation	4
		Results in persistent / significant disability / incapacity	5
		Consists of a congenital anomaly or birth defect	6
		Any episode of deliberate self harm	7
		Other:	8

2.	Participant Information		
2a.	Sex	Male	0
		Female	1
2b.	Date of birth	☐☐ ☐☐ ☐☐☐☐ Day Month Year	
2c.	Ethnicity	White	1
		Mixed	2
		Asian	3
		Black	4
		Chinese	5
		Other	6

3a.	Event Onset	☐☐ ☐☐ ☐☐☐☐ : Day Month Year
3b.	Date Became Serious (Only if different from event onset)	☐☐ ☐☐ ☐☐☐☐ : Day Month Year

4.	Brief description of event – diagnosis or main symptom(s) only (attach additional sheets if necessary)

5.	Severity	Mild	1
		Moderate	2
		Severe	3

6.	Trial Medication (ie Placebo / Mirtazapine / Sertraline) for Depression in Dementia	
6a.	Start Date	☐☐ ☐☐ ☐☐☐☐ Day Month Year

6b.	Anticipated Stop Date	☐☐ ☐☐ ☐☐☐☐ Day Month Year	
6c.	Dose at Event Onset	None	0
		Low	1
		Medium	2
		High	3
6d.	Date / Time of Last Dose (prior to event becoming serious)	☐☐ ☐☐ ☐☐☐☐ : Day Month Year	
6e.	Trial medication administered in accordance with the protocol?	No	0
		Yes	1
		Unknown	88
6f.	Code broken as a result of this event	No	0
		Yes (Reason:_____)	1

7a.	Action taken with trial medication	None	1
		Temporary Dose Reduction: Date of dose increase (if applicable): ☐☐ ☐☐ ☐☐☐☐ Day Month Year	2
		Permanent Dose Reduction	3
		Temporary Discontinuation Date of reintroduction (if applicable): ☐☐ ☐☐ ☐☐☐☐ Day Month Year	4
		Permanent Discontinuation	5
7b.	Use of corrective therapies for this event	No	0
		Yes (Specify:_____)	1
7c.	Did the event reappear after reintroduction or dose increase?	No	0
		Yes	1
		Not applicable	77
		Unknown	88

8.	Outcome		
8a.	Death (Cause: _____)	☐☐ ☐☐ ☐☐☐☐ Day Month Year	1
8b	Ongoing (persistence)		2
8c.	Recovered with significant sequelae (Specify:_____)	☐☐ ☐☐ ☐☐☐☐	3

		Day Month Year	
8d.	Recovered without significant sequelae	☐☐ ☐☐ ☐☐☐☐ Day Month Year	4
8e.	Unknown		88

9a.	Relationship to Study Medication	Definite	1
		Probable	2
		Possible	3
		Remote	4
		None	5
9b.	Relationship to Medical Conditions (including Dementia and/or Depression)	Definite	1
		Probable	2
		Possible	3
		Remote	4
		None	5

