University of Sussex

NORWICH CTU

Study of Mirtazapine or Carbamazepine for Agitation in Dementia: HTA-SYMBAD

A pragmatic, multi centre, double-blind, placebo controlled randomised trial to assess the safety, clinical and cost effectiveness of mirtazapine or carbamazepine in patients with Alzheimer's Disease (AD) and agitated behaviours.

Version	Final Version 1.3
Date	21 March 2016
Sponsor	The University of Sussex
Trial registration	EudraCT 2015-003410-25
Funder reference	HTA Project 13/115/76
CTA #	58810/0001/001-0001
NRES #	15/SC/0606

Authorisation: Chief Investigator

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Signature	
Date	29/4/2016.

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Date	3/5/16.

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Date	29th April 2016

Authorisation: Senior Operations Staff

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Date	4th May 2016.

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1 Administrative information

This document was constructed using the Norwich Clinical Trials Unit (NCTU) Protocol template Version 3. It describes the HTA-SYMBAD trial, sponsored by the University of Sussex and co-ordinated by NCTU.

It provides information about procedures for entering participants into the trial, and provides sufficient detail to enable: an understanding of the background, rationale, objectives, trial population, intervention, methods, statistical analyses, ethical considerations, dissemination plans and administration of the trial; replication of key aspects of trial methods and conduct; and appraisal of the trial's scientific and ethical rigour from the time of ethics approval through to dissemination of the results. The protocol should not be used as an aide-memoire or guide for the treatment of other patients. Every care has been taken in drafting this protocol, but corrections or amendments may be necessary. These will be circulated to registered investigators in the trial. Sites entering participants for the first time should confirm they have the correct version through a member of the trial team at NCTU.

NCTU supports the commitment that its trials adhere to the SPIRIT guidelines. As such, the protocol template is based on an adaptation of the Comprehensive Clinical Trials Unit at University College London protocol template (2012) and the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2012 Statement for protocols of clinical trials [1]. The SPIRIT Statement Explanation and Elaboration document [2] can be referred to, or a member of the HTA-SYMBAD trial team at NCTU can be contacted for further detail about specific items.

1.1 Compliance

The trial will be conducted in compliance with the approved protocol, the Declaration of Helsinki (2008), the principles of Good Clinical Practice (GCP) as laid down by the Commission Directive 2005/28/EC with implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, the UK Data Protection Act, and the National Health Service (NHS) Research Governance Framework for Health and Social Care (RGF). Agreements that include detailed roles and responsibilities will be in place between the Sponsor, NCTU and participating sites.

Participating sites will inform NCTU as soon as they are aware of a possible serious breach of compliance, so that NCTU can fulfil its requirement to report the breach if necessary within the timelines specified in the UK Clinical Trials Regulations (currently 7 days). For the purposes of this regulation a 'serious breach' is one that is likely to affect to a significant degree:

- The safety or physical or mental integrity of the subjects in the trial, or
- The scientific value of the trial.

1.2 Sponsor

The University of Sussex is the trial sponsor and has delegated the overall management of the HTA-SYMBAD trial to the Chief Investigator and NCTU. Queries relating to sponsorship of this trial should be addressed to the Director, NCTU, or via the trial team.

1.3 Structured trial summary

Primary Registry and Trial Identifying Number	ISRCTN number to be provided when available
Date of Registration in Primary Registry	
Secondary Identifying Numbers	Funder reference: HTA Project 13/115/76 Sponsor reference: G1612
Source of Monetary or Material Support	National Institute for Health Research HTA Programme is providing funding for research costs for the project duration to cover trial set up, trial conduct, analysis and report writing. IMP and placebo will be obtained by Catalent who will be responsible for primary and secondary packaging and labelling, storage and shipment to sites
Sponsor	University of Sussex
Contact for Public Queries	symbad@uea.ac.uk
Contact for Scientific Queries	Professor Sube Banerjee Brighton and Sussex Medical School, Centre for Dementia Studies, University of Sussex, Falmer, Brighton BN1 9RY E: s.banerjee@bsms.ac.uk Ph: 01273 678472
Public Title	Study of Mirtazapine or Carbamazepine for Agitation in Dementia
Scientific Title	A pragmatic, multi centre, double-blind, placebo controlled randomised trial to assess the safety, clinical and cost effectiveness of mirtazapine or carbamazepine in patients with Alzheimer's Disease (AD) and agitated behaviours.
Countries of Recruitment	UK
Health Condition or Problem Studied	Alzheimer's disease and agitated behaviours
Interventions	Mirtazapine – IMP Carbamazepine – IMP Placebo IMP and placebo will be identically encapsulated (15mg tablets for mirtazapine and 100mg tablets for carbamazepine) to produce capsules. Participants will be required to take capsules orally in a single dose at night as follows: Mirtazapine: 15mg starting dose increasing to 30mg after 2 weeks and up to 45 mg in total; or, Carbamazepine: 100mg starting dose increasing to 200mg after 2 weeks and up to 300mg in total; or, Placebo: 1 capsule starting dose increasing to 2 capsules after 2 weeks and up to 3 capsules in total IMP or placebo will be taken for 12 weeks in total.
Key Inclusion and Exclusion Criteria	This is a pragmatic trial, in routine practice. Patients will be included where a referring clinician makes:

	• clinical diagnosis of probable or possible Alzheimer's Disease using National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria • a diagnosis of co-existing agitated behaviours • evidence that the agitated behaviours have not responded to management according to the AS/DH algorithm • Patients taking stable (defined as three months on current dose) cholinesterase inhibitors or memantine • An assessment of Cohen Mansfield Agitation Inventory (Long Form) score of 45 or greater • Written informed consent to enter and be randomised into the trial • Availability of a suitable informant (consenting identifiable family carer or paid carer) to provide information on carer-completed outcome measures and who consents to take part in the trial. Exclusion criteria are: • Current treatment with antidepressants (including monoamine oxidase inhibitors (MAOIs)), anticonvulsants, antipsychotics. Patients must have completed treatment with these medications at least two weeks before trial drug administration. • Contraindications to the administration of carbamazepine and mirtazapine as per their current SmPCs • Patients with atrioventricular block, a history of bone marrow depression or history of hepatic porphyrias • Cases too critical for randomisation (ie where there is a suicide risk or where the patient presents a risk of harm to others) • Female subjects under the age of 55 of childbearing potential, defined as follows: postmenopausal females who have not had at least 12 months of spontaneous amenorrhea or 6 months of spontaneous amenorrhoea with serum FSH>40mIU/ml or females who have not had a hysterectomy or bilateral oophorectomy at least 6 weeks prior to enrolment.
Study Type	Pragmatic, phase III, multi-centre, double blind, superiority, randomised, placebo controlled trial. Patients will be randomised in a 1:1:1 ratio to mirtazapine, carbamazepine or placebo, stratified by study region and independent living using permuted block randomisation via a web-based system. There is an internal pilot study included to assess a single primary progression criterion based on the numbers

	recruited after 6 months of recruitment (ie 25% of the recruitment period).
Date of First Enrolment	Anticipated 1st June 2016
Target Sample Size	471
Primary Outcome	CMAI (Long form) score 12 weeks post randomisation
Key Secondary Outcomes	1. Costs derived from Client Service Receipt Inventory (CSRI), and QALYs from cost data alongside information from DEMQOL and EQ-5D-5L interviews 12 weeks post randomisation. 2. Cohen Mansfield Agitation Inventory (CMAI) score and cost at 6 weeks post randomisation. 3. Patient and carer quality of life, and carer outcomes at 6 and 12 weeks post randomisation. 4. Adverse events and adherence at 6 and 12 weeks post randomisation. 5. CMAI score, adverse events and adherence at 6 and 12 weeks post randomisation, conditional on evidence of effectiveness of one IMP over placebo. 6. Long term follow up: CMAI score, institutionalisation, death and clinical management at 26 and 52 weeks post-randomisation.

1.4 Roles and responsibilities

These membership lists are correct at the time of writing; please see terms of reference documentation in the TMF for current lists.

1.4.1 Protocol contributors

Name	Affiliation	Role
Julie Bakobaki	NCTU	Drafting protocol and co-ordinating protocol development
Sube Banerjee	CI – Brighton and Sussex Medical School	Protocol development
Lee Shepstone	NCTU	Statistical considerations
Sue Stirling	NCTU	Statistical considerations
Erika Sims	NCTU	Operational considerations
Matthew Hammond	NCTU	Operational considerations
Ann Marie Swart	NCTU	Protocol development

1.4.2 Role of trial sponsor and funders

Name	Affiliation	Role
Kevin Davies	University of Sussex	Sponsor representative – legal responsibility for trial conduct
Claire Gregory	NIHR HTA	Assistant Research Manager HTA

1.4.3 Trial Team

Name	Affiliation	Role and responsibilities
Sube Banerjee	Brighton and Sussex Medical School	Chief Investigator
Juliet High	UEA - NCTU	Trial Manager
Lee Shepstone	UEA - NCTU	Trial Statistician
Martin Knapp	LSE	Trial Health Economist
Antony Colles	UEA - NCTU	Database Programmer

1.4.4 Trial Management Group

Name	Affiliation	Role and responsibilities
Sube Banerjee	Brighton and Sussex Medical School (BSMS)	Chief Investigator and TMG Chair
Clive Ballard	KCL	Co-applicant and local PI
Paul Francis	KCL	Co-applicant
Martin Knapp	LSHTM	Co-applicant and Trial Heath Economist
Gill Livingston	UCL	Co-applicant and local PI
Shirley Nurock	Alzheimer's Society	Co-applicant and PPI representative
Alan Thomas	University of Newcastle	Co-applicant and local PI
Peter Bentham	University of Birmingham	Co-applicant and local PI
Alistair Burns	University of Manchester	Co-applicant and local PI
Iracema Leroi	University of Manchester	Co-applicant and local PI
John O'Brien	University of Cambridge	Co-applicant

Naji Tabet	Sussex Partnership Trust	Co-applicant and local PI
Chris Fox	UEA	Co-applicant and local PI
Robert Howard	KCL	Co-applicant and local PI
Lee Shepstone	UEA – NCTU	Co-applicant and trial statistician
Ann Marie Swart	UEA – NCTU	Co-applicant and NCTU director
Juliet High	UEA – NCTU	Trial Manager
Ramin Nilforooshan	SABP	Sub-Investigator, Sussex
PPI member	Sussex Partnership Trust	Representing LEAP

1.4.5 Trial Steering Committee

Name	Affiliation	Role and responsibilities
Sube Banerjee	Brighton and Sussex Medical School	CI – non-independent member
Ann Marie Swart	NCTU	Non-independent member
Lee Shepstone	NCTU	Non-independent member - Statistician
Peter Connolly		Chair- independent member
Andy Barker		Independent member
Chris Penrose		Independent public member
Julie West		Independent public member
Juliet High	NCTU	Non-independent observer/Trial manager

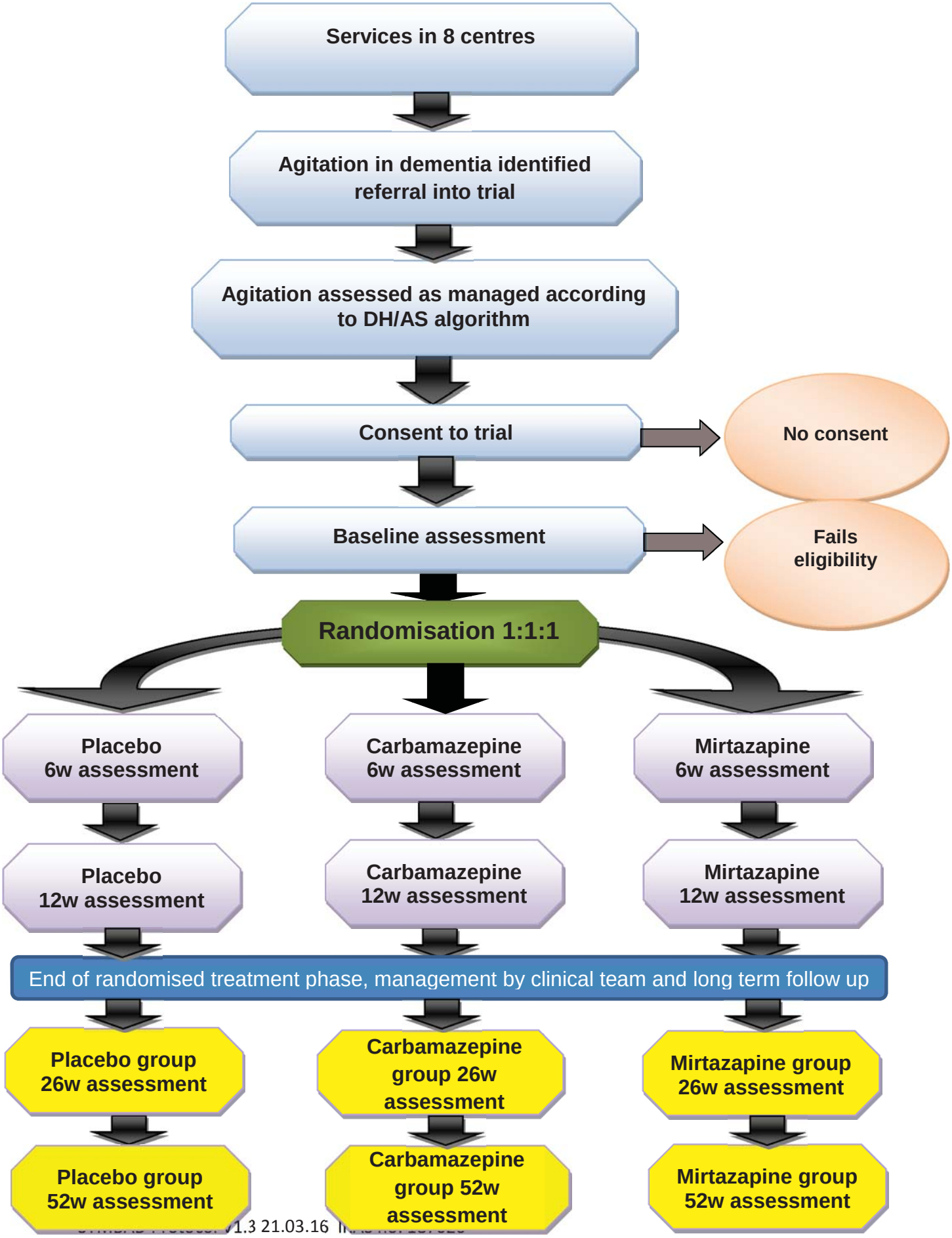
1.4.6 Data Monitoring Committee

Name	Affiliation	Role and responsibilities
Bart Sheehan		Chair
Siobhan Creanor		Statistician
Adrian Treloar		Clinician

