NETSCC, HTA

24 November 2009

HTA-SADD Trial

HTA Study of Antidepressants for Depression in Dementia: A Definitive Multi-centre Pragmatic Randomised Controlled Trial of Clinical and Cost Effectiveness

Full Trial Protocol Version 2.5
14th September 2009 ISRCTN88882979

Protocol Authorisation:

Chief Investigator: Professor Sube Banerjee

Signature: …….. Date: ……

Sponsor:

Signature: …….. Date: ……

Chair of Trial Steering Committee:

Signature: …….. Date: ……

Chair of Data Monitoring Committee:

Signature: …….. Date: ……

CONTENTS

Full title
A definitive multi-centre pragmatic randomised controlled double-blind trial of the clinical and cost effectiveness of mirtazapine and sertraline versus placebo for the treatment of depression in dementia presenting in secondary care

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.

1.2. 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 identified '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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Dolores Moniz-Cook
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

Pfizer UK Limited

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

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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 confidential 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 (eg 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 Diseases 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	Serum Glutamic Pyruvic Transaminase
GP	General Practitioner	SDW	Source Data Worksheet
HTA	Health & Technology Assessment	SmPC	Summary of Product Charactistics
IDMC	International Data Monitoring Committee (Charter)	SOP	Standard Operating Procedure
IMP	Investigational Medicinal Product	SNRI	Selective Noradrenergic Reuptake Inhibitor
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).

a. 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.

b. 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 to placebo on patient (eg quality of life, cognition) and family carer (eg 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 multi-centre 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 stratified by centre by stratified 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 identified 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-specific 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% significance 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% confidence intervals for the difference in the proportion of pre-specified adverse events between the antidepressant arms of (a clinically significant) 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) mirtazipine 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) mirtazipine 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 significance level will be 5% (2-sided) for all specified analyses of the primary outcome variable and 1% (2-sided) for all specified analyses of secondary outcome variables.

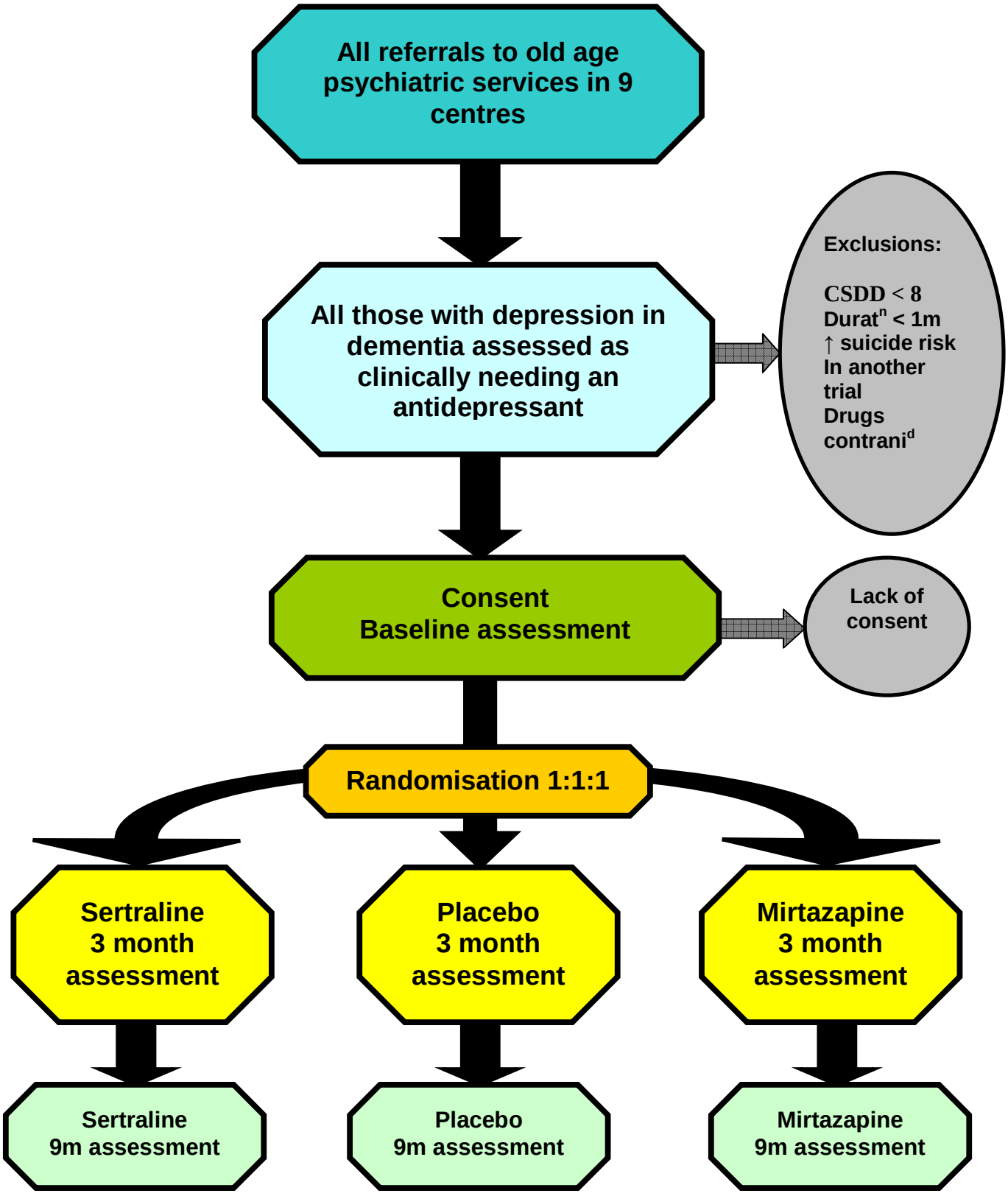
ECONOMICS

From the cost and the outcome data, we will compare total and component (by service or agency) costs, incremental cost-effectiveness ratios and net benefits (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 finalisation 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	final 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 identified 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 efficacy. 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. Reifler 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 final data were not available to the Cochrane review. In the final study 44 participants were recruited from a single university out-patient 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 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 finding 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 definitive research of "modern frequently used drugs". In addition they identified 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 Reifler et al (1989) requiring depression to meet 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 (Copeland et al 1990; Schaub et al 2003). Lyketsos et al (2003) 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.

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 benefit 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 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 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, benefit 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 benefit 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 fill these major gaps in the evidence base definitively.

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 Scientific 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 eg 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 eg 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 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 benefit 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 (Reifler et al 1989), whilst several studies of falls indicate that most antidepressants increase falls risk (eg 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 specific antidepressant agents requires careful consideration. For example, the best evidence of efficacy 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 profile and is widely used in clinical practice to treat depression in people with dementia, but has not been evaluated in an 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 reflect 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 (ie over 150mg of sertraline or 45mg of mirtazipine) 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 significantly. 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 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 (ie 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 influences on the outcomes.

4.5. Choice of 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 (eg 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 Benefits

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 significantly. 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 definitive 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 multi-centre 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 (eg quality of life, cognition) and family carer (eg carer burden, carer quality of life) outcomes at 13 and 39 weeks post-randomisation.

5.2.2.3 To determine the influence on clinical 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.

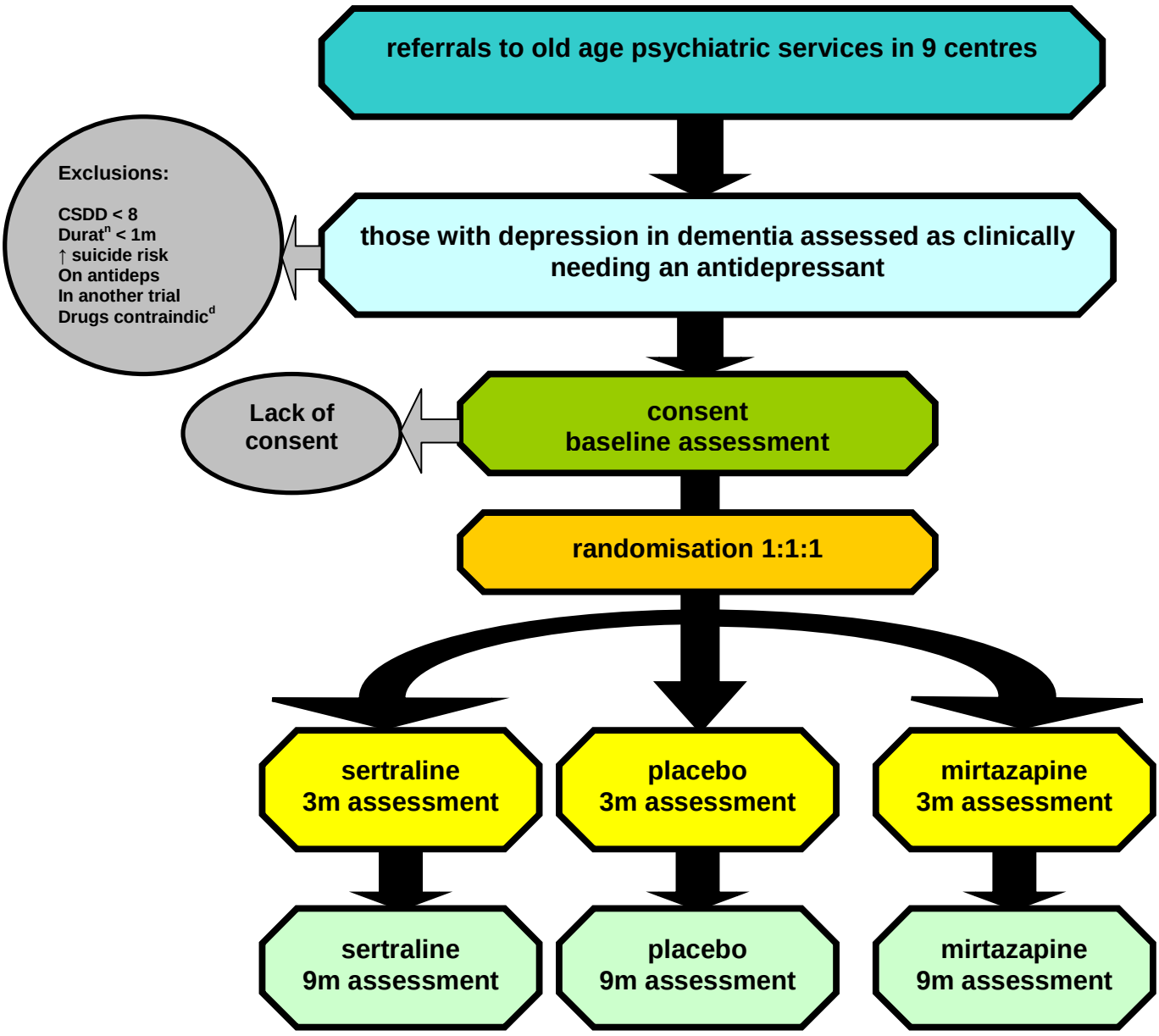
b. To investigate whether there are any differential predictors of response to the antidepressants (both vs. placebo) (ie treatment-covariate interactions).

6. TRIAL DESIGN

6.1. Description of Overall Trial Design and Plan

We propose to conduct a multi-centre 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 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 defined as 39 calendar weeks post randomisation to final 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.

6.3.3. Definition 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. Definition of the end of the trial

In ethics and regulatory terms, the end of the trial is defined as the end of data collection ie 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 defined as the provision of the final 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).

Table 6.4.1 Research assessments by timepoint

	Informant	Screening	Baseline & randomisation	Wk 4	Wk 8	Wk 13	Wk 39	Treatment discontin[n]	T dro
Verbal consent to referral to Recruiting PI	Patient / Carer	X By Referring Investigator							
Eligibility assessment	Referring & Recruiting PI/RW	X							
Informed consent	Patient / Carer	X							
NINCSD-ADRDA (for dementia)	Referring PI	X							
Modified Hachinski Ischemic Scale	Carer		X						
DSM-IV (for Depression)	Carer		X			X	X		
Olin (Depression in Dementia)	Carer		X			X	X		
Cornell Scale for Depression in Dementia (CSDD)	Patient/ Carer		X	X	X	X	X	X	
Participant demographics	Carer		X						
Carer demographics	Carer		X						
Client Service Receipt Inventory (CSRI)	Carer		X			X	X		
DEMQOL	Patient		X			X	X		
DEMQOL-Proxy	Carer		X			X	X		
EuroQol (Participant)	Patient		X			X	X		
EuroQol (Carer)	Carer		X			X	X		
SF-12 v2 (Carer)	Carer		X			X	X		
Standardised Mini-Mental State Examination (MMSE)	Patient		X			X	X		
GHQ-12 (Carer)	Carer		X			X	X		
Zarit Carer Burden Scale	Carer		X			X	X		
Neuropsychiatric Inventory (NPI)	Carer		X			X	X		
Bristol Activities of Daily Living (BADL)	Carer		X			X	X		
Carer global impression	Carer					X	X		
Medical history	Carer		X						

Table 6.4.1 cont.	Informant	Screening	Baseline & randomisation	Wk 4	Wk 8	Wk 13	Wk 39	Treatment discontin[n]	T dro
Non Serious Adverse Events Log	Carer			X	X	X	X	X	
Pill Count	RW					X	X	X	
Medication Preference	Carer		X						
Medication Guess	Carer/RW					X	X	X	
Concomitant Medications	Carer		X	X	X	X	X	X	
Concomitant Treatments	Carer		X	X	X	X	X	X	
Trial Medication Log	Carer			X	X	X	X	X	

Table 6.4.2 Other trial forms by timepoint

	Informant	Screening	Baseline & randomisation	Wk 4	Wk 8	Wk 13	Wk 39	Treatment discontin[n]	T dro
Registration Form Carer/Participant	RW	X							
Exclusion Form From Randomisation	RW	X							
Randomisation Request Form	RW		X						
Serious Adverse Event Report Form	RW/Doctor			X	X	X	X	X	
Withdrawal Form	RW/PI			X	X	X	X	X	
Routine Unblinding Request Form	RW/PI						X	X	

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 benefit 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 multi-centre approach. However both criteria also require that our participants are not simply drawn from highly specialist research centres first because of the need to maximise generalisability but also because the number needed could not be generated to time by existing research facilities (eg university memory clinics).