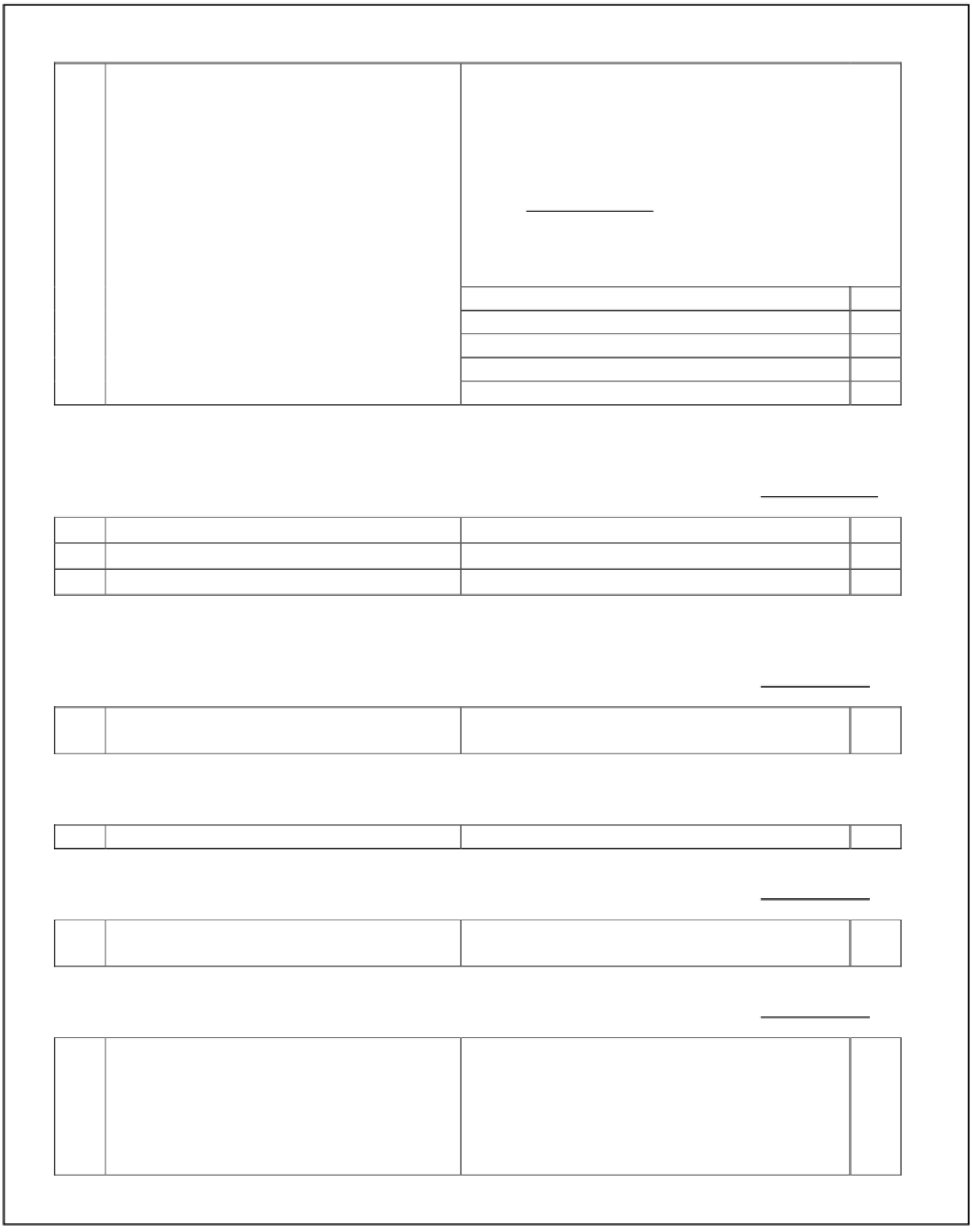
10.	Expected event (according to SmPC, protocol & medical history)	No	0
		Yes	1