1.4.7 Other Trial Oversight Groups

Name	Affiliation	Role and responsibilities
Protocol Review Committee	Norwich CTU	Independent review of protocol, patient information sheets and consent forms
CTU Management Committee	Norwich CTU	Oversight of quality management activities of NCTU trials including approval of risk assessment, quality management and monitoring plan and pharmacovigilance plan

2 Trial Diagram



3 Abbreviations

AD	Alzheimer's Disease
AE	Adverse Event
AR	Adverse Reaction
BPSD-NPI	Behavioural and Psychological Symptoms in Dementia Neuropsychiatric Inventory
BSMS	Brighton and Sussex Medical School
CA	Competent Authority
CBI	Carer Burden Inventory
CDS	Centre of Dementia Studies
CI	Chief Investigator
CMAI	Cohen-Mansfield Agitation Inventory
CRF	Case Report Form
CRN	Clinical Research Network
CRO	Contract Research Organisation
CSRI	Client Service Receipt Inventory
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTU	Clinical Trials Unit
DEMQOL	Dementia Specific Quality of Life
DeNDRoN	Dementia and Neurodegenerative Diseases Research Network
DSUR	Development Safety Update Report
EC	European Commission
ECG	Electrocardiogram
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance
FBC	Full Blood Count
GCP	Good Clinical Practice
GHQ12	General Health Questionnaire
GMP	Good Manufacturing Practice
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
ITT	Intention to Treat
LEAP	Lived Experience Advisory Panel
LFT	Liver Function (blood) Test
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
NCTU	Norwich Clinical Trials Unit
NHS R&D	National Health Service Research and Development
NICE	National Institute for Health and Care Excellence
NIMP	Non-Investigational Medicinal Product
NINCDS/ADRDA	National Institute of Neurological and Communicative Disorders and stroke / Alzheimer's Disease and Related Disorders Association
PI	Principal Investigator
PIC	Participant Identification Centre

PIN	Patient Identification Number
PIS	Participant Information Sheet
PPI	Patient and Public Involvement
QA	Quality Assurance
QC	Quality Control
QMMP	Quality Management and Monitoring Plan
QOL	Quality of Life
QP	Qualified Person
R&D	Research and Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SABP	Surrey and Borders Partnership NHS Trust
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SmPC	Summary of Product Characteristics
SSA	Site Specific Approval
SSI	Site Specific Information
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TMT	Trial Management Team
ToR	Terms of Reference
TSC	Trial Steering Committee
UEA	University of East Anglia
U&Es	Urea and Electrolytes blood test
UoS	University of Sussex

4 Introduction

4.1 Background and Rationale

Dementia is one of the most common and serious disorders faced by society today, affecting 800,000 people, with 200,000 new cases a year in the UK (Launer et al, 1992; Hoffman et al, 1991; Knapp et al, 2007) and 35.6 million people worldwide, 0.5% of the global population. It costs over £20 billion per year in the UK, more than stroke, heart disease and cancer put together (ART, 2010). In 30 years the numbers of affected people will double to over one and a half million and the costs will rise at least three-fold to over £50 billion (Knapp et al, 2007; Comas-Herrera et al, 2007). Globally predictions are that the number of people with dementia will double every 20 years, to 65.7 million in 2030 and 115.4 million in 2050 (ADI, 2009). In the 2010 World Alzheimer Report (ADI, 2010), the global economic impact of dementias was estimated to be US$604 billion.

Dementia causes irreversible decline in global intellectual and physical functioning. It causes progressive decline in memory, reasoning, communication skills and the ability to carry out daily activities. Alongside this decline, individuals may develop behavioural and psychological symptoms in dementia (BPSD) such as agitation, aggression, wandering, shouting, repeated questioning, sleep disturbance, depression, and psychosis (Burns et al, 2009). These cause problems in themselves, which complicate care and can occur at any stage of the illness. BPSD have a major impact on those with dementia, as well as profound, negative effects on family members. Family carers are often old and frail themselves and have high levels of carer burden, depression and physical illness, and decreased quality of life (Ryu et al, 2005; Wetzels et al, 2010; Cohen-Mansfield et al, 1989).

Dementia has been made a national and international health and social care priority with the development of the National Dementia Strategy (DH, 2009), the Prime Minister's Challenge (DH, 2012) and the 2013 G8 Summit on dementia (DH et al, 2013). Better management of behavioural disturbance in dementia is a particular priority (DH, 2008). One issue that has been identified as of particular policy importance is the concern that the antipsychotic drugs that are commonly used to treat agitation and aggression may be doing more harm than good, with their use likely to be responsible for 1,800 extra deaths per year in the UK (Banerjee, 2009). The reduction of the use of these unsafe medications has therefore been made a government priority and research into safe effective alternatives has been made a cross-departmental government research priority, articulated unequivocally by the Prime Minister in his Challenge on Dementia (DH, 2012) and the outputs of the 2013 G8 Dementia Summit (DH et al, 2013).

4.1.1 Agitation in dementia

BPSD are common, occurring in up to 90% of patients (Burns et al, 2009), causing direct distress and risk, and complicating care at all stages of the illness. Agitation, defined as inappropriate verbal, vocal or motor activity, which is not an expression of unmet need, and encompasses physical and verbal aggression (Cohen-Mansfield et al, 1986), is particularly problematic affecting nearly 50% of people with Alzheimer's Disease (AD) over a month (Okura et al, 2010). Agitation is persistent, 80% of patients with clinically significant symptoms will have them six months later (Ryu et al, 2005). Agitation is associated with deteriorating relationships with family and professional carers, institutionalisation, increased costs of care, carer burden and burnout, and decreased quality of life (Ryu et al, 2005; Wetzels et al, 2010; Cohen Mansfield et al, 1989). Antipsychotic medication is the current mainstay of drug treatment for agitation and aggression in dementia (Banerjee, 2009). The evidence base includes gaps, contradictions and complexity but there is emerging consensus with respect to the level of use and risk of antipsychotic drugs for people with dementia. These drugs appear to have only a limited positive effect in treating symptoms but can cause significant harm to people with dementia (Gill et al, 2007; Rochan et al, 2008). However, some people do benefit from these medications and there are groups (eg where there is severe and complex risk or where psychosis drives agitation) where trials have not been completed but where there may be particular

value in using these medications (Ballard et al, 2006, 2009). In 2009 it was estimated that around 180,000 people with dementia were treated with antipsychotic medication across the country per year. In terms of negative effects that are directly attributable to the use of antipsychotic medication, use at this level equates to an additional 1,800 deaths and an additional 1,620 cerebrovascular adverse events, around half of which may be severe, per year (Banerjee, 2009). Antipsychotics should be reserved for only the most severe and complex cases of BPSD and non-drug treatment and watchful waiting should be tried first, yet their use as a first line treatment persists (Banerjee, 2009). No other drugs have a proven positive role in the treatment of BPSD. As a consequence atypical antipsychotics are the most commonly used drugs for the pharmacological treatment of agitated behaviours in dementia. Such treatment is largely unlicensed or 'off-label'; in most countries, few or no treatments have been given regulatory approval for such use. In the UK the only drug with a relevant license is risperidone, which is indicated for the "short-term treatment (up to 6 weeks) of persistent aggression in patients with moderate to severe Alzheimer's dementia unresponsive to non-pharmacological approaches and when there is a risk of harm to self or others". There is therefore an urgent need for a safe alternative effective medication.

Non-pharmacological interventions as first-line treatment for agitation in dementia is best practice (AS, 2011). However, there is a need for second line treatments when these fail, and the main reason for the widespread use of antipsychotics is the limited evidence for alternative treatments. Other drug treatments include anticonvulsants (carbamazepine and sodium valproate), and antidepressants (trazadone, citalopram) (Tariot et al, 1995, 1998) and acetylcholinesterase and NMDA inhibitors (donepezil, memantine). A meta-analysis concluded that sodium valproate was only effective at high doses that were associated with unacceptable side effects (Lonergan et al 2006). The results of double-blind placebo-controlled trials of trazadone have been disappointing (Teri et al 2000). Recent systematic reviews and meta-analyses concluded that carbamazepine, memantine and citalopram were the most likely candidates for effectiveness in treating agitation in dementia (Ballard et al, 2009; Henry et al, 2011). The results of trials of donepezil have been negative (Howard et al, 2007). A recent double-blind placebo controlled trial showed no effect on agitation of memantine and only an equivocal effect on BPSD as measured by the Neuropsychiatric Inventory (NPI) (Fox et al, 2012). In the US, the FDA has raised safety concerns about the SSRI antidepressant with the most evidence, citalopram (US FDA, 2012). A recent trial of citalopram for agitated behaviours on dementia (CitAD) showed positive outcomes for clinical variables but also confirmed these safety concerns for citalopram (Porsteinsson et al, 2014). The CitAD trial provides evidence that a target dose of citalopram 30mg per day has a positive effect on agitation in dementia however, the adverse cardiac effects identified in the trial, and to a lesser effect the cognitive impairment observed, limit its use in clinical practice (Banerjee, 2014). This evidence of antidepressant efficacy strongly supports the use of what is likely to be a safer antidepressant, mirtazapine.

Thus, agitated behaviours drive poor quality of life in dementia and poor outcomes including hospitalisation, care home placement and high cost. Available non-drug treatments are not always successful and the antipsychotic drugs used are associated with unacceptable increases in mortality and morbidity and also low clinical effectiveness.

4.1.2 Rationale for choice of interventions

4.1.2.1 Mirtazapine for agitated behaviours in dementia

The antidepressant mirtazapine is a centrally active presynaptic α2antagonist, which increases central noradrenergic and serotonergic neurotransmission. The enhancement of serotonergic neurotransmission is specifically mediated via 5-HT1 receptors, because 5-HT2 and 5-HT3 receptors are blocked by mirtazapine. Both enantiomers of mirtazapine are presumed to contribute to the antidepressant activity, the S(+) enantiomer by blocking α2 and 5-HT2 receptors and the R(-)

enantiomer by blocking 5-HT3 receptors. The histamine H1-antagonistic activity of mirtazapine is responsible for its sedative properties. It has practically no anticholinergic activity unlike citalopram, and, at therapeutic doses, has minimal effects on the cardiovascular system. Mirtazapine is a relatively potent antagonist/inverse agonist at key receptors likely to be pivotal in target symptoms including antagonism of a2-adrenergic, 5HT1A and histamine H1 receptors. The overall effects are to increase noradrenergic and serotonergic neurotransmission which may explain its use in depression while the H1 antagonism is associated with useful acute sedative benefits. It is an established treatment for depression and is well tolerated by older people. Psychiatrists and care home staff will be familiar with its use. It is available generically at low cost in the NHS (£3.71 for 28 45mg tablets), therefore were it found to be an effective treatment, cost implications will be minimal. In pre-specified secondary analyses of the HTA-SADD trial which investigated the use of mirtazapine for depression in dementia (Banerjee et al, 2013), there was a positive effect of mirtazapine on decreasing BPSD (as measured by NPI score) at 13 weeks. Taking the top 50% of raw NPI scores (ie those with appreciable BPSD) there was a 7.1 point difference in NPI score (95%CI -0.50 to 14.68; p=0.067) between mirtazapine and placebo and a 13.2 point difference between mirtazapine and sertraline (95%CI 4.47 to 21.95; p=0.003). An additional encouraging finding from the cost effectiveness analyses was that over the trial, the time spent by unpaid carers caring for participants in the mirtazapine group was almost half that for patients in the placebo group (6.74 vs 12.27 hours per week) and sertraline group (6.74 vs 12.32 hours per week). Informal care costs were £1,510 (95% CI 3088 to -136) and £1,522 (95% CI -3,398 to -72) less for the mirtazapine-treated group when compared with placebo and sertraline respectively. In the secondary outcome evaluation, looking at quality of life gains and costs, treatment with mirtazapine had a high likelihood of cost-effectiveness compared to placebo or sertraline (Banerjee et al, 2013; Romeo et al, 2013). The improvements in quality of life for mirtazapine relative to the other treatments contributed to the cost-effectiveness result. It is plausible that this improvement comes from amelioration of sleep disturbances and anxiety (Schittecatte et al, 2002; Muhlbacher et al, 2006). Improvements in sleep could potentially improve quality of life for both patients and carers, and release carer time directly (Naglie et al, 2006). Two small scale open label pilot studies give supportive evidence for the potential of a trial in this area (Cakir et al, 2008 [those on mirtazapine did better]; Reichman et al, 2003 [NPI decreased by 5.8 points]). HTA SYMBAD will be the first placebo controlled RCT of mirtazapine for agitation in dementia.

4.1.2.2 Carbamazepine for agitated behaviours in dementia

Carbamazepine stabilises the inactivated state of voltage-gated sodium channels and potentiates GABA receptors. It is used for epilepsy, prophylaxis of bipolar disorder and trigeminal neuralgia. It is generally safe within the proposed dose ranges. There are few data on people with AD, but its use does not seem to be associated with an increase in mortality as in antipsychotics for AD (Hollis et al, 2007). Carbamazepine has been widely used in psychiatric disorders and AD to treat symptoms including agitation, aggression, irritability, and impulsivity. Open label studies and case reports have indicated promise in agitation in AD (Tariot et al, 1994). Two small 6 week parallel group RCTs of carbamazepine for BPSD have been published (Tariot et al, 1998; Olin et al, 2001). The first in 55 patients (modal dose 300mg) showed significant symptom decrease. It was well tolerated with no decrease in cognition, function or increased side effects relative to placebo. The second (400mg in 21 patients not responding to antipsychotics) showed a trend but not a significant advantage over placebo. Meta-analysis indicated significant benefit compared with placebo treatment on the Brief Psychiatric Rating Scale (mean diff -5.5 points, 95% CI -8.5 to -2.5 points) and on the Clinical Global Impression Scale (OR 10.2, 95% CI 3.1 to 33.1) (Ballard et al, 2009). A third small trial of the similar compound oxcarbazepine (n=103) indicated a trend towards benefit (p=0.07) with active drug performing better than placebo in all analyses (Sommer et al, 2009).