A final 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 (eg MRC CALM-AD) and the comments of reviewers and the Commissioning Board, we have designed a robust multi-centre 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 defined area. These catchment areas are typically described in terms of the numbers of older people (ie 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 configuration 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 identified 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 difficult 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 identified 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 specifically 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 findings) 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 efficacy 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 (ie 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 finds at the point of referral to the RW are:

- currently taking antidepressants;
- those with severe dementia (defined as the participant being unable to contribute to the CSDD);
- the case is considered as being too critical to be randomised (eg 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 identifiable family carer or other informant (eg a formal/professional carer who spends sufficient 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 finds 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 identified 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 eg 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 officers (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 specified 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 defined 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 specifically 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 Identification of Participants and Carers

The local RWs will assign Participant Identification Numbers (PINs) and Carer Identification 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 identification 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 final 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 significant 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 stratified by *centre* (Birmingham, Cambridge, Leicester, Liverpool, Manchester, Newcastle,

North London, Southampton, South London/Kent) by stratified 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 Office. 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 specific 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 identified 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 sertaline tablets. These will be identical to the active tablets in all respects.

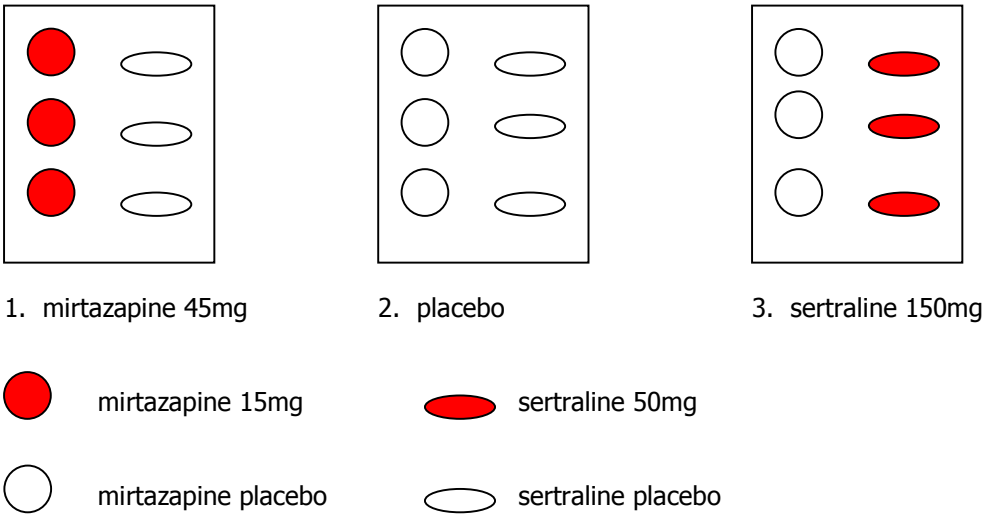
8.1.2. Mirtazapine and Sertraline

The experimental interventions are:

1) mirtazapine (a NASSA) with normal clinical care
2) 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



1. mirtazapine 45mg
2. placebo
3. sertraline 150mg

mirtazapine 15mg

sertraline 50mg

mirtazapine placebo

sertraline placebo

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
mirtazepine 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 (defined 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 – Pfizer 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 Product(s)

A trial specific prescription will be designed for use by all centres. This will be completed by Recruiting PIs or other medically qualified 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 file. 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 final 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 Trial 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 specific prescriptions will be maintained in the pharmacy file for audit purposes. Study medications supplies will not be destroyed until the end of the trial analysis, they will be sent back toCatalent. 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 significant instances of non-compliance with the dosing regimen will be recorded in the electronic case report form and source file. Details on how individuals receive their medication (eg 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 Catalentto Guy's Toxicology Unit, where an emergency unblinding service will be available 24 hours a day. The pharmacy site files will contain an emergency unblinding SOP. In office 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 (eg 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 (eg, 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 definitions:

- **Mild:** An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- **Moderate:** An event that is sufficiently 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 specific 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 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*

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.

- ***Definitely 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 definitely 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 identified 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 significant information on the specificity 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 clarification 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 filed 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 defined 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 fpr pharmacovigilance, as defined in Regulation 5 of the Medicines for Human Use (Clinical Trials) Regulations 2004 to the Joint Clinical Trials Office (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 qualifies 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 definitely 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 Pfizer 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 of suspected unexpected serious adverse reactions (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 (eg 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)
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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, granulocytopaenia, agranulocytosis, aplastic anaemia, thrombocytopaenia).

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, diarrhea

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 significantly 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 profile 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 significantly 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 first 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 (eg MMSE, DEMQOL); proxy report by the carer of the person with dementia (eg CSRI, NPI, DEMQOL-Proxy, EQ5D, adverse events, adherence); and self-report from the carer (eg 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 specifically 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 specific 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 filed 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 first 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 (eg 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 (eg 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% significance 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% significance 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 (eg 10% drop-outs and 15% drop-ins) the overall sample size required becomes 507 patients (ie 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 $\geq$ 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% significance 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% confidence intervals for the difference in the proportion of pre-specified adverse events between the antidepressant arms of (a clinically significant) 10% (i.e. 5% vs. 15%) $\pm$ 6% at 12 weeks and $\pm$ 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 first 39 week outcome data will only become available as recruitment into the trial is coming to an end (ie 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) mirtazipine 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) mirtazipine 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% confidence limits.

The significance level will be 5% (2-sided) for specified analyses of the primary outcome variable and 1% (2-sided) for specified 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 (eg 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 ProfessorMartin Knapp and his group at the Institute of Psychiatry with input from the London School of Economics (LSE) (linking to long term care financing 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 specific 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 difficulties 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 reflect 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-specific 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 benefits (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 modeling
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 specific 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% confidence intervals for the difference in the proportion of pre-specified 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 first order interactions. We will also explore the baseline "predictors" of costs measured for the first 13 weeks and the full 39 weeks post randomisation.

11.4. Changes to the Analysis Plan

Any significant 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. Confidentiality

The confidentiality of participant and carer identification details will be protected according to the Data Protection Act. Participants will be identified 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 identification and contact purposes. The CRFs will be regarded as confidential, and kept in locked filing 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 (ie 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 confidentiality.

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 indefinitely 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 filed in the Recruiting PI site file 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-defined 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 significant 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 identified 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 (eg 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 atCatalent.

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 01st 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) Clarification on the roles & responsibilities of Referring Investigators and Recruiting Investigators (section 1.2.4.)

6) Confirmation 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) Pfizer UK Ltd. pharmacovigilence 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 reflect the addition of week 4 and week 8 data collection points as agreed in the original ethics approval (sections 7.5.1, 8.3, 10.2.2 10.2.3)
11) Protocol amended to reflect alterations to the system of adverse event data collection (sections 9.1.1. – 9.1.8.)
12) Addition of information regarding 24 hour emergency unblinding service via Guy's Toxicology Unit (section 8.12.3)
13) 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.)
14) 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 Birmingham PI (1.2.4)
3) Change of role title for health economist Renee Romeo (1.2.10)
4) Change of name of drug supplier (1.2.12)
5) Changes in membership of Trial Steering Committee (1.3.1)
6) Addition of Clare Rutterford as statistician (1.2.9)
7) Week 4 and 8 assessments indexed on treatment start date rather than randomisation (7.5.1, 8.3, 10.2.2, 10.2.3)
8) 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. ANCILIARY 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 eCRFs (Electronic Case Report Forms)

A3.1	Additional Diagnostic Questions
A3.2	Adverse Events Aide Memoire
A3.3	Bristol Activities of Daily Living (BADL)
A3.4	Carer Demographic Information
A3.5	Carer Global Impression (CGI)
A3.6	Carer Registration Form
A3.7	Client Service Receipt Inventory (CSRI)
A3.8	Cornell Scale for Depression in Dementia (CSDD)
A3.9	Concomitant Medications / Drugs
A3.10	Concomitant Treatments / Non-Drugs
A3.11	DEMQOL
A3.12	DEMQOL – Proxy
A3.13	End of Trial (Routine) Unblinding Request Form
A3.14	EuroQol – Carer
A3.15	EuroQol – Participant
A3.16	Exclusion from Randomisation
A3.17	General Health Questionnaire (GHQ-12)
A3.18	Medical History
A3.19	Medication Guess
A3.20	Medication Preference
A3.21	Neuropsychiatric Inventory (NPI)
A3.22	Non-Serious Adverse Events Log (NS AE Log)
A3.23	Participant Demographic Information
A3.24	Participant Registration Form
A3.25	Pill Count
A3.26	Randomisation Request Form
A3.27	Serious Adverse Event Report Form (SAE Form)
A3.28	Short Form 12 (SF-12 Version 2)
A3.29	Standardised Mini-Mental State Examination (SMMSE)
A3.30	Trial Medication Log
A3.31	Withdrawal Form
A3.32	Zarit Caregiver Burden Inventory

A3.1 Additional Diagnostic Questions

Most of the questions required to make a diagnosis of depression based on DSM-IV (TR) criteria for a Major Depressive Episode and/or Olin (2002)'s Diagnostic Criteria for Depression of Alzheimer's Disease have already been asked as part of the CSDD, NPI and Medical History.

I would like to ask you some additional questions about (*participant*)'s mood so that we can establish whether he/she meets formal research diagnostic criteria for depression.

1.	How long have his/her current symptoms of depression lasted?	Less than one month	1
		Between one and two months	2
		Between two and six months	3
		Over six months	4
2.	Have his/her current symptoms of depression lasted for a period of at least two weeks at any time since the symptoms began?	No	0
		Yes	1
		Don't know	88
	Comments:		
3.	Have his/her current symptoms of depression been present solely while he/she has been very drowsy?	No	0
		Yes	1
		Don't know	88
4.	Has he/she been bereaved during the last year? (i.e. lost a loved one)	No	0
		Yes	1
		Don't know	88
	If so, what was the effect of the bereavement on the participant?		
5.	How many times has he/she been depressed before?	None, this is the first time	0
		Once before	1
		Twice before	2
		Many times before	3
		Don't know	88
6.	Does he/she have a reduced ability to think, concentrate or make decisions nearly every day?	No	0
		Yes	1
		Don't know	88

I would now like to ask you some additional questions about (*participant*)'s cognitive state so that we can establish the extent to which the memory problems may be attributed to vascular changes.

7.	Did the memory problems symptoms start gradually or suddenly?	Gradually	0
		Suddenly	1
		Don't know	88
8.	Did the memory problems symptoms get worse steadily over time or in stages?	Steadily over time	0
		In stages	1
		Don't know	88
9.	Are the memory problems symptoms much the same from day-to-day or are some days much worse or better	Much the same from day-to-	0
		Some days much worse/better	1
		Don't know	88
10.	Are the memory problems symptoms worse in the evenings?	No	0
		Yes	1
		Don't know	88
11.	Are his/her moods very changeable? Does he/she become tearful without any reason?	No	0
		Yes	1
		Don't know	88
12.	In terms of (*participant*)'s personality, has their character changed or do they seem to be much the same person?	Character changed	0
		Much the same	1
		Don't know	88
13.	Is (*participant*) weaker on one side compared to the other?	No	0
		Yes	1
		Don't know	88

NOTE: Questions 7 to 13 would only be asked during the baseline assessment visit.