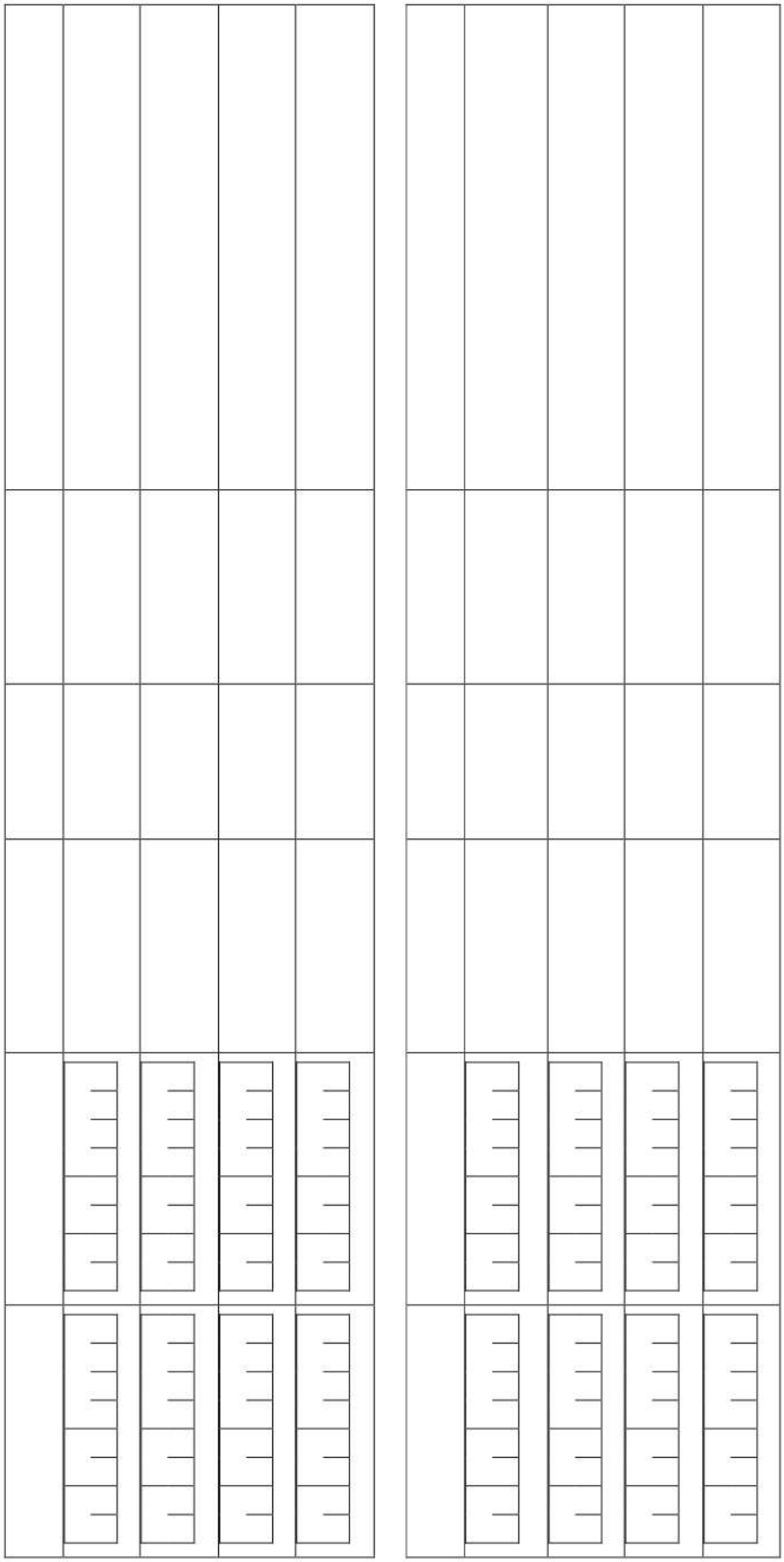
11.	Additional Comments (if any)

12.	Signature of Research Worker: _____ Date: __/__/_____

A3.28 Short Form 12 (SF-12 Version 2)

A3.29 Mini-Mental State Examination (SMMSE)