4.1.3 Trial duration

Agitated behaviours in dementia are different from the core cognitive or functional outcomes most often studied in dementia. For a treatment for agitation in dementia to be useful in clinical practice, it needs to be effective quickly. The primary outcome for the trial will test 12 weeks of masked treatment. Data from preliminary studies and experience with mirtazapine and carbamazepine suggest that beneficial effects emerge within a 4 to 12 week time frame. Comparisons at these time points are important secondary questions. Although the trial will close in all sites following completion of assessments in all patients for the 12 week intervention, assessment of longer term effects of 12 weeks of treatment on CMAI, treatment status, institutional transition and death will be completed by means of telephone follow-up at 26 and 52 weeks.

4.1.4 Explanation for choice of comparator

Active treatments described above will be compared with matched placebo. Usual care will be provided to all patients in the trial. The use of placebo is justified as there is genuine uncertainty as to whether either of the active interventions will be better than no treatment. Treatment is blinded to reduce potential bias as the main outcome measures are patient reported outcomes.

4.1.5 Risks mitigation strategy

In this trial our primary concern is the safety of participants. There are risks to all medications, in the case of mirtazapine and carbamazepine these are well understood. Mirtazapine and carbamazepine have been widely prescribed, including to older adults in general and those with dementia for a number of years. Although agitation in dementia is a new indication, the side effects are expected to be the same as in the current versions of the SmPCs. As the trial is blinded we have considered the contraindications of both drugs when entering patients into the trial, and they are considered together here.

Our risk mitigation strategy includes the addition of actions that may not be part of routine clinical practice by community mental health services in the management of agitation in dementia with mirtazapine and carbamazepine. So, the doses of carbamazepine that will be used are low in comparison to the doses often used in epilepsy so dose-related side effects should be minimised. The mirtazapine dose is within the normal dosage range. These actions include the careful monitoring for harms including side effects and adverse events that is a core element of the study. However in addition we are adding a set of safety blood tests (FBC, U&Es & LFTs) and, ECG testing at baseline and at the study end. Gradual dose escalation will also be used to help to minimise side effects.

The IMP in this trial is contraindicated in patients with atrioventricular block, a history of bone marrow depression or history of hepatic porphyrias as per the SmPC for carbamazepine and these are reflected in the exclusion criteria.

The blood tests and the ECG will help us to give careful consideration and to instigate monitoring if needed to patients with; moderate to severe renal impairment (creatinine clearance <40ml/min), hepatic impairment, cardiac diseases (such as conduction disturbances, angina pectoris and recent myocardial infarction), low blood pressure, diabetes and any other conditions as listed in the current versions of the SmPCs. Decreased platelet or white blood cell counts occur occasionally to frequently in patients taking carbamazepine. Blood counts including platelets and reticulocytes will be taken at

baseline and after 12 weeks of dosing. Further blood tests may be ordered during the trial if clinically indicated.

There is a well-recognised risk of drug interactions which will be managed by increased monitoring or through exclusion of some categories of drugs, as listed in the exclusion criteria.

An increase in suicidal thoughts has been observed as a rare effect in the early stages of treatment with antidepressants. We have therefore included the Columbia Suicide Severity Rating Scale (C-SSRS) at baseline and at the 6 and 12 week assessment timepoints to monitor this, again the PI will have access to these data following baseline assessment and from subsequent visits. Hyponatraemia is also a recognised rare side effect of antidepressant medication and the baseline and 12 week U&Es will allow us to monitor this.

4.2 Objectives

The overall trial aim is to assess the safety, clinical and cost effectiveness of mirtazapine and carbamazepine in the treatment of agitation in dementia.

The null hypothesis is that there is no difference in CMAI scores between patients treated with placebo and mirtazapine, and between patients treated with placebo and carbamazepine, at 12 weeks.

4.2.1 Primary objectives

Each drug is assessed independently, thus the primary objectives are:

To determine if mirtazapine is more clinically effective in reducing agitated behaviours in dementia than placebo, measured by CMAI score 12 weeks post randomisation.

To determine if carbamazepine is more clinically effective in reducing agitated behaviours in dementia than placebo, measured by CMAI score 12 weeks post randomisation.

4.2.2 Secondary objectives

Each drug is assessed independently, thus the secondary objectives are:

1 To determine if mirtazapine and carbamazepine are more cost-effective than placebo at 12 weeks post randomisation,
2 To determine if mirtazapine and carbamazepine are more clinically and cost effective than placebo in reducing CMAI score at 6 weeks post randomisation,
3 To determine differences in effectiveness between mirtazapine and carbamazepine and placebo on patient and carer,
4 To determine whether there are differences between the groups in adverse events and adherence,
5 To determine differences between carbamazepine and mirtazapine in effect on agitation by CMAI score 6 and12 weeks post randomisation and in adverse events and adherence, conditional on evidence of effectiveness of one IMP over placebo,
6 To determine long term differences between those randomised to placebo, carbamazepine and mirtazapine in three way head-to-head comparisons of agitation (measured by CMAI score), institutionalisation, death and clinical management at 26 and 52 weeks post-randomisation.

4.3 Trial Design

This is a pragmatic, multi-centre, double blind, placebo controlled superiority RCT of safety, clinical and cost effectiveness of mirtazapine and carbamazepine (all with usual care) at 6 and 12 weeks on agitated behaviours in dementia. We will include a long term follow up period to allow limited assessment of longer term outcomes at 26 and 52 weeks. An internal pilot phase will assess trial recruitment, with progression to a full trial dependent on the number of patients recruited after approximately 25% of the recruitment period.

Reasons for non-participation and non-consent to the trial, particularly acceptance of randomisation by patients, carers and clinicians will be continuously reviewed with trial procedures modified where appropriate to maximise efficiency in trial recruitment and retention.

4.3.1 Internal pilot phase

An internal pilot phase is designed to allow an assessment of stop/go criteria for progression to a full trial. At the end of this phase a decision will be made by the funder, in consultation with the TSC and IDMC, on whether or not to proceed with the trial. Recruitment will continue while data on patients in the internal pilot are analysed and reviewed by the TSC and IDMC and a funder decision is obtained. As an internal pilot, all data collected on study participants will be included in the further analyses. Clear progression criteria have been defined and agreed with the funder, TSC and IDMC.

The single primary progression criterion is based on accrual after 25% of the recruitment period. With staged site initiation anticipated over 3 months this would occur in month 14 of the study. With the expected recruitment rate relatively slower at first and then accelerating, we anticipated that approximately 20% of the recruitment target should have been reached by this point (n=94).

The objective of the pilot phase is to assess the number of patients recruited to the trial by month 14 of the study.

5 Methods

5.1 Site Selection

The trial sponsor has overall responsibility for site and investigator selection.

5.1.1 Study Setting

Participants will be drawn from existing patients and new patient referrals to old age psychiatric services, memory clinics and those in care homes in eight regional centres in England (Sussex, South London, North London, Cambridge, Birmingham, Norfolk, Manchester and Newcastle).

In the trial pathway, research workers will identify existing patients from a variety of sources including from case workers and care homes and advertisements for the study such as on the Join Dementia Research website. Notes will be reviewed and case workers consulted to ascertain if non-drug treatment conforms to the algorithm for adequate trial of non-pharmacological treatment for BPSD (AS/DH 2011 see Appendix 1). The AS/DH algorithm is published by the Alzheimer's Society. It provides a balanced, detailed approach which covers cases where situations are urgent, and which is specific about the content of the non-pharmacological approaches to be taken including the need to understand and address determinants of agitation. If a research worker identifies a new case where the algorithm has not been followed, then the clinical teams at home in the community or in care homes will be requested to provide treatment according to the AS/DH algorithm prior to reassessment.

Participants will remain under the care of their usual health services throughout their time on the trial. The only change to the usual care pathway is randomisation to the three trial arms and dispensing to them of mirtazapine, carbamazepine or placebo. Dispensing and delivering the trial medication to participants will be the responsibility of the trial research workers under the supervision of local PIs. The patient's usual clinical team will be informed of the patient's participation in the trial. Their usual clinical team can modify the dose of IMP during the trial within three dosing levels to manage perceived side effects and can initiate treatment with rescue therapy see section 5.4.9 at any time in the trial.

5.1.2 Site/Investigator Eligibility Criteria

Once a site has been assessed as being suitable to participate in the trial, the trial team will provide them with a copy of this protocol and the Summary of Product Characteristics (SPC) for both mirtazapine and carbamazepine.

To participate in the HTA-SYMBAD trial, investigators and trial sites must fulfil a set of criteria that have been agreed by the HTA-SYMBAD Trial Management Group (TMG) and that are defined below.

Eligibility criteria:

- A named clinician is willing and appropriate to take Principal Investigator responsibility
- Named research workers are available to be the main contacts with patients and carers to take informed consent, complete all trial assessments, manage drug supply from the site pharmacy and to complete trial CRFs
- The site has a pharmacy that is able to store and dispense IMP appropriately

Trial sites meeting eligibility criteria and that are accepted by the TMG as being suitable to recruit to the trial, will be issued with the HTA-SYMBAD Trial Master File (TMF) documentation to use when applying for Site-Specific Approval (SSA).

5.1.2.1 Principal Investigator's (PI) Qualifications and Agreements

The investigator(s) must be willing to sign a NCTU Clinical Trial Agreement and an Investigator Agreement to comply with the trial protocol (confirming their specific roles and responsibilities relating to the trial, and that their site is willing and able to comply with the requirements of the trial). This includes confirmation of appropriate qualifications, provision of appropriate training and supervision of Research Workers, familiarity with the appropriate use of the investigational products, agreement to comply with the principles of GCP, to permit monitoring and audit as necessary at the site, and to maintain documented evidence of all staff at the site who have been delegated significant trial related duties.

5.2 Site approval and activation

The Clinical Trial Authorisation (CTA) for the trial requires that the Medicines and Healthcare products Regulatory Agency (MHRA) is supplied with the names and addresses of all participating site Principal Investigators. Trial staff at NCTU will perform this task.

Written confirmation of receipt will be sent to the site PI on receipt of the signed Clinical Trial Agreement and Investigator Agreement, approved delegation of responsibilities log and staff contact details, which should include all Research Workers in each site responsible for any trial procedures. The trial manager or delegate will notify the PI in writing of the plans for site initiation. Sites will not be permitted to recruit any patients until a letter of site activation has been issued. The Trial

Manager or delegate will be responsible for issuing this after a green light to recruit process has been completed.

The site and all affiliated Research Workers must conduct the trial in compliance with the protocol as agreed by the Sponsor and, by the MHRA, and which was given favourable opinion by the Research Ethics Committee (REC). The PI or delegate must document and explain any deviation from the approved protocol, and communicate this to the trial team at NCTU.

A list of activated sites may be obtained from the Trial Manager.

5.3 Participants

5.3.1 Eligibility Criteria

Given the established safety profile of the IMPs, exclusion criteria have been minimised as much as safely possible in order to maximise generalisability.

5.3.1.1 Participant Inclusion criteria

- Patients with a clinical diagnosis of probable or possible Alzheimer's Disease using National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria (McKhann et Al, 1984 – see appendix 2)
- a diagnosis of co-existing agitated behaviours
- evidence that the agitated behaviours have not responded to management according to the AS/DH algorithm (AS/DH, 2011 appendix 1)
- If patients are taking cholinesterase inhibitors or memantine, they must be on a stable dose (defined as three months on current dose)
- An assessment of Cohen Mansfield Agitation Inventory (CMAI; Cohen-Mansfield et al, 1989, Long form, see appendix 3) score of 45 or greater
- Written informed consent to enter and be randomised into the trial
- Availability of a suitable informant (consenting identifiable family carer or paid carer) to provide information on carer-completed outcome measures and who consents to take part in the trial.

5.3.1.2 Participant Exclusion criteria

- Current treatment with antidepressants (including MAOIs), anticonvulsants, or antipsychotics. Patients must have completed treatment with these medications at least two weeks before trial drug administration.
- Contraindications to the administration of carbamazepine and mirtazapine as per their current SmPCs
- Patients with atrioventricular block, a history of bone marrow depression or history of hepatic porphyrias
- Cases too critical for randomisation (ie where there is a suicide risk or where the patient presents a risk of harm to others)
- Female subjects under the age of 55 of childbearing potential, defined as follows: postmenopausal females who have not had at least 12 months of spontaneous amenorrhea or 6 months of spontaneous amenorrhoea with serum FSH>40mIU/ml or females who have not had a hysterectomy or bilateral oophorectomy at least 6 weeks prior to enrolment.

5.3.2 Participant selection

There will be no exceptions (waivers) to eligibility requirements at the time of randomisation. Questions about eligibility criteria should be addressed prior to attempting to randomise the participant.

The eligibility criteria for this trial have been carefully considered and are the standards used to ensure that only medically appropriate participants are entered. Participants not meeting the criteria should not be entered into the trial for their safety and to ensure that the trial results can be appropriately used to make future treatment decisions for other people with similar diseases or conditions. It is therefore vital that exceptions are not made to these eligibility criteria.

Participants will be considered eligible for enrolment in this trial if they fulfil all the inclusion criteria and none of the exclusion criteria as defined above.

5.3.3 Co-enrolment Guidance

Participants will not be permitted to enrol in this trial if they have been enrolled in any other clinical trials of investigational medicinal products in the previous 6 months. This will be assessed by questioning the patient's carer as part of the screening exercise. HTA-SYMBAD screening failures will be permitted to re-screen providing this does not cause distress to the patient or carer. The screening log will record details of re-screening in the event that this occurs.