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 significantly 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
- Fits (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 significant disability or incapacity

- Deliberate self-harm

A3.3 Bristol Activities of Daily Living Scale

This questionnaire is designed to reveal the everyday ability of people who have memory difficulties of one form or another. For each activity, statements a-e refer to a different level of activity. Thinking of the **last two weeks**, circle the response that represents (*participant*)'s ability. Only one response should be ticked for each activity. *(If in doubt about which box to tick, choose the level of ability that represents their average performance over the last two weeks)*

1. FOOD

a	Selects and prepares food as required	0
b	Able to prepare food if ingredients set out	1
c	Can prepare food if prompted step by step	2
d	Unable to prepare food even with prompting and supervision	3
e	Not applicable	77

2. EATING

a	Eats appropriately using correct cutlery	0
b	Eats appropriately if food made manageable and / or uses spoon	1
c	Uses fingers to eat food	2
d	Needs to be fed	3
e	Not applicable	77

3. DRINK

a	Selects and prepares drinks as required	0
b	Can prepare drinks if ingredients left available	1
c	Can prepare drinks if prompted step by step	2
d	Unable to make a drink even with prompting and supervision	3
e	Not applicable	77

4. DRINKING

a	Drinks appropriately	0
b	Drinks appropriately with aids, beaker / straw, etc	1
c	Does not drink appropriately even with aids but attempts to	2
d	Has to have drinks administered (fed)	3
e	Not applicable	77

5. DRESSING

a	Selects appropriate clothing and dresses self	0
b	Puts clothes on in wrong order and / or back to front and / or dirty clothing	1
c	Unable to dress self but moves limbs to assist	2
d	Unable to assist and requires total dressing	3
e	Not applicable	77

6. HYGIENE

a	Washes regularly and independently	0
b	Can wash self if given soap, flannel, towel, etc	1
c	Can wash self if prompted and supervised	2
d	Unable to wash self and needs full assistance	3
e	Not applicable	77

7. TEETH

a	Cleans own teeth / dentures regularly and independently	0
b	Cleans teeth / dentures if given appropriate items	1
c	Requires some assistance, toothpaste on brush, brush to mouth, etc	2
d	Full assistance given	3
e	Not applicable	77

8. BATH / SHOWER

a	Bathes regularly and independently	0
b	Needs bath to be drawn / shower turned on but washes independently	1
c	Needs supervision and prompting to wash	2
d	Totally dependent, needs full assistance	3
e	Not applicable	77

9. TOILET / COMMODE

a	Uses toilet appropriately when required	0
b	Needs to be taken to the toilet and given assistance	1
c	Incontinent of urine or faeces	2
d	Incontinent of urine and faeces	3
e	Not applicable	77

10. TRANSFERS

a	Can get in / out of chair unaided	0
b	Can get into a chair but needs help to get out	1
c	Needs help getting in and out of a chair	2
d	Totally dependent on being put into and lifted from chair	3
e	Not applicable	77

11. MOBILITY

a	Walks independently	0
b	Walks with assistance, e.g. furniture, arm for support	1
c	Uses aids to mobilise, e.g. frame, sticks, etc	2
d	Unable to walk	3
e	Not applicable	77

12. ORIENTATION – TIME

a	Fully orientated to time / day / date etc	0
b	Unaware of time / day etc but seems unconcerned	1
c	Repeatedly asks the time / day / date	2
d	Mixes up night and day	3
e	Not applicable	77

13. ORIENTATION – SPACE

a	Fully orientated to surroundings	0
b	Orientated to familiar surroundings only	1
c	Gets lost in home, needs reminding where bathroom is, etc	2
d	Does not recognise home as own and attempts to leave	3
e	Not applicable	77

14. COMMUNICATION

a	Able to hold appropriate conversation	0
b	Shows understanding and attempts to respond verbally with gestures	1
c	Can make self understood but difficulty understanding others	2
d	Does not respond to or communicate with others	3
e	Not applicable	77

15. TELEPHONE

a	Uses telephone appropriately, including obtaining correct number	0
b	Uses telephone if number given verbally / visually or predialled	1
c	Answers telephone but does not make calls	2
d	Unable / unwilling to use telephone at all	3
e	Not applicable	77

16. HOUSEWORK / GARDENING

a	Able to do housework / gardening to previous standard	0
b	Able to do housework / gardening but not to previous standard	1
c	Limited participation even with a lot of supervision	2
d	Unwilling / unable to participate in previous activities	3
e	Not applicable	77

17. SHOPPING

a	Shops to previous standard	0
b	Only able to shop for 1 or 2 items with or without a list	1
c	Unable to shop alone, but participates when accompanied	2
d	Unable to participate in shopping even when accompanied	3
e	Not applicable	77

18. FINANCES

a	Responsible for finances at previous level	0
b	Unable to write cheque but can sign name and recognises money values	1
c	Can sign name but unable to recognise money values	2
d	Unable to sign name or recognise money values	3
e	Not applicable	77

19. GAMES / HOBBIES

a	Participates in pastimes / activities to previous standard	0
b	Participates but needs instruction / supervision	1
c	Reluctant to join in, very slow, needs coaxing	2
d	No longer able or willing to join in	3
e	Not applicable	77

20. TRANSPORT

a	Able to drive, cycle or use public transport independently	0
b	Unable to drive but uses public transport or bike, etc	1
c	Unable to use public transport alone	2
d	Unable / unwilling to use transport even when accompanied	3
e	Not applicable	77

A3.4 Carer Demographic Information

1.	Date of birth:	Day Month Year	
2.	Gender:	Male	0
		Female	1
3.	Ethnicity	White	1
		Mixed	2
		Asian	3
		Black	4
		Chinese	5
		Other	6
4.	Marital status	Single (never married)	1
		Married (first marriage)	2
		Re-married	3
		Separated (still legally married)	4
		Divorced	5
		Widowed	6
		Not known	88
5.	Relationship to participant	Spouse	1
		Son / Daughter	2
		Son-in-law / Daughter-in-law	3
		Sibling	4
		Other relative	5
		Friend / Neighbour	6
		Paid Carer	7
		Other:	8

A3.5 Carer Global Impression

Overall, how much do you feel (*participant*)'s mood has changed since the start of the study?

Please circle the response that most closely corresponds to this.

Very much better	1
Much better	2
A little better	3
No change	4
A little worse	5
Much worse	6
Very much worse	7

A3.6 Carer Registration #1

As soon as possible after a new referral letter is received from a known Referring Investigator the following should be completed and entered onto MACRO.

1.	Relationship to participant	Spouse	1
		Son / Daughter	2
		Son-in-law / Daughter-in-law	3
		Sibling	4
		Other relative	5
		Friend / Neighbour	6
		Paid Carer	7
		Other:	8

YOU NEED TO GENERATE CARER IDENTIFICATION NUMBER (CIN)			
2.	Centre:	Number	Name
		_____	_____
3.	CIN:	**C** ☐☐ ☐☐☐ **A** Centre Number Same as PIN First Carer	
4.	Carer initials: *(As appear throughout trial)*	☐☐☐☐	
5.	Date of registration: (*Date entered onto MACRO*)	☐☐ ☐☐ ☐☐☐☐ Day Month Year	
6.	Research worker initials: *(As appear throughout trial)*	☐☐☐☐	

A3.7 Client Service Receipt Inventory (CSRI)

Part One: Participant Schedule

A. PARTICIPANT ACCOMODATION

1.	Usual place of residence during the last three/six months?	Owner occupied house/flat	1
		Privately rented house/flat	2
		House/flat rented from housing associated/local authority	3
	(Also complete Question #3)	Sheltered housing/warden control	4
		Residential home	5
		Nursing home	6
		Acute psychiatric ward	7
		Rehabilitation ward	8
		General medical ward	9
		Other: _____	10

2.	Has (*participant*) lived anywhere else during the last three/six months?	No	0
		Yes	1

If yes, Accommodation type:

1 = Owner occupied house/flat
2 = Privately rented house/flat
3 = House/flat rented from housing associated/local authority
4 = Sheltered housing/warden control
5 = Residential home
6 = Nursing home
7 = Other: _____

Code	***Approximate number of nights spent***

Only complete if Question #1 is coded 4 to 10			
3a.	Organisation managing facility	Local authority social services	1
		NHS	2
		Private (for-profit)	3
		Voluntary (non-profit)	4
		Other: _____	5
3b.	(Participant)'s total contribution to weekly charge for facility	£ ☐☐☐☐.☐☐	
3c.	Who contributes towards placement *(circle all that apply)*	DSS	1
		NHS	2
		Local authority	3
		Voluntary organisation	4
		Participant	5
		Participant's family	6
		Insurance policy	7
		Other: _____	8

B. PARTICIPANT SERVICE RECEIPT

4a. **Hospital services** used over the last three/six months

(include normal accommodation given in Question #1)

Service	Name of ward / clinic / hospital / centre	Reason for using service *(eg nature of illness, regular respite arrangement)*	Unit of measurement	Total number of units received
Day hospital			Day attendance	
Accident & Emergency			Attendance	
Outpatient services			Appointment	
Psychiatric inpatient ward			Inpatient day	
Other inpatient ward			Inpatient day	
Other: _____			_____	

4b. **Day services** used over the last three/six months

(do not include any day services provided by the accommodation facility in which the participant is currently living)

Service		Name of centre / service	Unit of measurement	Number of units received per week
Day care:	local authority social services department		Days	
Day care:	voluntary organisation		Days	
Day care:	NHS *(not hospital)*		Days	
Lunch club			Visits	
Social club			Visits	
Other: _____			_____	

4c.	**Community – based services** used over the last three/six months *(do not include services provided by people employed directly by the accommodation facility in which the participant is currently living)*									
	Service *(do not include outpatient services)*	**Type of Visit**		**Provider Agency**				**Total number of contacts** *(Round to nearest whole number)*		**Average duration of each contact (minutes)** *(Round to nearest whole number)*
		Domiciliary	Office	Health service	Local authority	Voluntary organisation	Private Organisation			
i)	Geriatrician	0	1	1	2	3	4			
ii)	General practitioner	0	1	1	2	3	4			[redacted]
iii)	Practice nurse (GP clinic)	0	1	1	2	3	4			
iv)	District nurse	0	1	1	2	3	4			
v)	Health visitor	0	1	1	2	3	4			
vi)	CPN/CMHN	0	1	1	2	3	4			
vii)	Cardiac nurse	0	1	1	2	3	4			
viii)	Incontinence nurse	0	1	1	2	3	4			
ix)	Occupational therapist	0	1	1	2	3	4			
x)	Community psychiatrist	0	1	1	2	3	4			
xi)	Psychologist	0	1	1	2	3	4			
xii)	Care manager	0	1	1	2	3	4			
xiii)	Social worker	0	1	1	2	3	4			
xiv)	Home care worker	0	1	1	2	3	4			
xv)	Carer attendant /	0	1	1	2	3	4			
xvi)	Chiropodist	0	1	1	2	3	4			
xvii)	Sitting scheme	0	1	1	2	3	4			
xviii)	Self-help group	0	1	1	2	3	4			
xix)	Meals on wheels	0	1	1	2	3	4			[redacted]
xx)	Laundry service	0	1	1	2	3	4			[redacted]
xxi)	Dentist	0	1	1	2	3	4			
xxii)	Optician	0	1	1	2	3	4			
xxiii)	Counsellor	0	1	1	2	3	4			
xxiv)	Physiotherapist	0	1	1	2	3	4			
xxv)	Other doctor	0	1	1	2	3	4			
Other community – based services:										
xxvi)	_____	0	1	1	2	3	4			
xxvii)	_____	0	1	1	2	3	4			
xxiii)	_____	0	1	1	2	3	4			
xxix)	_____	0	1	1	2	3	4			

Client Service Receipt Inventory (CSRI)

Part Two: Carer Schedule

All the questions below relate only to the last three/six months.

C. CARER's EMPLOYMENT

5.	Regular employment status *(Circle one only)*	Paid employment	1
		Retired	2
		Housewife / husband	3
		Unemployed / Student	4

6.	Cut down on paid work in order to provide care for (*participant*).	No	0
	(Also complete Question #7 and #8)	Reduced hours	1
		Given up work	2
	By how many hours per week? (*Only if reduced hours or given up work*)	☐☐	

Only complete if in "Paid Employment"			
7.	Most recent occupation type *(State main type if more than one)*	Manager / administrator	1
		Professional	2
		Associate professional	3
		Clerical worker / Secretary	4
		Skilled labourer	5
		Services / Sales	6
		Factory worker	7
		Other: _____	8

Only complete if in "Paid Employment" or "Retired"		
8.	Total number of paid hours per week *(Round to the nearest whole number)*	☐☐

D. CARER's ACCOMODATION

9.	Usual place of residence during the last three months?	Owner occupied house/flat	1
		Privately rented house/flat	2
		House/flat rented from housing associated/local authority	3
		Sheltered housing/warden control	4
		Residential home	5
		Nursing home	6
		Other: _____	7

E. TIME SPENT WITH PARTICIPANT BY PRINCIPAL CARER *(i.e. Informant)*

10a.	Normally live with the participant	No	0
		Yes	1
10b.	***If No:*** How many hours are spent giving care to the participant each week? *(Round to the nearest whole number)*	☐☐	
10c.	***If Yes:*** On a typical day, how much of the time can you leave the participant at home alone?	Less than 25% of the time	1
		Between 25% and 49% of the time	2
		Between 50% and 74% of the time	3
		Between 75% and 100% of the time	4

F. TIME SPENT WITH PARTICIPANT BY OTHER INFORMAL CARERS

11a.	Do any other people (eg friends and relatives) regularly provide help for the participant?	No	0
		Yes	1
11b.	***If Yes:*** In an average/typical week, what is the total number of hours these people spend caring for the participant? *(Round to the nearest whole number)*	☐☐	

12a	Have any friends or relatives taken time off paid work (over the past three months) to help with care giving?	No	0
		Yes	1
12b.	***If Yes:*** Estimate the total number of days taken off work? *(Round to the nearest whole number)*	☐☐	

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

Instructions: 0=absent; 1=mild or intermittent, 2=severe, 88=unable to evaluate

	PARTICIPANT				CARER				RW RATING			
A. MOOD RELATED SIGNS												
1. Anxiety Anxious expression, ruminations, worrying	0	1	2	88	0	1	2	88	0	1	2	88
2. Sadness Sad expression, sad voice, tearfulness	0	1	2	88	0	1	2	88	0	1	2	88
3. Lack of reactivity to pleasant events	0	1	2	88	0	1	2	88	0	1	2	88
4. Irritability Easily annoyed, short tempered	0	1	2	88	0	1	2	88	0	1	2	88
B. BEHAVIOURAL DISTURBANCE												
5. Agitation Restlessness, handwringing, hairpulling	0	1	2	88	0	1	2	88	0	1	2	88
6. Retardation Slow movements, slow speech, slow reactions	0	1	2	88	0	1	2	88	0	1	2	88
7. Multiple physical complaints *(score 0 if gastro-intestinal symptoms only)*	0	1	2	88	0	1	2	88	0	1	2	88
8. Loss of interest less involved in usual activities *(score only if change occurred acutely i.e. in less than 1 month)*	0	1	2	88	0	1	2	88	0	1	2	88
C. PHYSICAL SIGNS												
9. Appetite loss Eating less than usual	0	1	2	88	0	1	2	88	0	1	2	88
10. Weight loss *(score 2 if greater than 5 Ibs in 1 month)*	0	1	2	88	0	1	2	88	0	1	2	88
11. Lack of energy Fatigues easily, unable to sustain activities *(score only if change occurred acutely i.e. in less than 1 month)*	0	1	2	88	0	1	2	88	0	1	2	88
D. CYCLIC FUNCTIONS												
12. Diurnal variation of mood Symptoms worse in the morning	0	1	2	88	0	1	2	88	0	1	2	88
13. Difficulty falling asleep Later than usual for this individual	0	1	2	88	0	1	2	88	0	1	2	88
14. Multiple awakenings during sleep	0	1	2	88	0	1	2	88	0	1	2	88
15. Early morning awakenings Early than usual for this individual	0	1	2	88	0	1	2	88	0	1	2	88
E. IDEATIONAL DISTURBANCE												
16. Suicide Feels life is not worth living, has suicidal wishes, or make suicide attempt	0	1	2	88	0	1	2	88	0	1	2	88
17. Poor self-esteem Self-blame, poor self depreciation, feelings of failure	0	1	2	88	0	1	2	88	0	1	2	88

18. Pessimism Anticipation of the worst	0	1	2	88	0	1	2	88	0	1	2	88
19. Mood congruent delusions Delusions of poverty, illness, or loss	0	1	2	88	0	1	2	88	0	1	2	88

A3.9 CONCOMITANT MEDICATIONS / DRUGS (PAGE ONE)

This is to be completed at each visit. Prompt questions include: Has (*participant*) seen a doctor since my last visit? Has (*participant*) stopped any of the following medications? Has (*participant*) changed the dose of any of the following medications? Has (*participant*) started any new medications?