A3.30 Trial medication log

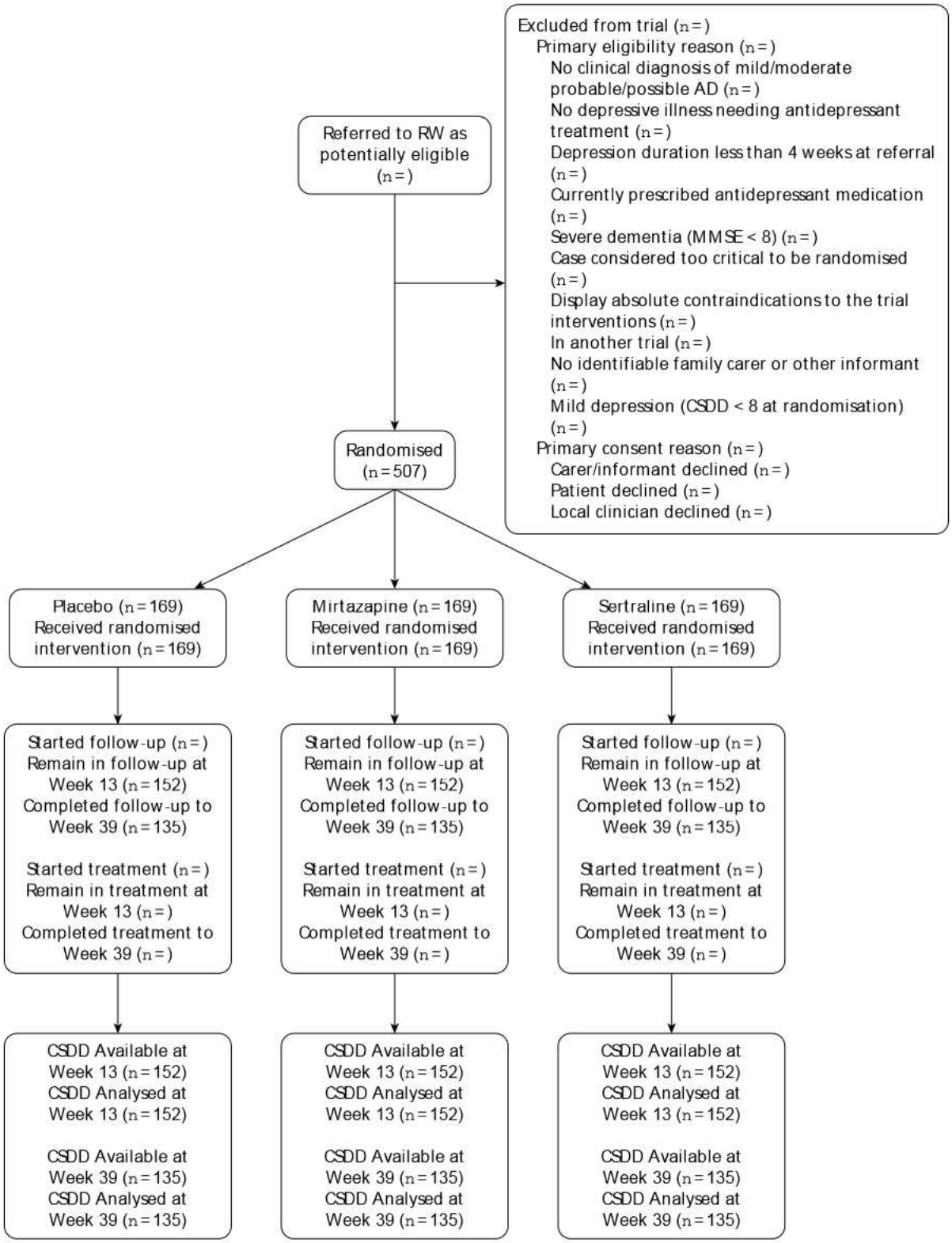
A3.31 Withdrawal Form

A3.32 Zarit Caregiver Burden Inventory

22.4 Appendix 4 Policy on Ancillary Studies

This is to be developed.

22.5 Appendix 5 CONSORT Diagram



22.6 Appendix 6 Statistical Analysis Strategy

To be agreed by the TMG and the TSC after the start of randomisation.

22.7 Appendix 7 Declaration of Helsinki 1996

Please see: http://www.hku.hk/facmed/research/ec/Declaration_of_Helsinki_1996_version.PDF

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