5.3.4 Participant Timeline

Assessment	Baseline[c]	Rx visit (0-7 days after baseline)	Week 2 (12-16 days after randomisation)***	Week 4 (21-35 days after randomisation)***	Week 6 (35-49 days after randomisation)[c]	Week 12 (77-91 days after randomisation)[c]	Week 16 (105-119 days after randomisation)***	Week 26* (wk 25-27)	Week 52* (wk 51-53)
Consent	X								
Cohen Mansfield Agitation Inventory CMAI (Long form)	X				X	X			
Safety Bloods FBC, U&Es, LFT	X[a]					X[b]			
Electrocardiogram (ECG)	X[a]					X[b]			
Client Service Receipt Inventory CSRI**	X				X	X			
Disease specific Quality of Life DEMQOL	X				X	X			
Carer assessed disease specific Quality of Life DEMQOL-Proxy	X				X	X			
Generic Quality of Life EQ-5D-5L	X				X	X			
Cognitive impairment sMMSE	X				X	X			
Behavioural and psychological	X				X	X			

symptoms in dementia BPSD-NPI									
Columbia Suicide Severity Rating Scale C-SSRS (Cognitively impaired version)	X				X	X			
Randomisation		X							
Dispensing		X			X				
Adherence			X	X	X	X			
Adverse events			X	X	X	X	X		
Medication assessment (for dose changes)			X	X	X				
Use of rescue medications					X	X			
Concomitant medications	X	X	X	X	X	X			
Withdrawal of treatment			X	X	X	X			
Carer mental health GHQ-12	X				X	X			
Carer quality of life EQ-5D-5L	X				X	X			
Carer burden index Zarit CBI	X				X	X			
Carer proxy report of CMAI score***								X	X

Carer proxy report of treatment***								X	X
Institutionalisation***								X	X
Death***								X	X

* Longer term assessments will be undertaken by site research workers employed on the research grant whilst the research sites remain open, and by Centre of Dementia Studies (CDS) staff at BSMS when the sites have closed.

**Medication and health service use may also be accessed from GP records by research workers.

*** At weeks 2, 4, 16, 26 and 52, carers will be contacted by telephone. All other visits will take place in the patient's place of residence, unless the patient requests otherwise.

[a] May utilise existing results (if available) up to 28 days prior to randomisation date.

[b] Ideally these tests would be done at week 12 visit, but may be done up ±14 days after last dose of study medication if required.

[c] Face-to-face visits may take place over more than one visit if required, particularly if blood/ECG tests are to be collected.

5.3.5 Patient assessments

Clinicians working in the settings described in 5.1.1 will be asked to identify potential patients to the site SYMBAD PI or research worker using a simple pro forma. On receipt of this information prior adherence to the AS/DH algorithm will be ascertained by the SYMBAD research worker. All potential patients will be recorded on a registration log. Recorded details will include name and contact details of the patient (and carer where available at this point), details of referral mechanism and evidence of adherence to the AS/DH algorithm. This will be supplemented with details of the patient's main carer once these become available. Patients will not be excluded where they are referred into the trial through other mechanisms. The trial will be advertised on websites such as the Join Dementia Research website, which may also be a source of referral into the trial. Referred patients meeting eligibility criteria at this point will have patient information sent to them and to a possibly un-named at this point carer by post. Following this, the research worker will contact them/their carer by phone to ascertain their interest in discussing trial participation further. If they express interest an appointment will be made for the research worker to visit the patient and their carer in their place of usual residence. These will be documented in site specific working instructions.

The study team will aim to conduct all study visits at the patient's place of usual residence (as recorded on the screening log), including community nurse visits for bloods to be taken and an ECG performed. If this is not possible the patient will be requested to attend their nearest phlebotomy/ECG facility (primary or secondary care) for blood tests/ECG. All other study procedures will take place at their usual place of residence, unless another venue is requested by the patient. Where the patient's place of usual residence changes during the course of the trial, this information will also be recorded in their participant notes. It is important that an accurate place of usual residence is recorded so that the longer term follow up can be fulfilled.

5.3.5.1 Screening home visit

The screening home visit will be scheduled to take place in the presence of the patient's named carer. If the named carer is unavailable the visit will be re-scheduled as appropriate. The research worker will go through the information in the information sheets in detail, and will give the individuals as much time as they require to answer any questions they have about participation in the trial. If they wish to participate in the trial then consent will be taken to join the study. The research worker will make an assessment of the capacity of the patient before proceeding with a consent process that is appropriate for them, including considering the provision of assent by the patient and consent on their behalf by their legal representative. If the patient has capacity to consent, the carer will consent to the provision of information on data for measures on the patient (eg CMAI) and also on themselves in terms of impact.

The patient/carer will be informed prior to consenting that recruitment to the trial is dependent on the results of the screening CMAI assessment, blood tests and ECG, with confirmation by the site PI that they consider the patient to be eligible. The CMAI and other baseline assessments as described in section 5.3.4 will be undertaken. Where a patient has a CMAI score of 45 or greater, the research worker will make a recommendation to the PI that the patient is eligible to join the trial. The patient/carer will be informed of this recommendation intention before the end of the home visit, and will be told that the research worker will contact them in the next week to inform them of their non-participation (in the event that the PI considers them to be ineligible for any clinical reason) or to arrange to deliver their trial medication to them.

The research worker may need to arrange a separate visit (either by a community nurse to the patient, or the patient to visit a local phlebotomy service) for their blood tests and ECG. Where the

patient has already had the requisite blood tests or an ECG, within the allowable timeframe of 28 days the results will be recorded from their medical notes and the test will not need to be repeated.

5.3.5.2 Randomisation

Once a patient's screening CMAI score has been assessed as being ≥45, the research worker will discuss the case with the site PI who is permitted to prescribe IMP. The PI will confirm or not the patient's eligibility to join the study, and on confirmation the research worker will use an on-line randomisation system to randomise the patient to the trial. This system requires confirmation of eligibility criteria. It will then provide a study number and IMP medication number. Details of the randomisation, including patient registration, randomisation and IMP allocation numbers will be confirmed by email to the research worker, site PI, central site pharmacist and co-ordinating team at NCTU. The PI will provide a signed prescription for the patient's trial medication. The research worker will collect this prescription from the central pharmacy and will deliver it to the patient at a scheduled baseline IMP delivery visit. Local policies for treating patients outside of their registered NHS Trust will be followed as appropriate.

5.3.5.3 First trial medication delivery visit

At this visit the research worker will discuss the trial medication prescription with the patient and their carer. They will be informed of the frequency and planned dosing of trial medication, and answer any questions the patient or carer may have. A 6 week supply of trial medication will be given to the patient's carer with instructions to take 1 capsule daily for the first 2 weeks, as a single dose at night.

Patients will be given a diary card at this visit and their carer instructed to record on it any deviations from the prescription the patient makes, and any side effects they notice. These will be reviewed at subsequent visits and will act as an aide memoire when reporting on adverse effects of the trial medications. The diary card should also be used to record any changes to medication as a result of advice from clinicians involved in the patient's care.

5.3.5.4 Two and four week medication assessment calls

Two weeks after the patient takes their first trial medication the research worker will phone their carer to discuss their treatment. The call will follow a structured written pro forma that will record details of adherence to medication prescription, changes to concomitant medications and reports of any adverse effects. Carers of patients without limiting issues including toxicity will be instructed to increase the trial medication by one capsule to two capsules. Where limiting issues are reported, the dose of trial medication prescribed should remain the same or the patient should be taken off trial medication. This will be determined by the site PI who will discuss all such cases with the research worker who will then feed back to the carer. This procedure will be repeated another 2 weeks later (four weeks after the patient takes their first trial medication), with a similar assessment to inform whether a patient should be dose escalated to a further capsule daily (maximum of 3 capsules daily), remain on the current dose, or be dose reduced or taken off trial medication as appropriate.

In the absence of symptoms clinical judgement will determine whether or not to escalate the trial medication dose or to remain on the current dose. A balanced consideration will take into account the fluctuating nature of symptoms over the disease course, the perspective of the carer and patient, and the potential negative impact on the results of the study and their interpretation if a large proportion of patients do not take the higher dose of trial medication. It is important that within the constraints of the trial emphasis is placed on reaching a therapeutic effect that can be generalised to a wide population.

5.3.5.5 Week 6 home visit

At this visit the full range of assessments described in the table of assessments in section 5.3.4 of the protocol will be performed. A further 6 week's supply of trial medication will be dispensed to the patient.

5.3.5.6 Week 12 home visit

At this visit the full range of assessments described in the table of assessments in section 5.3.4 of the protocol will be performed. Safety bloods and an ECG will be taken, if necessary the bloods may be collected at a separate visit, as per baseline blood collection. Bloods and ECG should take place within ±14 days of study drug discontinuation.

5.3.5.7 Week 16 phone call

At week 16 a phone call will be made to the carer to ask about any Adverse Events in the previous 4 weeks.

5.3.5.8 Week 26 and 52 phone calls

At weeks 26 and 52 a phone call will be made to the carer and the shorter range of assessments described in section 5.3.4 of the protocol will be completed. This phone call will be performed by the research worker whilst the research sites remain open, but will be performed by Centre of Dementia studies staff at BSMS once the sites have closed.

5.3.6 Consent

Written informed consent to enter and be randomised into the trial must be obtained from participants and their named carer, after explanation of the aims, methods, benefits and potential hazards of the trial and before any trial-specific procedures are performed. The only procedures that may be performed in advance of written informed consent being obtained are those that would be performed on all patients in the same situation as a usual standard of care.

The provision of informed consent to participate in the trial includes consenting to randomisation, to receiving and taking trial medication, to having blood tests and an ECG and to participating in trial follow up as described in the protocol and the participant information sheet. Patients will be requested to consent to their GP records being accessed as part of the trial, for supplementary data to be collected on any medications they are taking and on their health service use. Carers will be requested to consent to provide data for measures on the patient (eg CMAI) and on themselves in terms of impact of the protocol on their routines associated with the patient. Carers will also be requested to consent to help the patient take their medication as instructed and to complete the diary cards where appropriate.

A short version of the patient information sheet will be designed for those patients who are deemed not to have the capacity to consent for themselves. Research workers will be trained in making an individualised assessment of capacity of patients. Training materials will enable them to structure their assessment and decision making in this regard. Where patients are considered not to have capacity, a personal legal representative will be asked to consent on their behalf, and the patient will be asked to provide assent where considered appropriate. Where there is no personal legal representative available a professional legal representative will be sought.

The Principal Investigator (PI) retains overall responsibility for the informed consent of participants at their site and will ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki.

The right of a participant or carer to refuse participation without giving reasons will be respected. The participant and their carer will remain free to withdraw from the trial at any time without giving reasons and without prejudicing his/her further treatment and will be provided with a contact point where he/she may obtain further information about the trial. The consent process for this trial is one of dual consent. A patient will only be permitted to be on the trial if they have a named carer who is also willing to consent to the trial. In the unlikely event of the withdrawal of a carer's consent within the treatment phase, a suitable alternative named carer who consents to participate and provide the necessary ratings will be sought. In the absence of a suitable replacement carer, the patient will be withdrawn from treatment in the trial if the patient so wishes. If the patient continues to give consent, or if incapable and a new legal representative agrees to the participant's continuation, then data will continue to be collected. Consent will be re-sought if new information becomes available that affects the participant's consent in any way. This will be documented in a revision to the patient/carer information sheets and the participant and their carer will be asked to sign an updated consent form. These will be approved by the ethics committee prior to their use. Consent will also be re-sought if the participant's named carer changes.

The PI takes responsibility for ensuring that all vulnerable subjects are protected and participate voluntarily in an environment free from coercion or undue influence.

A copy of the approved consent forms are available from the NCTU trial team.

Patient and carer information and consent forms have been designed following NRES Guidance, and have had input from consumer representatives to ensure they are fit for purpose. The main potential ethical issue in this study is that dementia itself may interfere with an individual's ability to give informed consent. Where possible, fully informed written consent will be obtained from patients entering the HTA-SYMBAD study. However, some potentially suitable patients will have moderate or severe dementia and may lack the necessary mental capacity to give this. The aims of the study are incompatible with simply entering patients with milder degrees of dementia, as it is important to ensure that the findings can be generalised to clinical practice, where the majority of patients receiving treatment for behavioural disorder will have more severe illness. For a representative patient group to be randomised it must therefore include a proportion who lack capacity. In this situation the patient's agreement to participate will still be obtained to their best level of understanding and recruitment will not proceed if they refuse or show significant distress. In line with The Medicines for Human Use (Clinical Trials) Regulations 2004, consent will be also obtained from the patient's 'personal legal representative'. This person would most likely be the patient's main carer, who would have best knowledge of the individual's attitudes and stated preference to research and consequently best placed to judge whether they would have wished to participate if they had capacity. Except in the case where a professional carer (eg a care home worker or a home care worker) is the carer informant, if no suitable person is available to act as the patient's legal representative, they will be ineligible for the study. This is on scientific grounds because the scenario where we would need to use professional legal representatives unconnected with the day to day care of the potential participant suggests there is no one who knows the patient well enough to act as an informant to generate outcome data. It is likely that only a small number of participants entering HTA-SYMBAD may lose capacity during the 12 week course of the study. At entry patients will be asked whether they wish to be withdrawn at this point or a decision be made by their personal legal representative as described above.

5.3.7 Early Stopping of Follow-up

If a participant chooses to discontinue their trial treatment, they should continue to be followed up as closely as possible to the follow-up schedule defined in the protocol, providing they are willing. They should be encouraged and facilitated not to leave the whole trial, even though they no longer take the trial treatment. If, however, the participant exercises the view that they no longer wish to be followed up either, this view must be respected and the participant withdrawn entirely from the trial. NCTU should be informed of the withdrawal in writing using the appropriate HTA-SYMBAD trial documentation. Although not obliged to give a reason for discontinuing their trial treatment, a reasonable effort should be made to establish this reason, whilst remaining fully respectful of the participant's rights. Data already collected will be kept and included in analyses according to the intention-to-treat principle for all participants who stop follow up early.

Participants who stop trial follow-up early will not be replaced.

In consenting to the trial, patients are consenting to trial treatments, trial follow-up and data collection. However, an individual participant will stop treatment early or be stopped early for any of the following reasons:

- Unacceptable treatment toxicity or adverse event
- Inter-current illness that prevents further treatment
- Any change in the participant's condition that in the clinician's opinion justifies the discontinuation of treatment
- Withdrawal of consent for treatment

5.3.8 Participant Transfers

If a participant moves from the area, making continued follow up at their consenting centre inappropriate, every effort should be made for them to be followed at another participating trial centre. Written consent should be taken at the new centre and then a copy of the participant's CRFs and all eCRF data should be provided to the new centre. Responsibility for the participant remains with the original consenting centre until the new consent process is complete.

5.3.9 Loss to Follow-up

Contact details will be stored at participating sites for both patients and their carers. Given the nature of the condition that the patients suffer and the community involvement in their care provision, it is not anticipated that loss to follow up will be a problem in the trial. However, loss to follow up will be monitored by the Trial Management Group.