Name of Medication (Brand or Generic)	**Date Started (dd/mm/yyyy)**	**Date Stopped (dd/mm/yyyy)**	**Total Daily Dose**	**Units**	**Indication /Reason**	**Staff Initials & Date**	**Continuing**

A3.10 CONCOMITANT TREATMENTS/NON DRUGS

This is to be completed at each visit. **Only non-medicinal therapies received <u>for the participant's depression</u> should be listed here**. Prompt questions include: Has (*participant*) seen a doctor since my last visit? Has (*participant*) stopped any of the following treatments? Has (*participant*) changed the frequency of any of the following treatments? Has (*participant*) started any new treatments? **Please note medications are listed on a separate form**.

Name of Therapy	Date Started (dd/mm/yyyy)	Date Stopped (dd/mm/yyyy)	Frequency	Indication /Reason	Staff Initials & Date	Continuing

A3.11 DEMQOL

Instructions: *Read each of the following questions verbatim and show the respondent the response card.*

I would like to ask you about your life. There are no right or wrong answers. Just give the answer that best describes how you have felt in the last week. Don't worry if some questions appear not to apply to you. We have to ask the same questions of everybody.

Before we start we'll do a practice question: that's one that doesn't count. *(Show the response card and ask respondent to say or point to the answer).* In the last week, how much have you enjoyed watching television?

a lot quite a bit a little not at all

Follow up with a prompt question: Why is that? *or* Tell me a little more about that.

For all of the questions I'm going to ask you, I want you to think about the last week.

First I'm going to ask about <u>your feelings</u>.

In the last week, have you felt…	A lot	Quite a bit	A little	Not at all
1. cheerful?	1	2	3	4
2. worried or anxious?	1	2	3	4
3. that you are enjoying life?	1	2	3	4
4. frustrated?	1	2	3	4
5. confident?	1	2	3	4
6. full of energy?	1	2	3	4
7. sad?	1	2	3	4
8. lonely?	1	2	3	4
9. distressed?	1	2	3	4
10. lively?	1	2	3	4
11. irritable?	1	2	3	4
12. fed-up?	1	2	3	4
13. that there are things that you wanted to do but couldn't?	1	2	3	4

Next, I'm going to ask about <u>your memory.</u>

In the last week, how worried have you been about…	A lot	Quite a bit	A little	Not at all
14. forgetting things that happened recently?	1	2	3	4
15. forgetting who people are?	1	2	3	4
16. forgetting what day it is?	1	2	3	4
17. your thoughts being muddled?	1	2	3	4
18. difficulty making decisions?	1	2	3	4
19. poor concentration?	1	2	3	4

Next, I'm going to ask about <u>your everyday life.</u>

In the last week, how worried have you been about…	A lot	Quite a bit	A little	Not at all
20. not having enough company?	1	2	3	4
21. how you get on with people close to you?	1	2	3	4
22. getting the affection that you want?	1	2	3	4
23. people not listening to you?	1	2	3	4
24. making yourself understood?	1	2	3	4
25. getting help when you need it?	1	2	3	4
26. getting to the toilet in time?	1	2	3	4
27. how you feel in yourself?	1	2	3	4
28. your health overall?	1	2	3	4

We've already talked about lots of things: your feelings, memory and everyday life.

Thinking about all of these things in the last week, how would you rate….	Very good	Good	Fair	Poor
29. your quality of life overall?	1	2	3	4

A3.12 DEMQOL Proxy

Instructions: *Read each of the following questions verbatim and show the respondent the response card.*

I would like to ask you about *(participant)'s* life, as you are the person who knows him / her best. There are no right or wrong answers. Just give the answer that best describes how *(participant)* has felt in the last week. If possible try and give the answer that you think *(participant)* would give. Don't worry if some questions appear not to apply to *(participant)*. We have to ask the same questions of everybody.

Before we start we'll do a practice question; that's one that doesn't count. *(Show the response card and ask respondent to say or point to the answer)* In the last week, how much has *(participant)* enjoyed watching television?

a lot quite a bit a little not at all

Follow up with a prompt question: Why is that? *or* Tell me a little more about that.

For all of the questions I'm going to ask you, I want you to think about the last week.

First I'm going to ask about *(participant)'s* feelings.

In the last week, would you say that (*participant*) **has felt...**	A lot	Quite a bit	A little	Not at all
1. cheerful?	1	2	3	4
2. worried or anxious?	1	2	3	4
3. frustrated?	1	2	3	4
4. full of energy?	1	2	3	4
5. sad?	1	2	3	4
6. content?	1	2	3	4
7. distressed?	1	2	3	4
8. lively?	1	2	3	4
9. irritable?	1	2	3	4
10. fed-up?	1	2	3	4
11. that he / she has things to look forward to?	1	2	3	4

Next, I'm going to ask about *(participant)'s* memory.

In the last week, how worried would you say that (*participant*) **has been about…**	A lot	Quite a bit	A little	Not at all
12. his /her memory in general?	1	2	3	4
13. forgetting things that happened a long time ago?	1	2	3	4
14. forgetting things that happened recently?	1	2	3	4
15. forgetting people's names?	1	2	3	4
16. forgetting where he / she is?	1	2	3	4
17. forgetting what day it is?	1	2	3	4
18. his / her thoughts being muddled?	1	2	3	4
19. difficulty making decisions?	1	2	3	4
20. making him / herself understood?	1	2	3	4

Now, I'm going to ask about *(participant)'s* everyday life.

In the last week, how worried would you say (*participant*) **has been about…**	A lot	Quite a bit	A little	Not at all
21. keeping him / herself clean (e.g. washing and bathing)?	1	2	3	4
22. keeping him / herself looking nice?	1	2	3	4
23. getting what he / she wants from the shops?	1	2	3	4
24. using money to pay for things?	1	2	3	4
25. looking after his / her finances?	1	2	3	4
26. things taking longer than they used to?	1	2	3	4
27. getting in touch with people?	1	2	3	4
28. not having enough company?	1	2	3	4
29. not being able to help other people?	1	2	3	4
30. not playing a useful part in things?	1	2	3	4
31. his / her physical health?	1	2	3	4

We've already talked about lots of things: *(participant)'s* feelings, memory and everyday life.

Thinking about all of these things in the last week, how would you say *(participant)* would rate….	Very good	Good	Fair	Poor
32. his / her quality of life overall?	1	2	3	4

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	End of Trial	0
		Treatment Discontinuation / Trial Dropout	1
4a	Data Entry Complete	No	0
		Yes	1
4b	Data Cleaning Complete	No	0
		Yes	1
5	Notes		

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

8	Further Notes

A3.14 EuroQol (EQ-5D) – Carer

By circling one of the responses in each group below, please indicate which statements best describe (*participant*)'s health today. If possible try and give the answer that you think *(participant)* would give.

1. Mobility	
He/she has no problems in walking about	1
He/she has some problems in walking about	2
He/she is confined to bed	3

2. Self-Care	
He/she has no problems with self-care	1
He/she has some problems washing or dressing him/herself	2
He/she is unable to wash or dress him/herself	3

3. Usual Activities *(e.g. work, study, housework, family or leisure activities)*	
He/she has no problems with performing his/her usual activities	1
He/she has some problems with performing his/her usual activities	2
He/she is unable to perform his/her usual activities	3

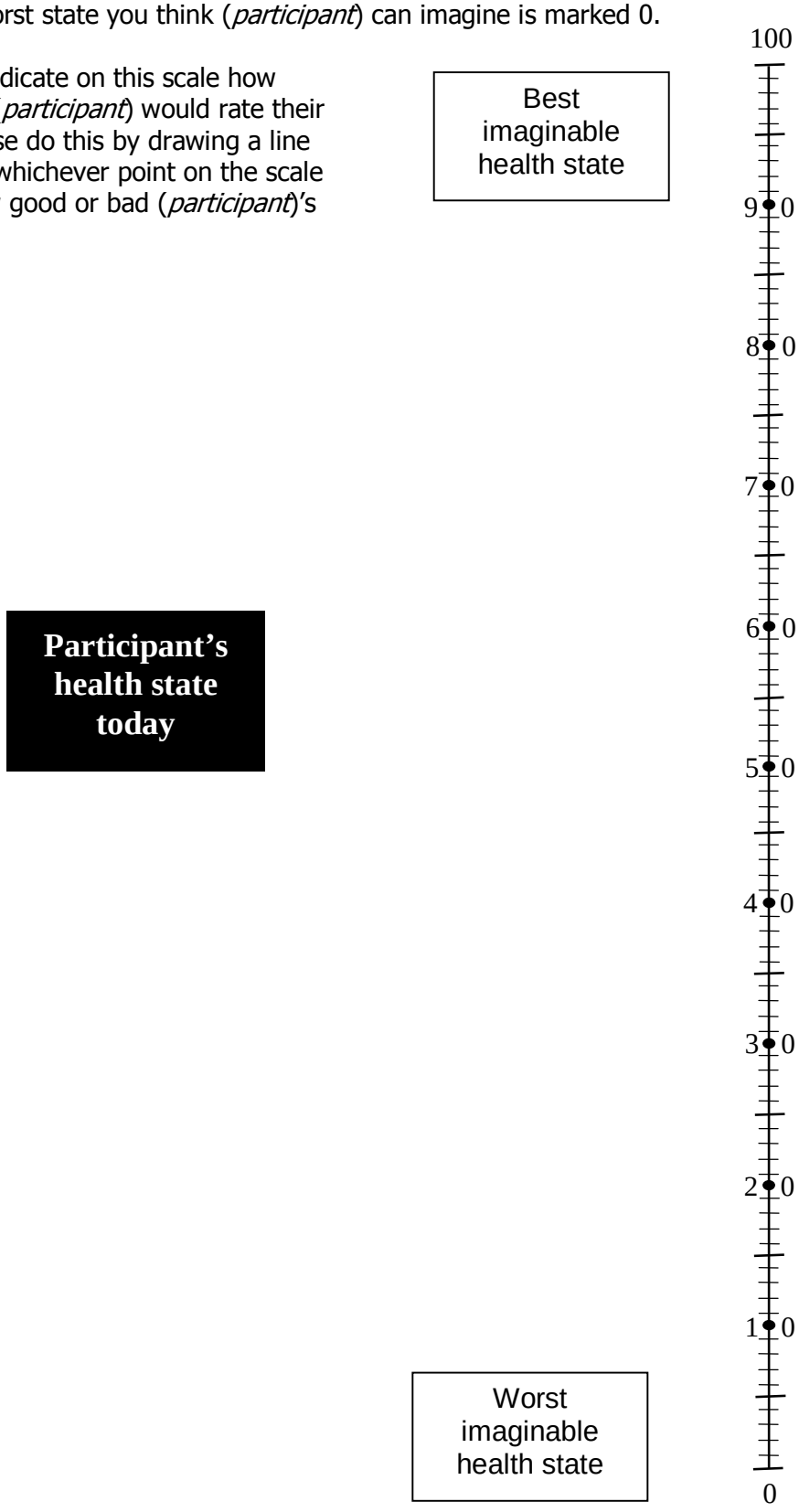
4. Pain/Discomfort	
He/she has no pain or discomfort	1
He/she has moderate pain or discomfort	2
He/she has extreme pain or discomfort	3

5. Anxiety/Depression	
He/she is not anxious or depressed	1
He/she is moderately anxious or depressed	2
He/she is extremely anxious or depressed	3

6. Compared with (*participant*)'s general level of health over the past 12 months, his/her health today is:	
Better	1
Much the same	2
Worse	3

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you think (*participant*) can imagine is marked 100 and the worst state you think (*participant*) can imagine is marked 0.

We would like you to indicate on this scale how good or bad you think (*participant*) would rate their own health today. Please do this by drawing a line from the box below to whichever point on the scale you think indicates how good or bad (*participant*)'s health state is today**.**



A3.15 EuroQol (EQ-5D) – Participant

By circling one of the responses in each group below, please indicate which statements best describe your own health today.