5.4 Interventions

There are three trial arms: (i) mirtazapine, (ii) carbamazepine and (iii) placebo, all with usual clinical care. To maintain the double-blind the two medications and the placebo are provided in identical capsules and prescribed at a dose of 1, 2 or 3 capsules per day, dose escalating at weeks 2 and 4 . The doses for mirtazapine will be 15mg, 30mg and 45mg and for carbamazepine (modified release preparation to allow once daily dosage) 100mg, 200mg and 300mg. The dosing protocol will start participants on 1 capsule with the expectation of increasing to 2 capsules at two weeks, and 3 capsules at four weeks. Medication will be given in a single dose at night. For those with side effects clinicians will have the option of continuing with the same or a lower dose as considered appropriate.

5.4.1 Treatment Schedule, dose modifications, interruptions and discontinuations

For the first two weeks of treatment patients will receive:

Carbamazepine 100mg (1 capsule), Mirtazapine 15mg (1 capsule), or Placebo (1 capsule) as a starting dose.

At weeks 2 and 4 (defined as day 12-16 and day 24-32 respectively), carers will be contacted by telephone and questions concerning adverse effects and adherence completed. Those with limiting issues will either remain on the starting dose or will stop study drug. Those without dose limiting issues will move to the next dose level. This dose escalation assessment will continue on a 2 weekly basis until the patient reaches the highest dose of 3 capsules per day. The last dose escalation assessment will be made at 4 weeks. If patients do not have their treatment dose escalated at 4 weeks they will not have it escalated again during the remainder of the 12 week treatment period.

With the above exceptions resulting from dose reductions, from week 4 until the primary endpoint of the trial, participants will receive:

Carbamazepine 300mg (3 capsules), Mirtazapine 45mg (3 capsules), or Placebo (3 capsules).

Dose adjustments can be made by reducing back to 2 capsules daily or to 1 capsule daily in participants experiencing troublesome side effects. Patients experiencing side effects that warrant reducing from the single capsule dose will be taken off treatment.

Treatment interruptions are not planned. If a patient comes off treatment they will not be re-started on treatment in the trial.

At the end of the treatment phase of the trial, the patient's clinician will continue to treat them as usual but with the added knowledge of their participation in the trial. They will not at this stage know which treatment the patient was allocated whilst on trial.

5.4.2 Non-pharmacological interventions

Non pharmacological interventions are permitted to be provided as part of treatment as usual in all patients.

5.4.3 Usual clinical care

Usual clinical care in all groups will include all care and support deemed needed by the community mental health services including: case management by a key worker, review by team members, continued non-drug treatment and support, carer support and social care. These "usual care" inputs will be recorded for all participants by the research worker. The detail of non-pharmacological and usual care interventions deployed by the referring team will be recorded in the CRF.

5.4.4 Arm A - Mirtazapine

5.4.4.1 Mirtazapine

Mirtazapine is licensed for use in the UK to treat major depressive disorder. The effective daily dose is usually between 15 and 45mg with a 15 or 30mg starting dose. It is not currently licensed to treat agitation in dementia patients.

Mirtazapine has a tetracyclic chemical structure and belongs to the piperazino-azepine group of compounds. It is designated 1,2,3,4,10,14b-hexahydro-2-methylpyrazino[2,1-a] pyrido [2,3-c] benzazepine and has the empirical formula of C17H19N3. Its molecular weight is 265.36.

5.4.4.2 Dispensing

Mirtazapine will be dispensed in 15mg blinded capsules and will follow the schedule described in 5.4.1 above.

5.4.4.3 Dose Modifications, Interruptions and Discontinuations

Using mirtazapine together with ethanol can increase nervous system side effects such as dizziness, drowsiness, and difficulty concentrating. Some people may also experience impairment in thinking and judgment. Patients should be instructed to avoid or limit the use of alcohol while being treated with mirtazapine.

The dose should be lowered or discontinued if the patient experiences any unacceptable toxicities or adverse events. Patients taking concomitant medications should be carefully monitored, a list of medications requiring extra caution is given in section 5.4.8. Any other contraindications in the SmPC should also be considered when prescribing the trial drug.

5.4.5 Arm B - Carbamazepine

5.4.5.1 Carbamazepine

Carbamazepine is licensed in the UK to treat seizures and nerve pain such as trigeminal neuralgia and diabetic neuropathy. It is also used to treat bipolar disorder. It is not currently licensed to treat agitation in dementia patients. The active ingredient is 5H-dibenzo[b,f]azepine-5-carboxamide.

5.4.5.2 Dispensing

Carbamazepine will be dispensed in 100mg blinded capsules and will follow the schedule described in 5.4.1 above.

5.4.5.3 Dose Modifications, Interruptions and Discontinuations

Using carbamazepine together with ethanol can increase nervous system side effects such as dizziness, drowsiness, and difficulty concentrating. Some people may also experience impairment in thinking and judgment. Patients should be instructed to avoid or limit the use of alcohol while being treated with carbamazepine.

The dose should be lowered or discontinued if the patient experiences any unacceptable toxicities or adverse events. Patients taking concomitant medications should be carefully monitored, a list of medications requiring extra caution is given in section 5.4.8. Any other contraindications in the SmPC should also be considered when prescribing the trial drug.

5.4.6 Accountability

Study drug is only to be prescribed by the trial Principal Investigators, for the patients within the trial as specified in this protocol.

Investigational medicinal product supply will be coordinated by NCTU with the CI. Study medication will be purchased by Catalent who will also complete primary and secondary packaging and labelling. Treatment box numbers will be linked to the randomisation system at NCTU and baseline packs of study medication will be ordered for delivery to sites by NCTU in order to ensure an adequate supply. Catalent and the trial manager will be informed automatically by email each time a participant is randomised into the trial, so they can update their systems. Re-supply of study medication to sites for dispensing to each patient at weeks 6 and 12 will be managed by Catalent

and monitored by the trial manager. Study medication labels will be designed by the NCTU manager and approved by the chief pharmacist at Sussex Partnership Foundation NHS Trust.

A full accountability trail of the trial medication and placebo will be maintained via the patient study number and pack numbers from receipt at the site pharmacy to patient and return. Patients/carers will be asked to return unused and empty trial medication packaging for this purpose.

5.4.7 Compliance and Adherence

Study drug will be dispensed to the patient on a 6 weekly basis by the research worker and the used treatment packs will be obtained from the patient by the research workers at subsequent visits. The treatment packs dispensed during the previous visit will be collected, the returns reconciled, and returned to the central pharmacy for destruction. Tablet counts will be completed with the number of capsules returned recorded in the case report forms. Patients/carers will be asked to record details of non-compliance on their diary cards. These can then be used as an aide memoire when answering questions about compliance. This study is a pragmatic trial and non-compliance and attempts to promote compliance are part of routine clinical practice.

5.4.8 Concomitant medications

5.4.8.1 Prohibited medications

Patients must not receive Monoamine oxidase inhibitors (MAO inhibitors) within 2 weeks of trial treatment. These include:
Isocarboxazid, Nialamide, Phenelzine, Hydracarbazine, Tranylcypromine, Moclobemide, Pirlindole, Toloxatone, Rasagiline, Selegiline and Linezolid.

Sites should ensure that there is a 2 week washout period after trial treatment discontinuation prior to starting MAO inhibitors.

Patients should also not be taking antidepressants, anticonvulsants or antipsychotics whilst they are taking trial medication. These include:

- Amitriptyline, Bupropion, Citalopram, Clomipramine, Fluoxetine, Fluvoxamine, Imipramine, Mianserin, Nefazodone, Nortriptyline, Paroxetine, Sertraline, Trazodone
- Clobazam, Clonazepam, Ethosuximide, Lamotrigine, Oxcarbazepine, Phenytoin, Primidone, Progabide, Tiagabine, Topiramate, Valnoctamide, Valproic acid, Valpromide, Vigabatrin, Zonisamide
- Clozapine, Haloperidol and Bromperidol, Olanzapine, Quetiapine, Risperidone, Aripiprazole, Paliperidone

The above lists may not be exhaustive and are included as a guide, please refer to latest version of SmPCs for any further exclusions and exercise clinical judgement for any other drugs in these categories.

5.4.8.2 Medications requiring increased monitoring

Therapies requiring caution or extra monitoring include serotonergic active substances, benzodiazepines and other sedatives, inhibitors and inducers of CYP 3A4, HIV protease inhibitors, azole antifungals, lithium, dextropropoxyphene, danazol, macrolide antibiotics (e.g. erythromycin, clarithromycin), ciprofloxacine, loratadine, olanzapine, isoniazid, acetazolamide, diltiazem, verapamil, cimetidine, omeprazole, grapefruit juice, nicotinamide (only in high dosage).

Increased monitoring of international normalized ratio (INR) may be required for patients also being treated with warfarin due to a potential interaction of warfarin with higher doses of mirtazapine. Mirtazapine may significantly elevate serum triglyceride and total cholesterol levels. Patients with pre-existing hyperlipidemia may require closer monitoring during mirtazapine therapy, and adjustments made accordingly in their lipid-lowering regimen.
Carbamazepine may lower the plasma levels of or even abolish the activity of certain drugs, these are listed in the SmPC and appropriate precautions should be taken.
For a full list of medications that may interact with the study drugs, please refer to the Summary of Product Characteristics.

5.4.9 Concomitant Care – Rescue Medication

Allowable rescue medication includes:

- Risperidone oral tablet 0.5mg twice daily for 7 days in addition to the randomised allocated treatment; or,
- Lorazepam oral tablet 0.5 to 1mg twice daily as required for 7 days in addition to the randomised allocated treatment.

These can be prescribed by a patient's clinical team if the patient's behaviour deteriorates or if there are safety concerns. A patient's responsible clinical team will be able to withdraw the patient from the trial at any time if clinically indicated, but previous experience is that having a rescue protocol helps maintain participants in such studies as well as facilitating referral into the trial. The research team will provide site training and information on the rescue protocol to referring clinicians. This is compatible with good clinical practice based on the DH/AS guidance (AS, 2011).

5.4.10 Overdose of Trial Medication

Present experience concerning overdose with mirtazapine alone indicates that symptoms are usually mild. Depression of the central nervous system with disorientation and prolonged sedation have been reported, together with tachycardia and mild hyper- or hypotension. However, there is a possibility of more serious outcomes (including fatalities) at dosages much higher than the therapeutic dose, especially with mixed overdoses. In these cases QT prolongation and Torsade de Pointes have also been reported. Cases of overdose should receive appropriate symptomatic and supportive therapy for vital functions. ECG monitoring should be undertaken. Activated charcoal or gastric lavage should also be considered.

There is no specific antidote for carbamazepine overdose. The presenting signs and symptoms of overdose involve the central nervous, cardiovascular or respiratory symptoms. Management of the overdose will vary according to the patient's condition. This includes possible admission to hospital. Measurement of plasma levels to confirm carbamazepine poisoning and to ascertain the size of the overdose. Evacuation of the stomach, gastric lavage, and administration of activated charcoal. Supportive medical care in an intensive care unit with cardiac monitoring and careful correction of electrolyte imbalance, if required.

5.4.11 Protocol Treatment Discontinuation

In consenting to the trial, participants are consenting to trial treatments, trial follow-up and data collection. However, an individual participant may stop treatment early or be stopped early for any of the following reasons:

- Unacceptable treatment toxicity or adverse events
- Inter-current illness that prevents further treatment
- Any change in the participant's condition that in the clinician's opinion justifies the discontinuation of treatment
- Withdrawal of consent for treatment

As participation in the trial is entirely voluntary, the participant may choose to discontinue trial treatment at any time without penalty or loss of benefits to which they would otherwise be entitled. Although not obliged to give a reason for discontinuing their trial treatment, a reasonable effort should be made to establish this reason, whilst remaining fully respectful of the participant's rights.

Participants who discontinue protocol treatment, for any of the above reasons, should remain in the trial for the purpose of follow up and data analysis.

5.5 Outcomes

All outcome assessment time frames are time from randomisation.

5.5.1 Primary Outcomes

Cohen Mansfield Agitation Inventory (CMAI) score (Long form) at 12 weeks.

5.5.2 Secondary Outcomes

1 Costs derived from Client Service Receipt Inventory (CSRI), and QALYs from cost data alongside supplemented information from DEMQOL and EQ-5D-5L interviews 12 weeks post randomisation.
2 Cohen Mansfield Agitation Inventory (CMAI) score and cost at 6 weeks post randomisation.
3 Patient and carer quality of life, and carer outcomes at 6 and 12 weeks post randomisation.
4 Adverse events and adherence at 6 and 12 weeks post randomisation.
5 CMAI score, adverse events and adherence at 6 and 12 weeks, conditional on evidence of effectiveness of one IMP over placebo.
6 Longer term follow up: CMAI score, institutionalisation, death and clinical management at 26 and 52 weeks post-randomisation.

5.6 Sample Size

An overall sample of 400 (randomised 1:1:1) provides 90% power using 2-sided 5% significance tests to detect a drug versus placebo mean difference in CMAI score at 12 weeks of 6 points. This equates to an effect size of d=0.4 (assuming a common standard deviation of 15) or a clinically significant 30% decrease in CMAI from placebo to active drug. With a realistic 15% attrition, a sample of 471 (157 per arm) will therefore be aimed for.

The primary outcome measure in this proposed trial is the CMAI. Active drug treatment, compared with placebo, may be associated with changes in the CMAI that are much greater than 6 points, but SYMBAD is powered to detect the smallest difference in the CMAI that could be considered clinically meaningful. This estimation is based on the changes and standard deviation of change score seen in the CALM trial

which included a similar patient population treated with donepezil where 6 CMAI points was 35% of the standard deviation.

5.7 Recruitment and Retention

5.7.1 Recruitment

Recruitment will be organised on a regional basis with the support of NIHR LCRNs. It is anticipated that 8 centres will each recruit 59 patients over 24 months. Each of the 8 centres is associated with an area with 200,000 people aged over 65. This corresponds to the area served by 14 to 20 consultants. The trial recruitment strategy focuses on three separate, complementary channels for recruitment with the aim that each site will recruit at least one case from each channel each recruitment month.

Clinicians working in the settings described below will be asked to identify potential patients to the site HTA-SYMBAD PI or research worker using a simple pro forma. On receipt of this information prior adherence to the AS/DH algorithm will be ascertained. Patients will not be excluded where they are referred into the trial through other mechanisms. The trial will be advertised on websites such as the Join Dementia Research website, which may also be a source of referral into the trial.

5.7.1.1 Recruitment strategy - Channel 1 – Community Mental Health Teams

Community mental health teams are the backbone of older people's mental health (OPMH) services and they are the team to which GPs are likely to refer people with BPSD. A catchment area of 200,000 will yield at least 200 referrals of people with dementia per month. At a conservative estimate, 20% will have BPSD that may require medication ie 40 potential cases per centre per month. It is acceptable to recruit both current cases and new referrals.

5.7.1.2 Recruitment strategy - Channel 2 – Care Homes

This an important group given the high level of agitation in care homes, the high use of antipsychotics there, and the fact that a third of people with dementia live in care homes. To support this channel CRN Division 4 will use its Enabling Research in Care Homes (ENRICH) Programme and the Research Ready Care Home Network. The network contains care home providers supportive of clinical research that wish to support local studies. It contains over 694 care homes across England and Scotland. These vary in size from 7 to 149 beds including larger corporate suppliers such as BUPA.

5.7.1.3 Recruitment strategy - Channel 3 – Memory Clinics

In all 8 sites there are memory clinics which are focused on early diagnosis and intervention in dementia. They initiate treatment and keep in contact with all cases that are initiated on anti-dementia drugs that are not passed on to community teams. These cases are reviewed on a six monthly basis and it is common for cases to have levels of agitated behaviours that would mean they were eligible for entry into this trial.

5.7.2 Retention

Participants and their carers will be followed up in their place of usual residence unless they request otherwise. Visit appointments will be made at previous visits.

5.8 Assignment of Intervention

5.8.1 Allocation

5.8.1.1 Sequence generation

Eligible, consented participants will be randomised on a 1:1:1 basis to one of three trial arms using a web based randomisation process. The randomisation scheme will be generated by the NCTU data manager and passed to the drug manufacturers so that drug labelling can be performed according to this allocation. Allocation will be stratified by study region and independent living versus non-independent living. Independent living for the purposes of stratifying will mean participants living in their own home (even if this is assisted). Non-independent living will mean participants living in communal care/nursing homes.
Randomisation within strata will be based upon blocks of varying block length (either 3 or 6).

5.8.1.2 Allocation concealment mechanism

At the point of randomisation the research worker will enter patient eligibility data into an online randomisation system. An immediate allocation will be provided by the system to the research worker, and a confirmatory email will be sent to the trial team, research worker, central site pharmacist and site PI. The allocated participant identification number will be recorded on a randomisation log that will periodically be sent to the co-ordinating centre as confirmation that the trial numbers allocated match the electronically stored data. Concealment of allocation will be guaranteed by using this central web based randomisation process.

5.8.1.3 Allocation Implementation

The PI is responsible for ensuring a participant is suitable to be randomised. In collaboration with the research worker, the PI will confirm eligibility and sign off the prescription of trial medication, according to the participant identification number allocated on randomisation. Each capsule pack will be identified by the participant identification number and trial details. Prior to making a trial dispensing visit the research worker will visit the central site pharmacy and pick up the treatment allocated. Accountability documentation will record the boxes with the participant identification numbers being dispensed from pharmacy to the research worker. This documentation will be updated when the research worker gives the trial medication to the participant/carer.

Only personnel who are named on the site delegation log will be permitted to confirm patient eligibility to join the study, sign off trial medication prescriptions and dispense trial medication to participants.

5.8.2 Blinding

The SYMBAD trial is intended to be a double blind trial and all members of the trial team, their clinicians, participants and their carers will be blinded to trial arm allocation. To maintain the blind both active medications and the placebo will be identically encapsulated.

5.8.3 Unblinding

Final unblinding of all trial participants will not take place until after the creation of a locked analysis dataset.

The decision to unblind a single case should be made when knowledge of an individual's allocated treatment is required:

- To enable treatment of severe adverse event/s, or
- In the event of an overdose

Where possible, requests for emergency or unplanned unblinding of individuals should be made via the trial manager, and agreement of the Chief Investigator will then be sought. However, in circumstances where there is insufficient time to make this request or for agreement to be sought, the treating clinician should make the decision to unblind immediately. This will be done via the study database (local PIs and the CI will have special logins which will allow unblinding and which will be closely audited within the database management system) or by contacting Prof Sube Banerjee who will authorise unblinding by the Data Management Team. All instances of unblinding should be recorded and reported to NCTU by the local principal investigator, including the identity of all recipients of the unblinding information.

5.9 Data Collection, Management and Analysis

5.9.1 Data Collection Methods

Data will be collected at the time-points indicated in the Trial Schedule (Section 5.3.4).

Research workers will complete paper CRFs during their visits to participants and their carers. They will then enter data onto a central database via an online system once they have internet access. Research workers will receive training on data collection and use of the online system. Identification logs, screening logs and enrolment logs will be kept locally, either in paper or electronic form.

Source data worksheets will be drafted by the data manager with the CI, trial statistician and PIs. These will be piloted and finalised. The database specification will be prepared by the NCTU data manager and approved by the CI and trial statistician prior to the database being built. The database will be prepared by the CTU data programmer and tested by the trial statistician and study site staff for user acceptability prior to the final system being launched.

Data collection, data entry and queries raised by a member of the HTA-SYMBAD trial team will be conducted in line with NCTU and trial specific Data Management Standard Operating Procedures.

Clinical trial team members will receive trial protocol training. All data will be handled in accordance with the Data Protection Act 1998.

5.9.2 Data Management

Within each trial site patients will be allocated a unique trial participant identification number (PIN). Data will be entered under this PIN onto the central database stored on the servers based at UEA. The database will be password protected and only accessible to members of the SYMBAD trial team at NCTU, the participating sites and external regulators. The server is in a secure room, which is protected by CCTV, where access is restricted to members of the UEA Information Systems team by security door access. The study database will be built using Microsoft SQL Server tools and direct access will be restricted to NCTU data management staff. Data entry will be via web pages created using Microsoft.NET technology. All internet traffic will be encrypted using the standard SSL (Secure Sockets Layer) methodology. The data entry system will validate data on entry to ensure it is of the expected type (e.g. integers, dates etc.) and range of values. Periodically and at database lock the data will be further validated for errors and inconsistencies. The database is linked to an audit tool where all data additions, modifications and deletions are recorded with date/time and the user ID of the person making the change. The database is designed to comply with the ICH Guideline for Good Clinical

Practice (GCP), within the Standard Operating Procedures for Data Management in NCTU and also where appropriate with UEA IT procedures.

The database and coding values have been developed by the NCTU data manager in conjunction with the CI, study statistician and other NCTU members and the trial team. The database software provides a number of features to help maintain data quality, including; maintaining an audit trail, allowing custom validations on all data, allowing users to raise data query requests, and search facilities to identify validation failure/ missing data. Further details can be found in the SYMBAD Trial Data Management Plan. After completion of the trial the database will be retained on the servers of UEA for 15 years.

The identification, screening and enrolment logs, linking participant identifiable data to the PIN, will be held locally by the research sites and potentially at NCTU. This will either be held in written form in a locked filing cabinet or electronically in password protected form on hospital computers. After completion of the trial the identification, screening and enrolment logs will be stored securely by the sites for a minimum of 15 years.

5.9.3 Non-Adherence and Non-Retention

The consent form will explain that if a participant wishes to withdraw from the study the data acquired prior to that point will be retained. Reason for withdrawal will be recorded, if given, as will loss to follow up.

Non adherence to trial medication will be assessed through capsule counts of unused returned drug supplies and review of the diary card at each study visit.

5.9.4 Statistical Methods

Primary analyses will compare mirtazapine with placebo and carbamazepine with placebo on CMAI score at 12 weeks post randomisation. Analyses of clinical effectiveness will be pragmatic using linear mixed modelling, based on the Intention to Treat (ITT) population with all available follow-up data from all randomized patients controlling for baseline levels of agitation and centre. Secondary cost-effectiveness analyses will be conducted from societal and health and social care perspectives and will compare comprehensive costs with CMAI change.

Analyses will be on an ITT basis so each patient will be defined by their randomisation group at recruitment. The primary ITT analysis is intended to provide inferences regarding the effectiveness of the intervention overall: not to provide inferences regarding the causal effect of the intervention itself, but on the intervention as deployed in ‘real life’. So compliance information is not necessary to ensure that the 'intention to treat' analysis is valid. The sample size is adjusted for up to a 15% drop out at 12 weeks.

5.9.4.1 Statistical Analysis Plan

A full Statistical Analysis Plan (SAP) will be developed between the trial statistician and Chief Investigator and agreed with the trial’s governance committees.

5.9.4.2 Statistical Methods – Outcomes

The primary outcome will be CMAI at 12 weeks post randomisation. The analysis will adhere to the principals of the ITT strategy for analysis: participants will be analysed according to assigned treatment group and data collection will be continued for all subjects irrespective of any discontinuation or change of treatment. Complete data collection will be aimed for.

A general linear model (assuming a CMAI has a Normal distribution) will be used. This will include centre as a random factor, the CMAI baseline score, plus any pre-determined prognostic variables at baseline, prior to randomisation. Treatment group will be added as a fixed effect, with three levels (placebo group and two active treatment groups). Using this model, the mirtazapine and carbamazepine effects, relative to placebo, will be estimated simultaneously. Statistical significance will be set at 5% (two-sided); no formal adjustments will be made for multiple testing. Parameter estimates will be presented with 95% confidence intervals. If CMAI does not follow a normal distribution (or, more accurately, the residuals from the model do not follow a normal distribution), transformations will be considered, e.g. a logarithmic transformation in the case of a positively skewed distribution.

There are no plans for adjustments for multiple comparisons or any hierarchy of comparisons in the primary analyses as we are addressing two separate questions (mirtazapine versus placebo and carbamazepine versus placebo) simultaneously. Multiple comparisons, using multiple outcomes or multiple time points, are not being used to address each individual question in the primary outcome analyses.

The analyses of secondary outcomes (including CMAI at 6 weeks) will follow an analogous approach. In each case, an appropriate linear model with inclusion of the outcome at baseline (if available), centre, prognostic variables and treatment group will be constructed.

Analyses will be carried out by the trial statistician blinded to group identity, (i.e. 'subgroup' blind). There are no plans for formal interim efficacy or subgroup analyses. Analyses will be carried out in SAS (currently version 9.4).

All cause withdrawal from randomised treatment will be reported. The prevalence of specific adverse events and reactions will be reported descriptively at weeks 6 and 12. The prevalence of patients experiencing one or more serious adverse events will be compared at 6 and 12 weeks post randomisation across the three trial arms (as randomised) using Chi Square tests conditional on evidence of effectiveness of one IMP over placebo. Mortality prevalence will be considered independently of any other serious adverse events.

The primary analyses will be with regard to placebo v carbamazepine and placebo v mirtazapine. However, carbamazepine v mirtazapine comparisons of efficacy and adverse effects will also be carried out as a secondary analysis. These will follow the same approach as above though the study sample size has not been selected with this comparison in mind, and any differences in efficacy are likely to be small compared to differences from placebo.

After the 12 week period of randomised treatment has finished, long term outcomes in terms of CMAI score, treatment state, institutionalisation and death will be completed at 26 and 52 weeks. The 6 and 12 week analyses will be reported separately once these have been completed to ensure no delay in communicating the primary outcomes of the study. The long term follow up data from 26 and 52 weeks will be collated at the CDS, linked to the prior data and analysed and reported separately once the core study has been completed.

5.9.4.3 Additional Analyses - Subgroup

No subgroup analyses are planned. During the trial, specific sub-groups may be suggested possibly as the result of new information becoming available, but any analyses will be agreed by the TMG and stated in the statistical analysis plan.

5.9.5 Analysis Population and Missing Data

The primary analysis will be based on the ITT population. It is anticipated that the proportion of patients with missing CMAI scores at 12 weeks will be low. Missing data will be investigated with respect to any possible patterns and associations with baseline variables. If appropriate (assessed and defined in the SAP) multiple imputation will be used to create imputed datasets which will be used for sensitivity analysis.

5.9.5.1 Economic evaluations

There are limitations in economic analyses that are a consequence of the short term nature of follow-up in this study. Cost-effectiveness will consequently be investigated as a secondary outcome. It remains vital to explore and test economic and service use outcomes, not least because of the findings of the SADD cost effectiveness analyses, and because of the value of such data to NICE and other health technology assessment bodies. Because of the short follow-up period we have also proposed decision-analytic modelling based on a combination of data from the trial and other published sources, in order to provide information useful to decision-makers on possible longer-term costs and benefits of the alternative treatments under 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 associated with carer support) using data gathered using the CSRI completed by key workers or family carers at baseline and 12 weeks. Unit costs will be best national estimates of the long-run marginal opportunity costs, built up from both national unit costs compendia (Curtis, 2013), NHS specialty costs and specific care homes (costs or charges, depending on availability). Carer time inputs will be costed (Netten, 1993). Aggregate and agency-specific costs will be reported. 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 CMAI), cost-utility ratios (using utility scores computed from the EQ-5D-5L and DEMQOL and societal weights) and cost-consequences results (using all non-cost outcomes measures). Two perspectives will be examined: health and social care, and societal. The primary evaluation will be the cost-effectiveness analysis using CMAI change as the outcome from a health and social care system perspective. The evaluation will include the plotting of cost-effectiveness acceptability curves generated from bootstrap analyses. Sensitivity analyses will explore the impact of key assumptions such as the costing of carer time and the choice of QALY-generating instrument. Further cost-effectiveness analyses will examine these costs in terms of QALY gain beyond the intervention period, over the lifetime of the population. The latter analysis will draw on data from the study and other published sources to populate a decision-analytic model, to be designed in Microsoft Excel or Tree-Age.

5.9.5.2 Health Economic Analysis Plan

A full health economics Statistical Analysis Plan (SAP) will be developed between the trial health economist and Chief Investigator and agreed with the trial's governance committees.

5.9.5.3 Within-trial analysis

No within-trial analyses are planned. During the trial, specific analyses may be suggested possibly as the result of new information becoming available, but any analyses will be agreed by the TMG and stated in the statistical analysis plan.

5.10 Data Monitoring

5.10.1 Interim Analyses

No efficacy interim analyses are planned. However, analysis of recruitment rates, withdraw rates, etc. will be conducted as part of the internal pilot.