1. Mobility	
I have no problems in walking about	1
I have some problems in walking about	2
I am confined to bed	3

2. Self-Care	
I have no problems with self-care	1
I have some problems washing or dressing myself	2
I am unable to wash or dress myself	3

3. Usual Activities *(e.g. work, study, housework, family or leisure activities)*	
I have no problems with performing my usual activities	1
I have some problems with performing my usual activities	2
I am unable to perform my usual activities	3

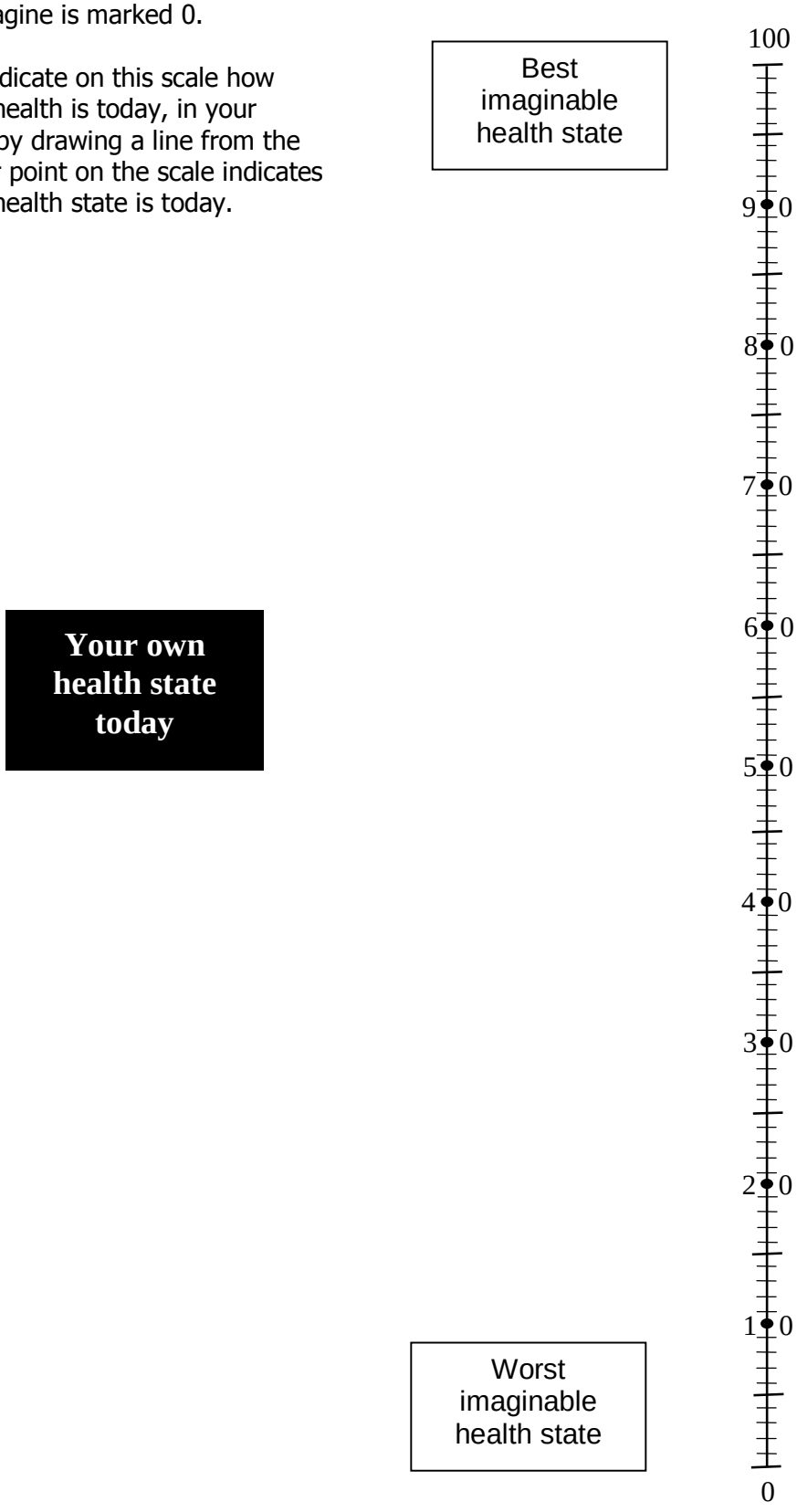
4. Pain/Discomfort	
I have no pain or discomfort	1
I have moderate pain or discomfort	2
I have extreme pain or discomfort	3

5. Anxiety/Depression	
I am not anxious or depressed	1
I am moderately anxious or depressed	2
I am extremely anxious or depressed	3

6. Compared with my general level of health over the past 12 months, my health today is:	
Better	1
Much the same	2
Worse	3

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.



A3.16 Exclusions from Randomisation

1.	Point of exclusion:	Prior to first contact by research worker with participant or carer	1
		During telephone contact with participant or carer prior to baseline assessment	2
		During baseline assessment	3
		After completion of baseline assessment but prior to randomisation	4

2.	Ineligible for the trial	No	0
		Yes	1
		Unknown	88
	If Yes:		***(circle all that apply)***
a.	No clinical diagnosis of mild to moderate probable or possible Alzheimer's Disease		1
b.	No co-existing depressive illness likely to need treatment with antidepressants		2
c.	Depression less than four weeks duration at referral		3
d.	Participant current taking antidepressants		4
e.	Participant's dementia is too severe to complete the baseline CSDD		5
f.	Case is considered too critical to be randomised (e.g. because of suicide risk)		6
g.	Participant displays absolute contraindications to one or more of the trial treatments		7
h.	Participant is entered on another trial		8
i.	There is no identifiable family carer or other informant to give collateral information		9
j	Participant has a baseline CSDD score of 0 to 7 inclusive		10

3.	Consent not given for the trial	No	0
		Yes	1
		Unknown	88
	If Yes:		***(circle all that apply)***
a.	Participant declined to give consent for the trial		1
b.	Carer declined to give consent for the trial on behalf of the participant		2
c.	Carer declined to give consent to provide collateral information		3
d.	Referring Investigator withdrew their consent for the participant to enter the trial		4
e.	Other: _____		5

A3.17 General Health Questionnaire (GHQ12)

We would like to know if you have had any medical complaints, and how your health has been in general, over the **past few weeks**. Please answer ALL the questions by circling the answer that you think most nearly applies to you. Remember that we want to know about present and recent complaints, not those you have had in the past. It is important that you answer ALL the questions.

HAVE YOU RECENTLY:

1. Been able to concentrate on what ever you are doing?	Better than usual 0	Same as usual 1	Less than usual 2	Much less than usual 3
2. Lost much sleep over worry?	Not at all 0	No more than usual 1	Rather more than usual 2	Much more than usual 3
3. Felt that you are playing a useful part in things?	More so than usual 0	Same as usual 1	Less useful than usual 2	Much less useful 3
4. Felt capable of making decisions about things?	More so than usual 0	Same as usual 1	Less so than usual 2	Much less capable 3
5. Felt constantly under strain?	Not at all 0	No more than usual 1	Rather more than usual 2	Much more than usual 3
6. Felt you couldn't overcome your difficulties?	Not at all 0	No more than usual 1	Rather more than usual 2	Much more than usual 3
7. Been able to enjoy your normal, day to day activities?	More so than usual 0	Same as usual 1	Less so than usual 2	Much less than usual 3
8. Been able to face up to your problems?	More so than usual 0	Same as usual 1	Less able than usual 2	Much less than usual 3
9. Been feeling unhappy and depressed?	Not at all 0	No more than usual 1	Rather more than usual 2	Much more than usual 3
10. Been losing confidence in yourself?	Not at all 0	No more than usual 1	Rather more than usual 2	Much more than usual 3
11. Been thinking of yourself as a worthless person?	Not at all 0	No more than usual 1	Rather more than usual 2	Much more than usual 3
12. Been feeling reasonably happy, all things considered?	More so than usual 0	About same as usual 1	Less so than usual 2	Much less than usual 3

A3.18 MEDICAL HISTORY (PAGE ONE)

(Excluding depression and dementia related symptoms)

Is there any relevant significant medical history in the following systems?

Code	System	*Yes	No	Code	System	*Yes	No
1	Cardiovascular			9	Neoplasia		
2	Respiratory			10	Neurological		
3	Hepatic			11	Psychological		
4	Gastro-intestinal			12	Immunological		
5	Genito-urinary			13	Dermatological		
6	Endocrine			14	Allergies		
7	Haematological			15	Eyes, ear, nose, throat		
8	Musculo-skeletal			00	Other		

*If ***YES*** for any of the above, enter the code for each condition in the boxes below, giving further details (including dates) and state if the condition is currently or potentially active. If giving details of surgery please specify the underlying cause. Use a separate line for each condition.

Specifically asked about pain (inc. angina), hypertension, current thyroid problems, cancer, strokes, thickening of arteries, breathing difficulties, slurred voice, drooping of the face, being weaker on one side than the other, and fits (inc. epilepsy)		Currently Active? *(Tick yes if medication ongoing)*

Code	Medical Condition	Dates	Yes	No

A3.19 Medication Guess

Carer Medication Guess

In order for us to plan future studies, it would help us very much to know how successful we were at making sure that you couldn't tell which trial medication (*participant*) was randomly prescribed for the trial.

Please guess even if you don't know.

I strongly think he/she was prescribed an antidepressant	I think he/she was prescribed an antidepressant	I think he/she was prescribed placebo	I strongly think he/she was prescribed placebo
1	**2**	**3**	**4**

Research Worker Medication Guess

In order for us to plan future studies, it would help us very much to know how successful we were at making sure that you couldn't tell which trial medication this participant was randomly prescribed for the trial.

Please guess even if you don't know.

I strongly think he/she was prescribed an antidepressant	I think he/she was prescribed an antidepressant	I think he/she was prescribed placebo	I strongly think he/she was prescribed placebo
1	**2**	**3**	**4**

A3.20 Medication Preference

As you are aware, (*participant*) has been given a choice as to whether to join this trial or to maintain clinical care with his/her doctor outside of this trial. Their doctor can prescribe the medications we are using in this trial if that is what they wish.

However, noone really knows which medication will work best for (*participant*) or whether indeed he/she may be better off without medication. We very much appreciate (*participant*) joining this trial to help us find out which medication does work for people with dementia.

With this in mind, we would be interested to know how you feel about the person you are caring for being given the medications in this trial.

Please note that in this trial people are allocated a treatment (i.e. placebo, mirtazapine or sertraline) randomly by a computer program set up by an independent group. The information you are providing us with today is not released to this group and so your answer cannot in any way affect the type of medication given in the trial.

Question 1: Antidepressant versus nothing

I strongly prefer him/her to have an antidepressant	I prefer him/her to have an antidepressant	I do not mind	I prefer him/her not to have an antidepressant	I strongly prefer him/her not to have an antidepressant
1	**2**	**3**	**4**	**5**

Question 2: Mirtazapine versus Sertraline

I strongly prefer him/her to have mirtazapine	I prefer him/her to have mirtazapine	I do not mind	I prefer him/her to have sertraline	I strongly prefer him/her to have sertraline
1	**2**	**3**	**4**	**5**

A3.21 Neuropsychiatric Inventory (NPI)

These questions are designed to evaluate (*participant*)'s behaviour. They can usually be answered 'yes' or 'no' so please try to be brief in your responses. The questions relate to changes in (*participant*)'s behaviour since he/she developed memory problems, and that have been present in the last four weeks.

A. DELUSIONS

Does (*participant*) have beliefs that you know are not true? For example, insisting that people are trying to harm him/her or steal from him/her. Has he/she said that family members are not who they say they are or that the house is not their home? I'm not asking about mere suspiciousness; I am interested if the patient is convinced that these things are happening to him/her.

0	**NO** (*proceed to next screening question*)
1	**YES** (*proceed to subquestions*)
77	Not applicable
88	Not able to evaluate

Instructions: *Insert '1' if present, '0' if absent, '77' if deemed unnecessary, '88' if unable to evaluate*

1	Does the participant believe that he/she is in danger – that others are planning to hurt him/her?	
2	Does the participant believe that others are stealing from him/her?	
3	Does the participant believe that his/her spouse is having an affair?	
4	Does the participant believe that unwelcome guests are living in his/her house?	
5	Does the participant believe that his/her spouse or others are not who they claim to be?	
6	Does the participant believe that that his/her house is not his/her home?	
7	Does the participant believe that family members plan to abandon him/her?	
8	Does the participant believe that television or magazine figures are actually present in the home? (Does he/she try to talk or interact with them?)	
9	Does the participant believe any other unusual things that I haven't asked?	

If the screening question is confirmed, determine the frequency and severity of the delusions.

Now I want to find out how often these things (*define using the description of the behaviours they noted as most problematic on the subquestions*) occur. Would you say that they occur less than once per week, about once per week, several times per week but less than everyday, or once or more per day?

FREQUENCY	***Occasionally*** – less than once per week	1
	Often – about once per week	2
	Frequently – several times per week but less than every day	3
	Very frequently – once or more per day	4

Now I would like to find out how severe these behaviours are. By severity, I mean how disturbing or disabling they are for the participant. Would you say that (the behaviours) are mild, moderate or severe?

SEVERITY	***Mild*** – delusions present but seem harmless and produce little distress in the participant	1
	Moderate – delusions are distressing and disruptive	2
	Marked – delusions are very disruptive and are a major source of behavioural disruption. *(If PRN medications are prescribed, their use signals that the delusions are of marked severity)*	3

B. HALLUCINATIONS

Does the participant have hallucinations such as false visions or voices? Does he/she seem to see, hear or experience things that are not present? By this question we do not mean just mistaken beliefs such as stating that someone who has died is still alive; rather we are asking if the participant actually has abnormal experiences of sounds, or visions.

0	**NO** (*proceed to next screening question*)
1	**YES** (*proceed to subquestions*)
77	Not applicable
88	Not able to evaluate

Instructions: *Insert '1' if present, '0' if absent, '77' if deemed unnecessary, '88' if unable to evaluate*

1	Does the participant describe hearing voices or act as if he/she hears voices?	
2	Does the participant talk to people who are not there?	
3	Does the participant describe seeing things not seen by others or behave as if he/she is seeing things not seen by others (people, animals, lights etc)?	
4	Does the participant report smelling odours not smelled by others?	
5	Does the participant describe feeling things on his/her skin or otherwise appear to be feeling things crawling or touching him/her?	
6	Does the participant describe tastes that are without any known cause?	
7	Does the participant describe any other unusual sensory experience?	

If the screening question is confirmed, determine the frequency and severity of the hallucinations.

Now I want to find out how often these things (*define using the description of the behaviours they noted as most problematic on the subquestions*) occur. Would you say that they occur less than once per week, about once per week, several times per week but less than everyday, or once or more per day?

FREQUENCY	***Occasionally*** – less than once per week	1
	Often – about once per week	2
	Frequently – several times per week but less than every day	3
	Very frequently – once or more per day	4

Now I would like to find out how severe these behaviours are. By severity, I mean how disturbing or disabling they are for the participant. Would you say that (the behaviours) are mild, moderate or severe?

SEVERITY	***Mild*** – hallucinations are present but harmless and cause little distress for the participant	1
	Moderate – hallucinations are distressing and are disruptive to the participant	2
	Marked – hallucinations are very disruptive and are a major source of behavioural disturbance. *(PRN medications may be required to control them)*	3

C. AGITATION / AGGRESSION

Does the participant have periods when he/she refuses to cooperate or won't let people help him/her? Is he/she hard to handle?

0	**NO** (*proceed to next screening question*)
1	**YES** (*proceed to subquestions*)
77	Not applicable
88	Not able to evaluate

Instructions: *Insert '1' if present, '0' if absent, '77' if deemed unnecessary, '88' if unable to evaluate*

1	Does the participant get upset with those trying to care for him/her or resist activities such as bathing or changing clothes?	
2	Is the participant stubborn, having to have things his/her way?	
3	Is the participant uncooperative, resistant to help from others?	
4	Does the participant have any other behaviours that make him/her hard to handle?	
5	Does the participant shout or curse angrily?	
6	Does the participant slam doors, kick furniture, throw things?	
7	Does the participant attempt to hurt or hit others?	
8	Does the participant have any other aggressive or agitated behaviours?	

If the screening question is confirmed, determine the frequency and severity of the hallucinations.

Now I want to find out how often these things (*define using the description of the behaviours they noted as most problematic on the subquestions*) occur. Would you say that they occur less than once per week, about once per week, several times per week but less than daily, or once or more per day?

FREQUENCY	***Occasionally*** – less than once per week	1
	Often – about once per week	2
	Frequently – several times per week but less than daily	3
	Very frequently – once or more per day	4

Now I would like to find out how severe these behaviours are. By severity, I mean how disturbing or disabling they are for the participant. Would you say that (the behaviours) are mild, moderate or severe?

SEVERITY	***Mild*** – behaviour is disruptive but can be managed with redirection or reassurance	1
	Moderate – behaviours disruptive and difficult to redirect or control	2
	Marked – agitation is very disruptive and a major source of difficulty; there may be a threat of personal harm. Medications are often required.	3

D. DEPRESSION / DYSPHORIA

Does the participant seem sad or depressed? Does he/she say that he/she feels sad or depressed?

0	**NO** (*proceed to next screening question*)
1	**YES** (*proceed to subquestions*)
77	Not applicable
88	Not able to evaluate

Instructions: *Insert '1' if present, '0' if absent, '77' if deemed unnecessary, '88' if unable to evaluate*

1	Does the participant have periods of tearfulness or sobbing that seem to indicate sadness?	
2	Does the participant say or act as if he/she is sad or in low spirits?	
3	Does the participant put him/herself down or say that he/she feels like a failure?	
4	Does the participant say that he/she is a bad person or deserves to be punished?	
5	Does the participant seem very discouraged or say that he/she has no future?	
6	Does the participant say he/she is a burden to the family or that the family would be better off without him/her?	
7	Does the participant express a wish for death or talk about killing him/herself?	
8	Does the participant show any other signs of depression or sadness?	

If the screening question is confirmed, determine the frequency and severity of the depression.

Now I want to find out how often these things (*define using the description of the behaviours they noted as most problematic on the subquestions*) occur. Would you say that they occur less than once per week, about once per week, several times per week but less than everyday, or essentially continuously present?

FREQUENCY	***Occasionally*** – less than once per week	1
	Often – about once per week	2
	Frequently – several times per week but less than everyday	3
	Very often – essentially continuously present	4

Now I would like to find out how severe these behaviours are. By severity, I mean how disturbing or disabling they are for the participant. Would you say that (the behaviours) are mild, moderate or severe?

SEVERITY	***Mild*** – depression is distressing but usually responds to redirection or reassurance	1
	Moderate – depression is distressing, depressive symptoms are spontaneously voiced by the participant and difficult to alleviate	2
	Marked – depression is very distressing and a major source of suffering for the participant.	3

E. ANXIETY

Is the participant very nervous, worried, or frightened for no apparent reason? Does he/she seem very tense or fidgety? Is the participant afraid to be apart from you?

0	**NO** (*proceed to next screening question*)
1	**YES** (*proceed to subquestions*)
77	Not applicable
88	Not able to evaluate

Instructions: *Insert '1' if present, '0' if absent, '77' if deemed unnecessary, '88' if unable to evaluate*

1	Does the participant say that he/she is worried about planned events?	
2	Does the participant have periods of feeling shaky, unable to relax, or feeling excessively tense?	
3	Does the participant have periods of [or complain of] shortness of breath, gasping or sighing for no other reason other than nervousness?	
4	Does the participant complain of butterflies in his/her stomach, or of racing or pounding of the heart in association with nervousness? [Symptoms not explained by ill health]	
5	Does the participant avoid certain places or situations that make him/her more nervous such as riding in the car, meeting with friends, or being in crowds?	
6	Does the participant become nervous when separated from you [or his/her caregiver?] [Does he/she cling to you to keep from being separated?]	
7	Does the participant show any other signs of anxiety?	

If the screening question is confirmed, determine the frequency and severity of the anxiety.

Now I want to find out how often these things (*define using the description of the behaviours they noted as most problematic on the subquestions*) occur. Would you say that they occur less than once per week, about once per week, several times per week but less than everyday, or once or more per day?

FREQUENCY	***Occasionally*** – less than once per week	1
	Often – about once per week	2
	Frequently – several times per week but less than every day	3
	Very frequently – once or more per day	4

Now I would like to find out how severe these behaviours are. By severity, I mean how disturbing or disabling they are for the participant. Would you say that (the behaviours) are mild, moderate or severe?

SEVERITY	***Mild*** – anxiety is distressing but usually responds to redirection or reassurance	1
	Moderate – anxiety is distressing, anxiety symptoms are spontaneously voiced by the participant and difficult to alleviate	2
	Marked – anxiety is very distressing and a major source of suffering for the participant.	3

F. ELATION / EUPHORIA

Does the participant seem too cheerful or too happy for no reason? I don't mean the normal happiness that comes from seeing friends, receiving presents, or spending time with family members. I am asking if the participant has a persistent and abnormally good mood or finds humour where others do not.

0	**NO** (*proceed to next screening question*)
1	**YES** (*proceed to subquestions*)
77	Not applicable
88	Not able to evaluate

Instructions: *Insert '1' if present, '0' if absent, '77' if deemed unnecessary, '88' if unable to evaluate*

1	Does the participant appear to feel too good or to be too happy, different from his/her usual self?	
2	Does the participant find humour and laugh at things that others do not find funny?	
3	Does the participant seem to have a childish sense of humour with a tendency to giggle or laugh inappropriately (such as when something unfortunate happens to others)?	
4	Does the participant tell jokes or make remarks that have little humour for others but seem funny to him/her?	
5	Does he/she play childish pranks such as pinching or playing "keep away" (*i.e. taking things and refusing to give them back*) for the fun of it?	
6	Does the participant "talk big" or claim to have more abilities or wealth than is true?	
7	Does the participant show any other signs of feeling too good or being too happy?	

If the screening question is confirmed, determine the frequency and severity of the elation/euphoria.

Now I want to find out how often these things (*define using the description of the behaviours they noted as most problematic on the subquestions*) occur. Would you say that they occur less than once per week, about once per week, several times per week but less than everyday, or essentially continuously present?

FREQUENCY	***Occasionally*** – less than once per week	1
	Often – about once per week	2
	Frequently – several times per week but less than every day	3
	Very frequently – essentially continuously present	4

Now I would like to find out how severe these behaviours are. By severity, I mean how disturbing or disabling they are for the participant. Would you say that (the behaviours) are mild, moderate or severe?

SEVERITY	***Mild*** – elation is notable to friends and family but is not disruptive	1
	Moderate – elation is notably abnormal	2
	Marked – elation is very pronounced; participant is euphoric and finds nearly everything to be humorous	3

G. APATHY / INDIFFERENCE

Has the participant lost interest in the world around him/her? Has he/she lost interest in doing things or lack of motivation for starting new activities? Is he/she more difficult to engage in conversation or in doing chores? Is the participant apathetic or indifferent?

0	**NO** (*proceed to next screening question*)
1	**YES** (*proceed to subquestions*)
77	Not applicable
88	Not able to evaluate

Instructions: *Insert '1' if present, '0' if absent, '77' if deemed unnecessary, '88' if unable to evaluate*

1	Does the participant seem less spontaneous and less active than usual?	
2	Is the participant less likely to initiate a conversation?	
3	Is the participant less affectionate or lacking in emotions when compared to his/her usual self?	
4	Does the participant contribute less to household chores?	
5	Does the participant seem less interested in the activities and plans of others?	
6	Has the participant lost interest in friends and family members?	
7	Is the participant less enthusiastic about his/her usual interests?	
8	Does the participant show any other signs that he/she doesn't care about doing new things?	

If the screening question is confirmed, determine the frequency and severity of the apathy/indifference.

Now I want to find out how often these things (*define using the description of the behaviours they noted as most problematic on the subquestions*) occur. Would you say that they occur less than once per week, about once per week, several times per week but less than everyday, or nearly always present?

FREQUENCY	***Occasionally*** – less than once per week	1
	Often – about once per week	2
	Frequently – several times per week but less than every day	3
	Very frequently – nearly always present	4

Now I would like to find out how severe these behaviours are. By severity, I mean how disturbing or disabling they are for the participant. Would you say that (the behaviours) are mild, moderate or severe?

SEVERITY	***Mild*** – apathy is notable but produces little interference with daily routines; only mildly different from participant's usual behaviour; participant responds to suggestions to engage in activities	1
	Moderate – apathy is very evident; may be overcome by the caregiver with coaxing and encouragement; responds spontaneously only to powerful events such as visits from close relatives or family members	2
	Marked – apathy is very evident and usually fails to respond to any encouragement or external events	3

H. DISINHIBITION

Does the participant seem to act impulsively without thinking? Does he/she do or say things that are not usually done or said in public? Does he/she do things that are embarrassing to you or others?

0	**NO** (*proceed to next screening question*)
1	**YES** (*proceed to subquestions*)
77	Not applicable
88	Not able to evaluate

Instructions: *Insert '1' if present, '0' if absent, '77' if deemed unnecessary, '88' if unable to evaluate*

1	Does the participant act impulsively without appearing to consider the consequences?	
2	Does the participant talk to total strangers as if he/she knew them?	
3	Does the participant say things to people that are insensitive or hurt their feelings?	
4	Does the participant say crude things or make sexual remarks that they would not usually have said?	
5	Does the participant talk openly about very personal or private matters not usually discussed in public?	
6	Does the participant take liberties or touch or hug others in way that is out of character for him/her?	
7	Does the participant show any other signs of loss of control of his/her impulses?	

If the screening question is confirmed, determine the frequency and severity of the disinhibition.

Now I want to find out how often these things (*define using the description of the behaviours they noted as most problematic on the subquestions*) occur. Would you say that they occur less than once per week, about once per week, several times per week but less than everyday, or essentially continuously present?

FREQUENCY	***Occasionally*** – less than once per week	1
	Often – about once per week	2
	Frequently – several times per week but less than every day	3
	Very often – essentially continuously present	4

Now I would like to find out how severe these behaviours are. By severity, I mean how disturbing or disabling they are for the participant. Would you say that (the behaviours) are mild, moderate or severe?

SEVERITY	***Mild*** – disinhibition is notable but usually responds to redirection and guidance	1
	Moderate – disinhibition is very evident and difficult to overcome by the caregiver	2
	Marked – disinhibition usually fails to respond to any intervention by the caregiver, and is a source of embarrassment or social distress	3

I. IRRITABILITY/ LABILITY

Does the participant get irritated and easily disturbed? Are his/her moods very changeable? Is he/she abnormally impatient? We do not mean frustration over memory loss or inability to perform usual tasks; we are interested to know if the participant has abnormal irritability, impatience, or rapid emotional changes different from his/her usual self.

0	**NO** (*proceed to next screening question*)
1	**YES** (*proceed to subquestions*)
77	Not applicable
88	Not able to evaluate

Instructions: *Insert '1' if present, '0' if absent, '77' if deemed unnecessary, '88' if unable to evaluate*

1	Does the participant have a bad temper, flying "off the handle" easily over little things?	
2	Does the participant rapidly change moods from one to another, being fine one minute and angry the next?	
3	Does the participant have sudden outbursts of anger?	
4	Is the participant impatient, having trouble coping with delays or waiting for planned activities?	
5	Is the participant cranky and irritable?	
6	Is the participant argumentative and difficult to get along with?	
7	Does the participant show any other signs of irritability?	