5.10.2 Data Monitoring for Harm

The Trial Management Group will review line listings of cumulative serious adverse events at each meeting. Any concerns about potential emerging toxicity will be escalated to the IDMC. The IDMC will review unblinded safety data including reported frequencies of non serious adverse events, serious adverse reactions and suspected unexpected serious adverse reactions by treatment arm.

5.10.2.1 Safety reporting

Definitions of harm of the EU Directive 2001/20/EC Article 2 based on the principles of ICH GCP apply to this trial: any unfavourable and intended sign, symptom or illness that develops or worsens during the period of the study will be classified as an adverse event (AE), whether or not it is considered to be related to the study treatment. Adverse events will include unwanted side effects, sensitivity reactions, abnormal laboratory results, injury or inter-current illnesses, and may be expected or unexpected. These will be recorded on the CRF.

The period for SAE reporting will be from the time of first dose until 30 days post final trial medication administration. The participants will be followed up by a telephone interview 30 days after the last dose of trial medication. All events will be followed until resolution, including if that means beyond 30 days post-final trial medication implementation.

Table 1: Adverse Event Definitions

Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this product.
Adverse Reaction (AR)	Any untoward and unintended response to an investigational medicinal product related to any dose administered
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg Investigator's Brochure for an unauthorised product or summary of product characteristics (SPC) for an authorised product.
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)	Any AE or AR that at any dose: • results in death • is life threatening* • requires hospitalisation or prolongs existing hospitalisation** • results in persistent or significant disability or incapacity • is a congenital anomaly or birth defect • or is another important medical condition***

* the term life threatening here refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event that might hypothetically cause death if it was more severe (eg a silent myocardial infarction)

** Hospitalisation is defined as an in-patient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisation for pre-existing conditions (including elective procedures that have not worsened) do not constitute an SAE

*** Medical judgement should be exercised in deciding whether an AE or AR is serious in other situations. Important AEs or ARs that may not be immediately life threatening or result in death or hospitalisation, but may seriously jeopardise the participant by requiring intervention to prevent one of the other outcomes listed in the table (eg a secondary malignancy, an allergic bronchospasm requiring intensive emergency treatment, seizures or blood dyscrasias that do not require hospitalisation, or development of drug dependency).

Adverse events include:

- an exacerbation of a pre-existing illness
- an increase in the frequency or intensity of a pre-existing episodic event or condition
- a condition (regardless of whether PRESENT prior to the start of the trial) that is DETECTED after trial drug administration. (This does not include pre-existing conditions recorded as such at baseline – as they are not detected after trial drug administration.)
- continuous persistent disease or a symptom present at baseline that worsens following administration of the trial treatment

Adverse events do NOT include:

- Medical or surgical procedures: the condition that leads to the procedure is the adverse event
- Pre-existing disease or a condition present before treatment that does not worsen
- Hospitalisation where no untoward or unintended response has occurred eg elective cosmetic surgery
- Overdose of medication without signs or symptoms

5.10.2.3 Other Notifiable Adverse Events

There are no notifiable adverse events defined in the trial.

5.10.2.4 Procedures to follow in the event of female participants becoming pregnant

In the event of a female participant becoming pregnant, trial drug should be stopped. Unblinding should be discussed with the CI. An SAE form should be completed and the pregnancy followed for outcome of mother and child.

5.10.2.5 Investigator responsibilities relating to safety reporting

All non-serious AEs and ARs, whether expected or not, should be recorded in the patient's medical notes and reported in the toxicity (symptoms) section of the Follow-up Form/eCRF. SAEs and SARs

should be notified to NCTU immediately the investigator becomes aware of the event (in no circumstance should this notification take longer than 24 hours).

5.10.2.5.1 Seriousness assessment

When an AE or AR occurs, the research worker and site PI responsible for the patient must first assess whether or not the event is serious using the definition given in Table 1. If the event is classified as 'serious' then an SAE form must be completed and sent to NCTU within 24 hours.

5.10.2.5.2 Severity or grading of Adverse Events

The severity of all AEs and/or ARs (serious and non-serious) in this trial is based on the Research Worker and site PI's clinical judgement and should be graded using the following definitions:

1 – Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with every day activities.
2 – Moderate: An event that is sufficiently discomforting to interfere with normal every day activities.
3 – Severe: An event that prevents normal every day activities

5.10.2.5.3 Causality

The investigator must assess the causality of all serious events or reactions in relation to the trial therapy using the definitions in Table 2.

Table 2: Causality definitions

Relationship	Description	Event type
Unrelated	There is no evidence of any causal relationship	Unrelated SAE
Unlikely to be related	There is little evidence to suggest that there is a causal relationship (eg the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (eg the participant's clinical condition or other concomitant treatment)	Unrelated SAE
Possibly related	There is some evidence to suggest a causal relationship (eg because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (eg the participant's clinical condition or other concomitant treatment)	SAR
Probably related	There is evidence to suggest a causal relationship and the	SAR

	influence of other factors is unlikely	
Definitely related	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	SAR

If an SAE is considered to be related to trial treatment, and treatment is discontinued, interrupted or the dose modified, refer to the relevant Interventions sections of the protocol.

5.10.2.5.4 Expectedness

If there is at least a possible involvement of the trial medications (including the placebo), the investigator and sponsor must assess the expectedness of the event. An unexpected adverse reaction is one that is not reported in the SPCs, or one that is more frequently reported or more severe than previously reported. A list of expected toxicities associated with the drugs being used in this trial will be provided to each trial site. If a SAR is assessed as being unexpected it becomes a SUSAR (suspected, unexpected, serious adverse reaction) and MHRA and REC reporting guidelines apply (see Notifications sections of the protocol).

5.10.2.6 Notifications

5.10.2.6.1 Notifications by the Investigator to NCTU

NCTU must be notified of all SAEs within 24 hours of the investigator becoming aware of the event.

Investigators should notify NCTU of any SAEs occurring from the time of randomisation until 30 days after the last protocol treatment administration. SARs and SUSARs must be notified to NCTU until trial closure. Any subsequent events that may be attributed to treatment should be reported to the MHRA using the yellow card system (https://yellowcard.mhra.gov.uk/the-yellow-card-scheme/).

The SAE form must be completed by the investigator (the consultant named on the delegation of responsibilities list who is responsible for the participant's care in the trial) with attention paid to the grading, causality and expectedness of the event. In the absence of the responsible investigator, the SAE form should be completed and signed by a member of the site trial team and emailed as appropriate within the timeline. The responsible investigator should check the SAE form at the earliest opportunity, make any changes necessary, sign and then email to NCTU. Detailed written reports should be completed as appropriate. Systems will be in place at the site to enable the investigator to check the form for clinical accuracy as soon as possible.

The minimum criteria required for reporting an SAE are the patient trial number and date of birth, name of reporting investigator and sufficient information on the event to confirm seriousness. Any further information regarding the event that is unavailable at the time of the first report should be sent as soon as it becomes available.

The SAE form must be scanned and sent by email to the trial team at NCTU on

nctu.safety@uea.ac.uk

Participants must be followed up until clinical recovery is complete and laboratory results have returned to normal or baseline values, or until the event has stabilised. Follow-up should continue after completion of protocol treatment and/or trial follow-up if necessary. Follow-up SAE forms (clearly marked as follow-up) should be completed and emailed to NCTU as further information becomes available. Additional information and/or copies of test results etc may be provided separately. The participant must be identified by trial number, date of birth and initials only. The participant's name should not be used on any correspondence and should be blacked out and replaced with trial identifiers on any test results.

5.10.2.6.2 NCTU responsibilities

The Chief Investigator or medically qualified delegate will review all SAE reports received. In the event of disagreement between the causality assessment given by the local investigator and the CI, both opinions and any justifications will be provided in subsequent reports.

The delegated staff at NCTU will review the assessment of expectedness and, based on possible wider knowledge of the reference material for the treatment or comparator, and after discussion with the CI, may over-rule the investigator assessment of expectedness for the purposes of onward reporting.

NCTU is responsible for the reporting of SUSARs and other SARs to the MHRA and the RECs as appropriate. Fatal and life threatening SUSARs must be reported to the competent authorities within seven days of NCTU becoming aware of the event; other SUSARs must be reported within 15 days.

NCTU will keep investigators informed of any safety issues that arise during the course of the trial in a joint communication with the CI.

The trial manager or delegate at NCTU will submit Development Safety Update Reports (DSURs) to competent authorities.

5.10.3 Quality Assurance and Control

5.10.3.1 Risk Assessment

The Quality Assurance (QA) and Quality Control (QC) considerations for the HTA-SYMBAD trial are based on the standard NCTU quality management practices that include a formal Risk Assessment, and that acknowledges the risks associated with the conduct of the trial and proposals of how to mitigate them through appropriate QA and QC processes. Risks are defined in terms of their impact on: the rights and safety of participants; project concept including trial design, reliability of results and institutional risk; project management; and other considerations.

QA is defined as all the planned and systematic actions established to ensure the trial is performed and data generated, documented and/or recorded and reported in compliance with the principles of GCP and applicable regulatory requirements. QC is defined as the operational techniques and activities performed within the QA system to verify that the requirements for quality of the trial related activities are fulfilled.

5.10.3.2 Central Monitoring at NCTU

NCTU staff will review electronic Case Report Form (eCRF) data for errors and missing key data points. The trial database will be programmed to generate reports on errors and error rates.

Essential trial issues, events and outputs, including defined key data points, will be detailed in the HTA-SYMBAD trial Data Management Plan.

5.10.3.3 On-site Monitoring

The frequency, type and intensity of routine and triggered on-site monitoring will be detailed in the HTA-SYMBAD Quality Management and Monitoring Plan (QMMP). The QMMP will also detail the procedures for review and sign-off of monitoring reports. In the event of a request for a trial site inspection by any regulatory authority NCTU must be notified as soon as possible.

5.10.3.3.1 Direct access to participant records

Participating investigators must agree to allow trial related monitoring, including audits, REC review and regulatory inspections, by providing access to source data and other trial related documentation as required. Participant consent for this must be obtained as part of the informed consent process for the trial.

5.10.3.4 Trial Oversight

Trial oversight is intended to preserve the integrity of the trial by independently verifying a variety of processes and prompting corrective action where necessary. The processes reviewed relate to participant enrolment, consent, eligibility, and allocation to trial groups; adherence to trial interventions and policies to protect participants, including reporting of harms; completeness, accuracy and timeliness of data collection; and will verify adherence to applicable policies detailed in the Compliance section of the protocol.

In multi-centre trials this oversight is considered and described both overall and for each recruiting centre by exploring the trial dataset or performing site visits as described in the HTA-SYMBAD Quality Management and Monitoring Plan.

5.10.3.4.1 Trial Management Team

The Trial Management Team (TMT) will be set up to assist with developing the design, co-ordination and day to day operational issues in the management of the trial, including budget management. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TMT terms of reference.

5.10.3.4.2 Trial Management Group

A Trial Management Group (TMG) will be set up to assist with developing the design, co-ordination and strategic management of the trial. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TMG terms of reference.

5.10.3.4.3 Independent Trial Steering Committee

The Independent Trial Steering Committee (TSC) is the independent group responsible for oversight of the trial in order to safeguard the interests of trial participants. The TSC provides advice to the CI, NCTU, the funder and sponsor on all aspects of the trial through its independent Chair. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TSC terms of reference.

5.10.3.4.4 Independent Data Monitoring Committee

The Independent Data Monitoring Committee (IDMC) is the only oversight body that has access to unblinded accumulating comparative data. The IDMC is responsible for safeguarding the interests of

trial participants, monitoring the accumulating data and making recommendations to the TSC on whether the trial should continue as planned. The membership, frequency of meetings, activity (including review of trial conduct and data) and authority will be covered in the IDMC terms of reference. The IDMC will consider data in accordance with the statistical analysis plan and will advise the TSC through its Chair.

5.10.3.4.5 Trial Sponsor

The role of the sponsor is to take on responsibility for securing the arrangements to initiate, manage and finance the trial. Sussex University is the trial sponsor and has delegated its activities to the Chief Investigator and NCTU.

5.11 Trial Closure

The end of the trial is defined as 4 weeks after the last treatment visit of the last patient recruited to the trial.

6 Ethics and Dissemination

6.1 Research Ethics Approval

Before initiation of the trial at any clinical site, the protocol, all informed consent forms and any material to be given to the prospective participant and their carers will be submitted to the relevant REC for approval. Any subsequent amendments to these documents will be submitted for further approval. Before initiation of the trial at each additional clinical site, the same/amended documents will be submitted for local Research and Development (R&D) approval.

The rights of the participants to refuse to participate in the trial without giving a reason must be respected. After the participant has entered the trial, the clinician remains free to give alternative treatment to that specified in the protocol, at any stage, if s/he feels it to be in the best interest of the participant. The reasons for doing so must be recorded. After randomisation the participant must remain within the trial for the purpose of follow up and data analysis according to the treatment option to which they have been allocated. However, the participant remains free to change their mind at any time about the protocol treatment and follow-up without giving a reason and without prejudicing their further treatment.

6.2 Competent Authority Approvals

This protocol will be submitted to the UK national competent authority (MHRA).

This is a Clinical Trial of an Investigational Medicinal Product (IMP) as defined by the EU Directive 2001/20/EC. Therefore, a CTA is required in the UK.

The progress of the trial, safety issues and reports, including expedited reporting of SUSARs, will be reported to the Competent Authority, regulatory agency or equivalent in accordance with relevant national and local requirements and practices.

6.3 Other Approvals

The protocol will be submitted by those delegated to do so to the relevant R&D department of each participating site or to other local departments for approval as required in each country. A copy of

the local R&D approval (or other relevant approval as above) and of the Participant Information Sheet (PIS) and consent form on local headed paper must be forwarded to the co-ordinating centre before participants are randomised to the trial.

The protocol has received formal approval and methodological, statistical, clinical and operational input from the NCTU Protocol Review Committee.

6.4 Protocol Amendments

Substantial protocol amendments (e.g. changes to eligibility criteria, outcomes, sample size calculations, analyses) will be decided by the Chief Investigator. Each site-PI will be informed of the potential changes. Such amendments will be submitted to the Competent Regulatory Authority and Ethics Committee and approval must be received from both before being implemented. Once approved, the protocol amendments will be circulated to trial personnel.

6.5 Consent or Assent in Ancillary Studies

There is no intention to collect any specimens for storage or use in future studies. There is no current intention to perform any ancillary studies but should plans emerge they will require additional funding and ethics applications to be made.