If the screening question is confirmed, determine the frequency and severity of the irritability/lability.

Now I want to find out how often these things (*define using the description of the behaviours they noted as most problematic on the subquestions*) occur. Would you say that they occur less than once per week, about once per week, several times per week but less than everyday, or essentially continuously present?

FREQUENCY	***Occasionally*** – less than once per week	1
	Often – about once per week	2
	Frequently – several times per week but less than every day	3
	Very frequently – essentially continuously present	4

Now I would like to find out how severe these behaviours are. By severity, I mean how disturbing or disabling they are for the participant. Would you say that (the behaviours) are mild, moderate or severe?

SEVERITY	***Mild*** – irritability or lability is notable but usually responds to redirection and reassurance	1
	Moderate – irritability and lability are very evident and difficult to overcome by the caregiver	2
	Marked – irritability and lability are very evident, they usually fail to respond to any intervention by the caregiver, and they are a major source of distress	3

J. ABERRANT MOTOR BEHAVIOUR

Does the participant pace, do things over and over again such as opening closets (*i.e. cupboards*) or drawers, or repeatedly pick at things or wind strings or threads?

0	**NO** (*proceed to next screening question*)
1	**YES** (*proceed to subquestions*)
77	Not applicable
88	Not able to evaluate

Instructions: *Insert '1' if present, '0' if absent, '77' if deemed unnecessary, '88' if unable to evaluate*

1	Does the participant pace around the house without any apparent purpose?	
2	Does the participant rummage around opening and unpacking drawers or closets (*i.e. cupboards*)?	
3	Does the participant repeatedly put on and take off clothing?	
4	Does the participant have repetitive activities or "habits" that he/she performs over and over?	
5	Does the participant engage in repetitive activities such as handling buttons, picking, wrapping string etc.?	
6	Does the participant fidget excessively, seem unable to sit still, or bounce his/her feet or tap his/her fingers a lot?	
7	Does the participant do any other activities over and over?	

If the screening question is confirmed, determine the frequency and severity of the aberrant motor activity.

Now I want to find out how often these things (*define using the description of the behaviours they noted as most problematic on the subquestions*) occur. Would you say that they occur less than once per week, about once per week, several times per week but less than everyday, or essentially continuously present?

FREQUENCY	***Occasionally*** – less than once per week	1
	Often – about once per week	2
	Frequently – several times per week but less than every day	3
	Very frequently – essentially continuously present	4

Now I would like to find out how severe these behaviours are. By severity, I mean how disturbing or disabling they are for the participant. Would you say that (the behaviours) are mild, moderate or severe?

SEVERITY	***Mild*** – abnormal motor activity is notable but produce little interference with daily routines	1
	Moderate – abnormal motor activity is very evident; can be overcome by the caregiver	2
	Marked – abnormal motor activity is very evident, it usually fails to respond to any intervention by the caregiver, and is a major source of distress	3

K. SLEEP

Does the participant have difficulty sleeping (do not count as present if the participant simply gets up once or twice per night only to go to the bathroom and falls back asleep immediately)? Is he/she up at night? Does he/she wander at night, get dressed or disturb your sleep?

0	**NO** (*proceed to next screening question*)
1	**YES** (*proceed to subquestions*)
77	Not applicable
88	Not able to evaluate

Instructions: *Insert '1' if present, '0' if absent, '77' if deemed unnecessary, '88' if unable to evaluate*

1	Does the participant have difficulty falling asleep?	
2	Does the participant get up during the night (do not count if the participant simply gets up once or twice per night only to go to the bathroom and falls back asleep immediately)?	
3	Does the participant wander, pace, or get involved in inappropriate activities at night?	
4	Does the participant awaken you during the night?	
5	Does the participant awaken during the night, dress and plan to go out thinking that it is morning and time to start the day?	
6	Does the participant awaken too early in the morning (earlier than was his/her habit)?	
7	Does the participant sleep excessively during the day?	
8	Does the participant have any other night-time behaviours that bother you that we haven't talked about?	

If the screening question is confirmed, determine the frequency and severity of the night-time behaviour.

Now I want to find out how often these things (*define using the description of the behaviours they noted as most problematic on the subquestions*) occur. Would you say that they occur less than once per week, about once per week, several times per week but less than everyday, or once or more per day (every night)?

FREQUENCY	***Occasionally*** – less than once per week	1
	Often – about once per week	2
	Frequently – several times per week but less than every day	3
	Very frequently – once or more per day (every night)	4

Now I would like to find out how severe these behaviours are. By severity, I mean how disturbing or disabling they are for the participant. Would you say that (the behaviours) are mild, moderate or severe?

SEVERITY	***Mild*** – night-time behaviours occur but they are not particularly disruptive	1
	Moderate – night-time behaviours occur and disturb the participant and the sleep of the caregiver; more than one type of night-time behaviour may be present	2
	Marked – night-time behaviours occur; several types of night-time behaviour may be present; the participant is very distressed during the night and the caregiver's sleep in markedly disturbed	3

L. APPETITE AND EATING DISORDERS

Has he/she had any change in appetite, weight, or eating habits (count as "77" if the participant is incapacitated and has to be fed)? Has there been any change in type of food he/she prefers?

0	**NO** (*proceed to next screening question*)
1	**YES** (*proceed to subquestions*)
77	Not applicable
88	Not able to evaluate

Instructions: *Insert '1' if present, '0' if absent, '77' if deemed unnecessary, '88' if unable to evaluate*

1	Has he/she had a loss of appetite?	
2	Has he/she had an increase in appetite?	
3	Has he/she had a loss of weight?	
4	Has he/she gained weight?	
5	Has he/she had a change in eating behaviour such as putting too much food in his/her mouth at once?	
6	Has he/she had a change in the kind of food he/she likes such as eating too many sweets or other specific types of food?	
7	Has he/she developed eating behaviours such as eating exactly the same types of food each day or eating the food in exactly the same order?	
8	Have there been any other changes in appetite or eating that I haven't asked about?	

If the screening question is confirmed, determine the frequency and severity of the changes in eating habits or appetite.

Now I want to find out how often these things (*define using the description of the behaviours they noted as most problematic on the subquestions*) occur. Would you say that they occur less than once per week, about once per week, several times per week but less than everyday, or once or more per day or continuously?

FREQUENCY	***Occasionally*** – less than once per week	1
	Often – about once per week	2
	Frequently – several times per week but less than every day	3
	Very frequently – once or more per day or continuously	4

Now I would like to find out how severe these behaviours are. By severity, I mean how disturbing or disabling they are for the participant. Would you say that (the behaviours) are mild, moderate or severe?

SEVERITY	***Mild*** – changes in appetite or eating are present but have not led to changes in weight and are not disturbing	1
	Moderate – changes in appetite or eating are present and cause minor fluctuations in weight	2
	Marked – obvious changes in appetite or eating are present and cause fluctuations in weight, are embarrassing, or otherwise disturb the participant	3

A3.22 NON-SERIOUS ADVERSE EVENTS LOG (PAGE ONE)

Has the participant experienced any Adverse Events since signing the Informed Consent to the trial?	**YES, specify below**	1	**NO**	0

AE no.	**Adverse Event** [Diagnosis or symptom (if known) or signs/symptoms]	**Start Date** (dd/mm/yyyy)	**Stop Date** (dd/mm/yyyy)	**Severity** Mild = 1 Moderate = 2 Severe = 3	**Relationship to Study Drug?** Definite = 1 Probable = 2 Possible = 3 Remote = 4 None = 5	**Action Taken with Study Drug** None (1) Temp. Dose Reduction = 2 Perm. Dose Reduction = 3 Temp. Discontinuation = 4 Perm. Discontinuation = 5	**Staf Initia & Dat**
1				1	1	1	
				2	2	2	
				3	3	3	
					4	4	
					5	5	
2				1	1	1	
				2	2	2	
				3	3	3	
					4	4	
					5	5	
3				1	1	1	
				2	2	2	
				3	3	3	
					4	4	
					5	5	

A3.23 Participant Demographic Information

1.	Date of birth:	☐☐ ☐☐ ☐☐☐☐ Day Month Year	
2.	Gender:	Male	0
		Female	1
3.	Ethnicity	White	1
		Mixed	2
		Asian	3
		Black	4
		Chinese	5
		Other	6
4.	Marital status	Single (never married)	1
		Married (first marriage)	2
		Re-married	3
		Separated (still legally married)	4
		Divorced	5
		Widowed	6
		Not known	88
5.	Number of adults/residents aged 16 or over living in the household: *(or residential/nursing facility, including participant)*	☐☐☐	
6.	Number of children aged 15 and under living in the household: *(or residential/nursing facility)*	☐☐	

A3.24 Participant Registration

As soon as possible after a new referral letter is received from a known Referring Investigator the following should be completed and entered onto MACRO.

1.	Date on referral letter:	Day Month Year	
2.	Name of Referring Investigator:	_____	
3.	Referring Investigator known to Trial Office *(If No: Inform Trial Manager immediately)*	No	0
		Yes	1
4.	Referring Investigator has confirmed eligibility (except for CSDD)	No	0
		Yes	1
5.	NINCSD – ADRDA Criteria for dementia (*Taken from referral letter*)	Confirmed Met	2
		Confirmed Unmet	1
		Information Not Given	0
6.	Criteria for Dementia of the Alzheimer Type (DSM-IV-TR) (*Taken from referral letter*)	Confirmed Met	2
		Confirmed Unmet	1
		Information Not Given	0

MACRO WILL GENERATE PARTICIPANT IDENTIFICATION NUMBER (PIN)			
7.	Centre:	Number	Name
		_____	_____
8.	PIN:	**P** Centre Number Consecutive Number within Centre	
9.	Participant initials: *(As appear throughout trial)*		
10.	Date of registration: (*Date entered onto MACRO*)	Day Month Year	
11.	Research worker initials: *(As appear throughout trial)*		

A3.25 Pill Count

MIRTAZAPINE (Active or Placebo) Box Number_____

Bottle ID	Date Dispensed	Amount Dispensed	Date Returned	Amount Returned
1	|__|__|/|__|__|/|__|__|__|__| day month year		|__|__|/|__|__|/|__|__|__|__| day month year	
2	|__|__|/|__|__|/|__|__|__|__| day month year		|__|__|/|__|__|/|__|__|__|__| day month year	
3	|__|__|/|__|__|/|__|__|__|__| day month year		|__|__|/|__|__|/|__|__|__|__| day month year	

SERTRALINE (Active or Placebo) Box Number_____

Bottle ID	Date Dispensed	Amount Dispensed	Date Returned	Amount Returned
1	|__|__|/|__|__|/|__|__|__|__| day month year		|__|__|/|__|__|/|__|__|__|__| day month year	
2	|__|__|/|__|__|/|__|__|__|__| day month year		|__|__|/|__|__|/|__|__|__|__| day month year	
3	|__|__|/|__|__|/|__|__|__|__| day month year		|__|__|/|__|__|/|__|__|__|__| day month year	

A3.26 Randomisation Request Form: HTA-SADD Trial

To register a participant in the HTA-SADD Trial, please first complete this form and then email, fax or telephone the Mental Health & Neurology Clinical Trials Unit (MH&N CTU) at the Institute of Psychiatry.

The office is open for randomisations 9am to 5pm, Monday to Fridays, not Bank Holidays.

Email: randomization_request@iop.kcl.ac.uk **Telephone No.**: 0207 848 5282 Fax **No.**: 0207 848 5229

NB: It is important to identify the HTA-SADD Trial – this telephone line is used for randomisations for a number of trials. There may be delay in response of up to 24 hours from request.

Request from:			**Date of Request:** _ _/_ _/_ _ _ _ (dd/mm/yyyy)	
Centre *(Circle which centre request is for)*	Birmingham	01	Newcastle	06
	Cambridge	02	North London	07
	Leicester	03	Southampton	08
	Liverpool	04	South London & Kent	09
	Manchester	05		

PARTICIPANT DETAILS:

PIN		**PIN Initials**	
Gender	Male / Female	**Date of Birth** (dd/mm/yyyy)	_ _/_ _/_ _ _ _
CIN		**CIN Initials**	

INCLUSION CRITERIA – *All answers must be **YES** for the participant to be eligible*	**YES**	**NO**
1 Participant has a clinical diagnosis of mild to moderate probable or possible Alzheimer's Disease		
2 Participant has a co-existing depressive illness likely to need treatment with antidepressants		
3 Depression duration more than four weeks at referral		

EXCLUSION CRITERIA – *All answers must be **NO** for the participant to be eligible*	**YES**	**NO**
1. Participant is currently taking antidepressants		
2. Dementia too severe to complete baseline CSDD		
3. The case is considered too critical to be randomised (eg because of suicide risk)		
4. Participant displays absolute contraindications to one or more of the trial treatments		
5. Participant is entered on another trial		
6. There is no identifiable family carer or other informant to give collateral information		
7. Participant has a baseline CSDD score of 7 or under		

BASELINE DATA:

CSDD Available & Ratable	**Score:**_____

I confirm that the above is complete and correct and that all vital baseline data is available:	
Signature:	**Date:**

A3.27 Serious Adverse Event (SAE) Form

Must be entered onto eCRF within 24 hours (regulatory requirement)

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)

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. *Thank you for completing this survey!*

For each of the following questions, please circle the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	1
Very good	2
Good	3
Fair	4
Poor	5

2. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

		Yes, limited a lot	Yes, limited a little	No, not limited at all
a	<u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or <u>playing golf</u>	1	2	3
b	Climbing <u>several</u> flights of stairs	1	2	3

3. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health?</u>

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
a	<u>Accomplished less</u> than you would like	1	2	3	4	5
b	Were limited in the <u>kind</u> of work or other activities	1	2	3	4	5

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
a	Accomplished less than you would like	1	2	3	4	5
b	Did work or other activities less carefully than usual	1	2	3	4	5

5. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	1
A little bit	2
Moderately	3
Quite a bit	4
Extremely	5

6. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
a	Have you felt calm and peaceful?	1	2	3	4	5
b	Did you have a lot of energy?	1	2	3	4	5
c	Have you felt downhearted and low?	1	2	3	4	5

7. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc)?

All of the time	1
Most of the time	2
Some of the time	3
A little of the time	4
None of the time	5

A3.29 Standardised Mini-Mental State Examination (SMMSE)

***Instructions**: insert '1' in box if task completed correctly, '0' if attempted but failed, '88' if participant unable / unwilling to attempt.*

I'm going to ask you some questions and give you some problems to solve. Please try to answer as best you can.

ORIENTATION

(Allow ten seconds for each reply)

1a.	What year is this?	*Accept exact answer only*	
1b.	What season is this?	*During last week of old season or first week of new season, accept either season*	
1c.	What month of the year is this?	*On the first day of a new month, or last day of a previous month, accept either*	
1d.	What is today's date?	*Accept previous or next date, e.g. on 7th accept 6th or 8th*	
1e.	What day of the week is this?	*Accept exact answer only*	

2a.	What country are we in?	*Accept exact answer only*	
2b.	What borough / county are we in?	*Accept exact answer only*	
2c.	What city / town are we in?	*Accept exact answer only*	
2d.	***(In clinic / care home)*** What is the name of this hospital / building? ***(In home)*** What is the street address of this house?	*Accept exact name of hospital or institution only* *Accept street name and house number or equivalent in rural areas*	
2e.	***(In clinic / care home)*** What floor of the building are we on? ***(In home)*** What room are we in?	*Accept exact answer only* *Accept exact answer only*	

REGISTRATION

I am going to name three objects. After I have said all three objects, I want you to repeat them. Remember what they are because I am going to ask you to name them again in a few minutes.

Say them slowly at approximately one second intervals.

3a.	Ball	*Accept correct reply on first attempt only*	
3b.	Car	*Accept correct reply on first attempt only*	
3c.	Man	*Accept correct reply on first attempt only*	

Please repeat the three items for me. *(Allow twenty seconds for reply).*

If participant did not repeat all three, repeat until they are learned, or up to a maximum of five times.

ATTENTION AND CALCULATION

4.	Spell the word WORLD. Now spell it backwards please?	*You may help participant to spell WORLD correctly.* *Allow thirty seconds to spell backwards. If participant cannot spell world even with assistance – score '0'*	
		4a. Record first letter	
		4b. Record second letter	
		4c. Record third letter	
		4d. Record fourth letter	
		4e. Record fifth letter	

RECALL

Now what were the three objects that I asked you to remember? *(Allow ten seconds)*

5a.	Ball	*Accept correct response regardless of order*	
5b.	Car	*Accept correct response regardless of order*	
5c.	Man	*Accept correct response regardless of order*	

LANGUAGE

Show wristwatch. *(Allow ten seconds)*

6.	What is this called?	*Accept WRISTWATCH or WATCH. Do not accept CLOCK, TIME, etc.*	

Show pencil.

7.	What is this called?	Accept PENCIL only. Do not accept PEN.	

I'd like you to repeat a phrase after me: *(Allow ten seconds)*

8.	"No ifs ands or buts"	*Must be an exact repetition. Do not accept NO IFS OR BUTS*	

Hand participant the laminated sheet with CLOSE YOUR EYES on it. *(Allow ten seconds)*

9.	Read the words on this page and then do what it says	*If participant just reads and does not then close eyes – you may repeat: read the words on this page and then do what it says, to a maximum of three times. Accept only if participant closes eyes. Participant does not have to read aloud.*	

Ask if the participant is right or left handed. (*Allow thirty seconds)*

Take a piece of paper – hold it up in front of participant and say the following:

If right-handed: Take this paper in your left hand, fold the paper in half once with both hands and put the paper down on the floor

If left-handed: Take this paper in your right hand, fold the paper in half once with both hands and put the paper down on the floor

10a.	*Takes paper in correct hand*	*Accept if correctly executed*	
10b.	*Folds it in half*	*Accept if correctly executed*	
10c.	*Puts it on the floor*	*Accept if correctly executed*	

Hand participant a pencil and paper. *(Allow thirty seconds)*

11.	Write any complete sentence on that piece of paper.	*The sentence should make sense. Ignore spelling errors.*	

Place design, pencil, eraser and paper in front of the participant *(Maximum time one minute)*

12.	Copy this design please.	*Allow multiple tries until participant is finished and hands it back. Accept correctly copied diagram only. The participant must have drawn a 4-sided figure between two 5-sided figures.*	

A3.30 TRIAL MEDICATION LOG

This is to be completed to record changes in dosage of trial medication based on prescriptions and advice to carers.

Start Date (dd/mm/yyyy)	Stop Date (dd/mm/yyyy)	Name of Medication	Total Daily Dose	Staff Initials & Date	Comments
		Mirtazapine / Placebo			
		Mirtazapine / Placebo			
		Mirtazapine / Placebo			
		Mirtazapine / Placebo			

Start Date (dd/mm/yyyy)	Stop Date (dd/mm/yyyy)	Name of Medication	Total Daily Dose	Staff Initials & Date	Comments
		Sertraline / Placebo			
		Sertraline / Placebo			
		Sertraline / Placebo			
		Sertraline / Placebo			

A3.31 Withdrawal Form

1.	Has the participant withdrawn from:	Treatment Only	*(ie Placebo / Mirtazapine / Sertraline)*	0
		Trial	*(ie Treatment and Follow-Up)*	1

2.	Brief description of the reason for withdrawal *(attach additional sheets if necessary)*

3.	Date of withdrawal	☐☐ ☐☐ ☐☐☐☐ Day Month Year

4.	Reason for withdrawal *(Circle all that apply)*	Eligibility criterion no longer met (Specify: _____)	1
		Death of participant *(SAE no. _____)*	2
		Other adverse event (AE / SAE no. _____)	3
		Deterioration of pre-existing medical condition	4
		Poor adherence to treatment	5
		Perceived lack of efficacy of medication	6
		Unable to locate participant	7
		Unable to locate a carer	8
		Other (Specify: _____)	9

5.	Withdrawal decision initiated by: *(Circle all that apply)*	Chief Investigator	1
		Principal Investigator	2
		Referring Investigator	3
		Carer	4
		Participant	5
		Other (Specify: _____)	6

6.	Would the Principal Investigator have independently recommended withdrawal from treatment	No	0
		Yes	1

7.	Permission given to use data collected:	No, use of all data collected to date denied	1
		Yes, partial permission to use data up to withdrawal (Specify: _____)	2
		Yes, permission to use all data up to withdrawal	3
		Yes, permission to collect and use all follow-up data	4

8.	Treatment code broken: *(Not unless absolutely necessary)*	No	0
		Yes (Emergency Unblinding Request no. _____)	1

9.	***Signature of Research Worker:***	***Signature of Principal Investigator***

A3.32 Zarit Caregiver Burden Inventory

The following questions reflect how people sometimes feel when taking care of another person. After each question, indicate how often you feel that way, never, rarely, sometimes, quite frequently or nearly always. There are no right or wrong answers.

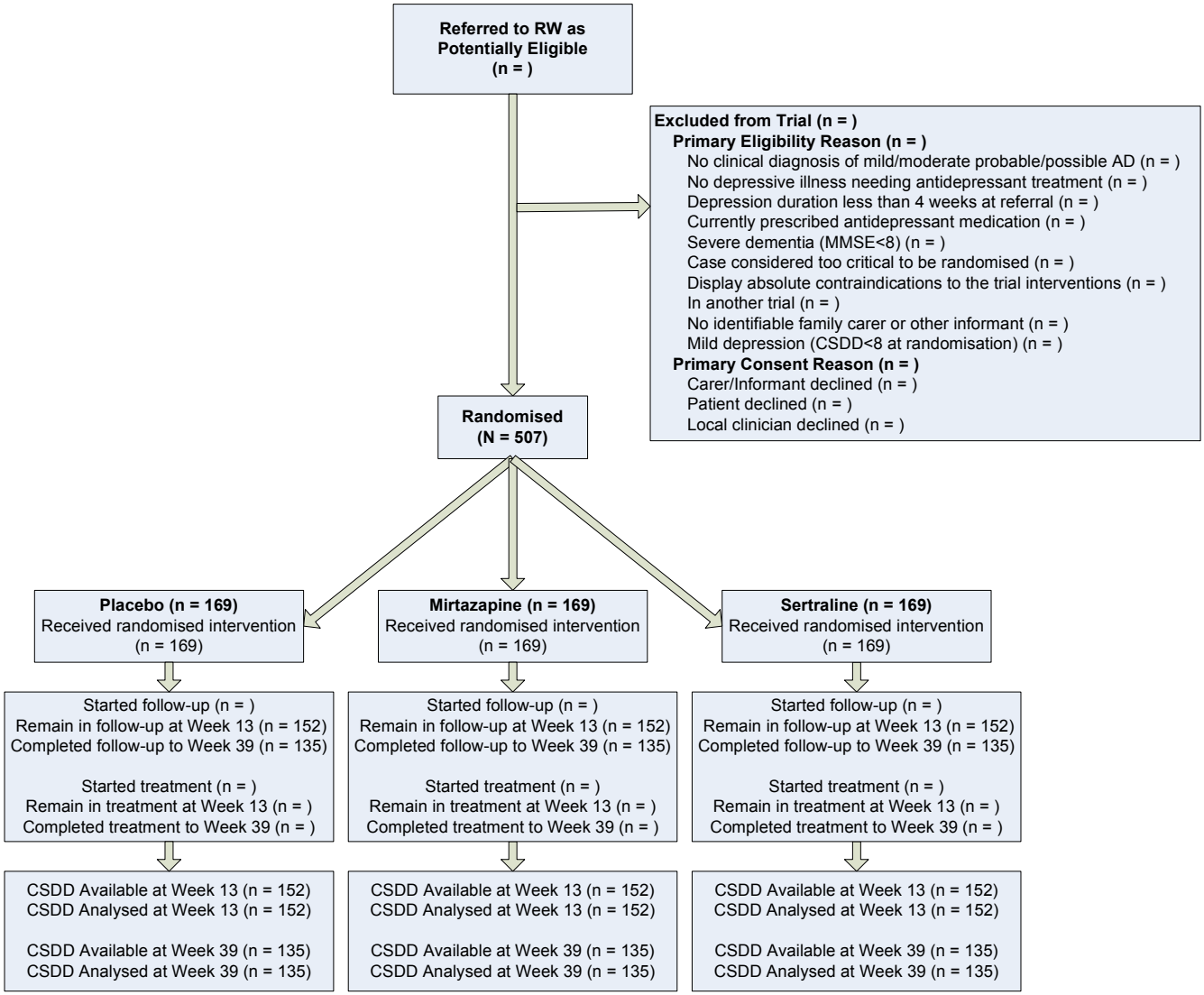
		Never	**Rarely**	**Sometimes**	**Quite frequently**	**Nearly always**
1	Do you feel that (*the participant*) asks for more help than he/ she needs?	0	1	2	3	4
2	Do you feel that because of the time you spend with (*the participant*) that you do not have enough time for yourself?	0	1	2	3	4
3	Do you feel stressed between caring for (*the participant*) and trying to meet other responsibilities for your family or work?	0	1	2	3	4
4	Do you feel embarrassed over (*the participant*)'s behaviour?	0	1	2	3	4
5	Do you feel angry when you are around (*the participant*)?	0	1	2	3	4
6	Do you feel that (*the participant*) currently affects your relationship with other family members or friends in a negative way?	0	1	2	3	4
7	Are you afraid what the future holds for (*the participant*)?	0	1	2	3	4
8	Do you feel that (*the participant*) is dependant upon you?	0	1	2	3	4
9	Do you feel strained when you are around (*the participant*)?	0	1	2	3	4
10	Do you feel your health has suffered because of your involvement with (*the participant*)?	0	1	2	3	4
11	Do you feel that you do not have as much privacy as you would like, because of (*the participant*)?	0	1	2	3	4
12	Do you feel that your social life has suffered because you are caring for (*the participant*)?	0	1	2	3	4

		Never	**Rarely**	**Sometimes**	**Quite frequently**	**Nearly always**
13	Do you feel you are uncomfortable about having friends over, because of (*the participant*)?	0	1	2	3	4
14	Do you feel that (*the participant*) seems to expect you to take care of her/him, as if you were the only one she/he could depend on?	0	1	2	3	4
15	Do you feel that you do not have enough money to care for (*the participant*), in addition to the rest of the expenses?	0	1	2	3	4
16	Do you feel that you will be unable to take care of (*the participant*) much longer?	0	1	2	3	4
17	Do you feel you have lost control of your life since (*the participant*)'s illness?	0	1	2	3	4
18	Do you wish you could just leave the care of (*the participant*) to someone else?	0	1	2	3	4
19	Do you feel uncertain about what to do about (*the participant*)?	0	1	2	3	4
20	Do you feel you should be doing more for (*the participant*)?	0	1	2	3	4
21	Do you feel you could do a better job in caring for (*the participant*)?	0	1	2	3	4
		Not at all	**A little**	**Fairly**	**Quite a bit**	**Very**
22	Overall, how burdened do you feel in caring for (*the participant*)?	0	1	2	3	4

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