6.6 Confidentiality

Any paper copies of personal trial data will be kept at the participating site in a secure location with restricted access. Only non-identifiable data will be kept at the NCTU office with authorised NCTU staff members having access. Only staff working on the trial will have password access to this information.

Confidentiality of patient's personal data is ensured by not collecting patient names on CRFs that will be sent to NCTU and storing the data in a pseudonymised fashion at NCTU. At trial enrolment the patient will be issued a participant identification number and this will be the primary identifier for the patient, with secondary identifiers of month and year of birth and initials.

The patient and carer's consent forms will carry their name and signature. These will be kept at the trial site, and a copy sent to NCTU for monitoring purposes. They will not be kept with any additional patient data.

6.7 Declaration of Interests

The investigators named on the protocol have no financial or other competing interests that impact on their responsibilities towards the scientific value or potential publishing activities associated with the trial.

6.8 Indemnity

University of Sussex (UoS) holds insurance to cover participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if they can prove that UoS has been negligent.

UEA does not accept liability for any breach in a hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or not. This does not affect the participant's right to seek compensation via the non-negligence route.

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of UoS or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to UoS's insurers, via the Sponsor's office.

NHS Trust sites selected to participate in this clinical trial shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to NCTU, upon request.

6.9 Finance

HTA-SYMBAD is fully funded by a National Institute for Health Research HTA Programme grant number [3/115/76]. It is not expected that any further external funding will be sought.

6.10 Archiving

The investigators agree to archive and/or arrange for secure storage of HTA-SYMBAD trial materials and records for a minimum of 5 years after the close of the trial unless otherwise advised by the Sponsor.

6.11 Access to Data

Requests for access to trial data will be considered, and approved in writing where appropriate, after formal application to the TMG and TSC. Considerations for approving access are documented in the TMG and TSC Terms of Reference. The CI and trial statistician at NCTU will have access to the full trial dataset.

6.12 Ancillary and Post-trial Care

The sponsor does not intend to provide any interventions or other care to patients after trial completion.

6.13 Publication Policy

6.13.1 Trial Results

The results of the trial will be disseminated regardless of the direction of effect. Ownership of the data arising from the study resides with the trial team. The publication policy will be in line with rules of the International Committee of Medical Journal Editors. The TMG will decide on authorship with any difficulties being resolved by the TSC.

6.13.2 Authorship

The TMG will nominate a writing group, which will consist of members of the TMG and will be responsible for drafting the manuscript for publication. These individuals will be named on the final publication.

6.13.3 Reproducible Research

The HTA Symbad Trial Protocol will be published and made available for public access throughout the trial period.

7 Ancillary Studies

No ancillary studies are currently planned. Any that are proposed during the lifetime of the trial will require funding applications to be made, and will be submitted for ethical approval prior to initiation.

8 Protocol Amendments

8.1 Amendments made to protocol v1.1

8.2 Amendments made to protocol v1.2

1. Version and date details updated
2. Exclusions criteria amended in line with MHRA comments; pages 3, 18-19
3. New abbreviations added in line with amended text
4. New section 4.1.7 added 'Risks and benefits' in line with MHRA discussions
5. Safety blood and ECG testing and Columbia Suicide Rating Scale (C-SSRS) added as requested by MHRA; pages 20-21, 23-25, 29
6. Clarification of week 16 phone call added in line with MHRA comments; pages 21, 25
7. Expanded list of con-meds to be more specific, as requested by MHRA, new sections 5.4.8.1 and 5.4.8.2; pages 29, 30-31
8. Amended wording for notification of SAEs to CTU from 'one working day' to 'within 24 hours'; pages 41, 43
9. Approval of protocol amendments wording changed to clarify that competent authority and EC approval must be received before being implemented, where relevant. Page 46

8.3 Amendments made to protocol v1.3

1. Version and date details updated
2. Minor typographical errors and amendments for consistency and clarity added throughout
3. New abbreviations added in line with amended text
4. Trial management group lists updated, there haven't been any changes to the groups themselves, but not all names were listed on the protocol when it was first produced
5. CMAI questionnaire should be the Long Form and this has been updated throughout the protocol for clarity and appendix 3 amended to show the correct version; pages 11--12, 17, 19, 31
6. The word 'tablet' has been changed to 'capsule' throughout the protocol, procedures haven't changed but as the product will be a capsule the wording has been made consistent for clarity; pages 10, 23, 26-29, 36
7. In some places the word 'bottle' had been used to describe packaging, as with point 6 this has been amended for clarity and consistency to packs/boxes as relevant; page 34
8. Wording has been added to the participant timeline table (5.3.1) to clarify windows of acceptability for visits/tests and confirm that face-to-face visits may take place over more than one visit if required
9. Window for acceptability of blood tests has been amended from 4 weeks to 28 days, to be consistent throughout all documents. Post –dosing blood test window has been changed from 7 days to 28 days as requested by TMG, to aid compliance
10. Stratifying has been changed from 'by centre' to 'by independent living' and text has been updated; pages 11, 33-34
11. Safety email address has been updated with the new contact details, the procedure remains the same, it's just the email address that has been updated – recruitment hasn't started so this doesn't need to be immediately notified to sites.
12. This section (8) has been updated as there was no previous record of amendments

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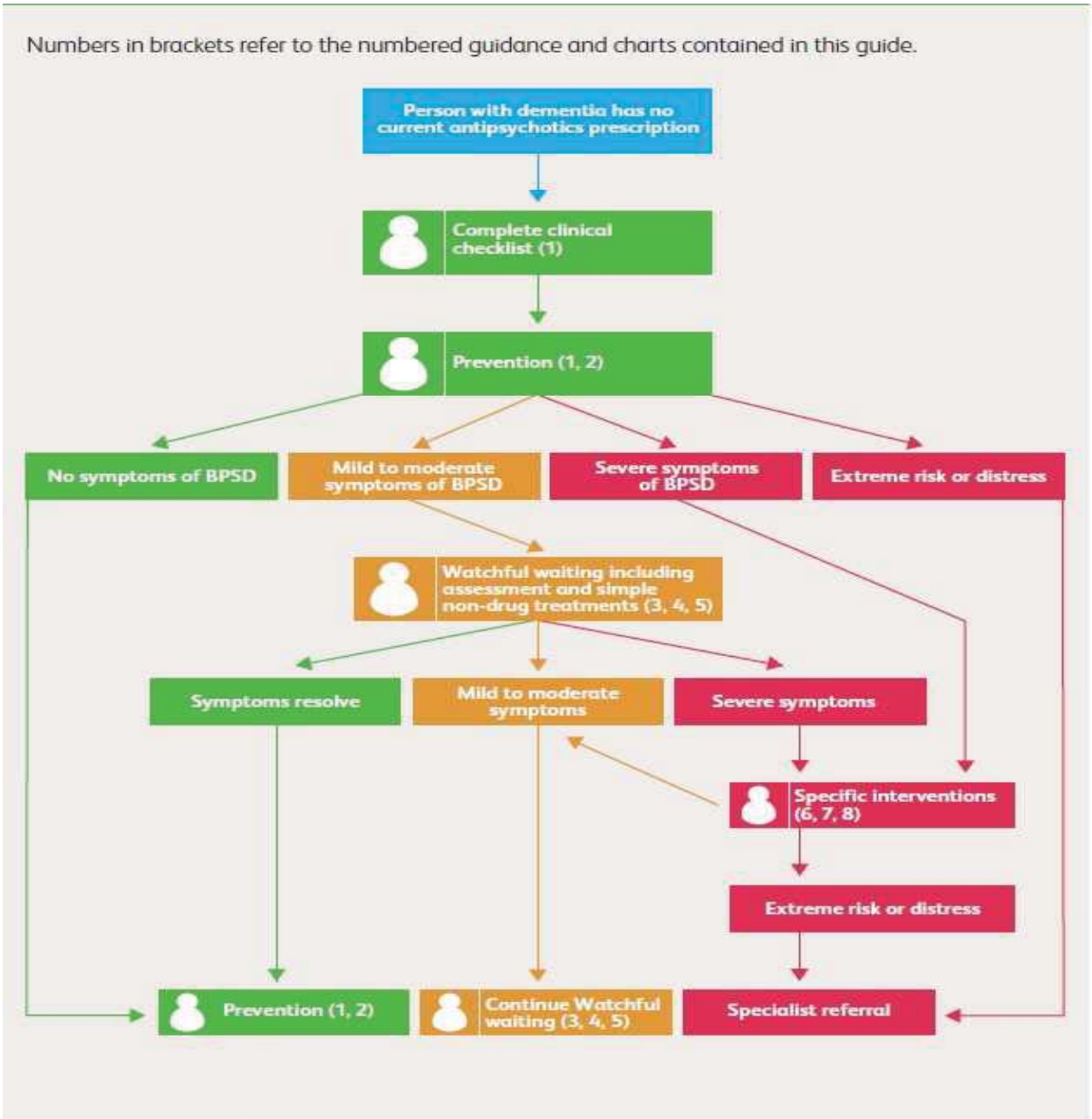
10 Appendices

Appendix 1: AS/DH Algorithm for adequate trial of non-pharmacological treatment for BPSD (2011)

Appendix 2: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria (McKhann et Al, 1984)

Appendix 3: Cohen Mansfield Agitation Inventory (CMAI; Cohen-Mansfield et al, 1989) Long Form

10.1 Appendix 1: Algorithm for adequate trial of non-pharmacological treatments for BPSD



10.2 Appendix 2: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria (McKhann et Al, 1984).

Table 1. Criteria for clinical diagnosis of Alzheimer's disease

I. The criteria for the clinical diagnosis of PROBABLE Alzheimer's disease include:

dementia established by clinical examination and documented by the Mini-Mental Test,[1] Blessed Dementia Scale,[2] or some similar examination, and confirmed by neuropsychological tests;

deficits in two or more areas of cognition;

progressive worsening of memory and other cognitive functions;

no disturbance of consciousness;

onset between ages 40 and 90, most often after age 65; and

absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition.

II. The diagnosis of PROBABLE Alzheimer's disease is supported by:

progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perception (agnosia);

impaired activities of daily living and altered patterns of behavior;

family history of similar disorders, particularly if confirmed neuropathologically; and

laboratory results of:

normal lumbar puncture as evaluated by standard techniques,

normal pattern or nonspecific changes in EEG, such as increased slow-wave activity, and

evidence of cerebral atrophy on CT with progression documented by serial observation.

III. Other clinical features consistent with the diagnosis of PROBABLE Alzheimer's disease, after exclusion of causes of dementia other than Alzheimer's disease, include:

plateaus in the course of progression of the illness;

associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, catastrophic verbal, emotional, or physical outbursts, sexual disorders, and weight loss;

other neurologic abnormalities in some patients, especially with more advanced disease and including motor signs such as increased muscle tone, myoclonus, or gait disorder;

seizures in advanced disease; and

CT normal for age.

IV. Features that make the diagnosis of PROBABLE Alzheimer's disease uncertain or unlikely include:

sudden, apoplectic onset;

focal neurologic findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness; and

seizures or gait disturbances at the onset or very early in the course of the illness.

V. Clinical diagnosis of POSSIBLE Alzheimer's disease:

may be made on the basis of the dementia syndrome, in the absence of other neurologic, psychiatric, or systemic disorders sufficient to cause dementia, and in the presence of variations in the onset, in the presentation, or in the clinical course;

may be made in the presence of a second systemic or brain disorder sufficient to produce dementia, which is not considered to be *the* cause of the dementia; and

should be used in research studies when a single, gradually progressive severe cognitive deficit is identified in the absence of other identifiable cause.

VI. Criteria for diagnosis of DEFINITE Alzheimer's disease are:

the clinical criteria for probable Alzheimer's disease and

histopathologic evidence obtained from a biopsy or autopsy.

VII. Classification of Alzheimer's disease for research purposes should specify features that may differentiate subtypes of the disorder, such as:

familial occurrence;

onset before age of 65;

presence of trisomy-21; and

coexistence of other relevant conditions such as Parkinson's disease.

10.3 Appendix 3: Cohen Mansfield Agitation Inventory (CMAI; Cohen-Mansfield et al, 1989)

THE COHEN-MANSFIELD AGITATION INVENTORY - Long Form

Please read each of the 29 agitated behaviours, and circle how often (from 1-7) each was manifested by the resident during the last 2 weeks:

		Never	Less than once a week	Once or twice a week	Several times a week	Once or twice a day	Several times a day	Several times an hour
1	Pace, aimless wandering	1	2	3	4	5	6	7
2	Inappropriate dress or disrobing	1	2	3	4	5	6	7
3	Spitting (including at meals)	1	2	3	4	5	6	7
4	Cursing or verbal aggression	1	2	3	4	5	6	7
5	Constant unwarranted request for attention or help	1	2	3	4	5	6	7
6	Repetitive sentences or questions	1	2	3	4	5	6	7
7	Hitting (including self)	1	2	3	4	5	6	7
8	Kicking	1	2	3	4	5	6	7
9	Grabbing onto people	1	2	3	4	5	6	7
10	Pushing	1	2	3	4	5	6	7
11	Throwing things	1	2	3	4	5	6	7
12	Strange noises (weird laughter or crying)	1	2	3	4	5	6	7
13	Screaming	1	2	3	4	5	6	7
14	Biting	1	2	3	4	5	6	7
15	Scratching	1	2	3	4	5	6	7
16	Trying to get to a different place (e.g. out of the room, building)	1	2	3	4	5	6	7
17	Intentional falling	1	2	3	4	5	6	7
18	Complaining	1	2	3	4	5	6	7
19	Negativism	1	2	3	4	5	6	7

20	Eating/drinking inappropriate substances	1	2	3	4	5	6	7
21	Hurt self or other (cigarette, hot water, etc.)	1	2	3	4	5	6	7
22	Handling things inappropriately	1	2	3	4	5	6	7
23	Hiding things	1	2	3	4	5	6	7
24	Hoarding things	1	2	3	4	5	6	7
25	Tearing things or destroying property	1	2	3	4	5	6	7
26	Performing repetitious mannerisms	1	2	3	4	5	6	7
27	Making verbal sexual advances	1	2	3	4	5	6	7
28	Making physical sexual advances	1	2	3	4	5	6	7
29	General restlessness	1	2	3	4	5	6	7