PROTOCOL

COBALT

COmBining memantine And cholinesterase inhibitors in Lewy body dementia Treatment trial

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Version: 3.0

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Sponsors:

United Kingdom: Cumbria, Northumberland Tyne and Wear NHS Foundation Trust

Australia: University of Melbourne

This is not a co-sponsored clinical trial.

This clinical trial is not sponsored by any pharmaceutical company or other commercial entity.

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RESEARCH REFERENCE NUMBERS

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Trial Registration

COBALT will be prospectively registered with ISRCTN. ISRCTN is a registry and curated database containing the basic set of data items deemed essential to describe a study at inception, as per the requirements set out by the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) and the International Committee of Medical Journal Editors (ICMJE) guidelines. ISRCTN has been chosen as it is an acceptable registry for both UK and Australia.

CONFIDENTIAL

Statement of Compliance

This trial will be conducted in compliance with all stipulation of this protocol, the conditions of the ethics committee approval/s, standards of Good Clinical Practice (as defined by the International Conference on Harmonisation), ethical principles that have their origin in the Declaration of Helsinki and all applicable national and local regulations. In Australia this includes the NHMRC National Statement on ethical Conduct in Human Research (2007 and all updates), the Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2), dated November 2016 annotated with TGA comments and the NHMRC guidance Safety monitoring and reporting in clinical trials involving therapeutic goods (EH59, 2016).

Protocol use

UK specific instructions and regulations are highlighted in BLUE and should ONLY be adhered to by UK trial teams. Australian specific instructions and regulations are highlighted in GREEN throughout the protocol and should ONLY be adhered to by the Australian trial teams.

Statement regarding COBALT

The COBALT Trial (DLB module and PDD module) will be carried out in both the UK and Australia using the same protocol. The UK trial and Australian trial will run completely separately given they are separately funded, sponsored, and managed, as well as having separate clinical data management systems. Ethical and regulatory approval will be sought separately in each country.

Following closure of the trial the data collected in Australia and the UK will be analysed together, using statistical approaches which account for the separate nature, and conduct of these trials between the two countries.

PROTOCOL APPROVAL SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted. The Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, Good Clinical Practice (GCP) guidelines, the relevant Standard Operating Procedures and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

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PROTOCOL ACCEPTANCE SIGNATURE PAGE

Short Trial Title: COmBining memantine and cholinesterase inhibitors in Lewy body dementia treatment Trial

Principal Investigator

I have carefully read and understood protocol version 3.0. I agree to conduct the trial in compliance with Good Clinical Practice and all required regulatory requirements.

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1. TRIAL SYNOPSIS

Title:	**CO**m**B**ining memantine **A**nd cholinesterase inhibitors in **L**ewy body dementia **T**reatment Trial
Short Title:	COBALT
Phase	3
Design:	The trial is made up of two independent modules, namely COBALT-DLB and COBALT-PDD. Each module will use a multi-centre, parallel arm, double-blind, randomised placebo-controlled design.
Trial Centres:	Twenty-five (25) sites in England and the Devolved Nations, and five (5) sites in Australia.
Trial Question:	What is the clinical and cost effectiveness of memantine compared to placebo in patients on a stable dose of an acetylcholinesterase inhibitor with a diagnosis of 1) DLB and 2) PDD?
Trial Objective:	COBALT is a multi-centre, parallel arm, double-blind, randomised placebo-controlled trial to assess the clinical and cost effectiveness of memantine augmentation in patients with DLB or PDD who are on an acetylcholinesterase inhibitor (AChEI) for 52 weeks with primary outcome assessed at 26 weeks.
Inclusion Criteria:	• Patients with a diagnosis or clinical features consistent with established consensus criteria for probable DLB or probable PDD. • Aged ≥55. • MMSE score ≥ 8.* • Receiving a stable dose of AChEI for ≥ 12 weeks prior to baseline, with no expected plans for dose adjustment during the trial period; dose adjustment will be allowed during the trial, if clinically indicated, following discussion with PI and, if required, the central trial team. • If receiving any antiparkinsonian treatment, antidepressants, anxiolytics, antipsychotics, or other drugs with significant psychotropic effects then dose must be stable for a minimum of 4 weeks prior to enrolment with no expected plans for dose adjustment during the trial period.† • Patients who lack capacity will be required to have a personal/professional nominated representative who is able to give informed consent on the patient's behalf. • Females must be postmenopausal and not receiving IVF treatment or must have undergone permanent sterilisation†† • Patients with sufficient knowledge of the English language or support to understand the Patient Information Sheet and complete the trial assessments

	**Evidence of mild, moderate, or moderate to severe cognitive impairment on similar global cognitive scales previously completed by their clinical care team (e.g., Addenbrooke's Cognitive Examination, Mini-Addenbrooke's Cognitive Examination, Montreal Cognitive Assessment) can be used to pre-screen the patient, prior to approach.* *[†]If a change in medication with psychotropic effects is required, this decision can be made by the treating clinician (e.g., starting an antidepressant in clinic) without consultation with the CI. In some instances the clinician may feel it is appropriate/relevant to discuss this with the PI prior to prescribing, for example, if the clinician feels that the medication change may have an impact on the trial and/or trial medication.* *Any changes should however be documented in the patient's concomitant medications electronic Case Report Form (eCRF).* *[††] Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.*
Exclusion Criteria:	• Atypical clinical features or course suggestive of an alternative dementia diagnosis. • Any clinically relevant concomitant disease that will affect ability to participate in the trial including, but not limited to, chronic renal disease stage 5, history of acute or chronic pancreatitis, epilepsy or former history of convulsions, patients with recent myocardial infarction (within last 6 months), uncompensated congestive heart failure (NYHA III-IV), or uncontrolled hypertension. • Patients with severe hepatic impairment based on known history and/or significant abnormalities identified in blood liver function tests (for example, levels in liver function tests that are 2-3 times higher than the upper limit of normal), which in the judgement of the local PI would exclude the patient from the trial.* • Patients taking memantine, amantadine, ketamine, or dextromethorphan. • Any neurological or major psychiatric diagnosis that may be contributing to cognitive impairment above and beyond that caused by the patients DLB or PDD. • Renally impaired patients with eGFR <35 mL/min/1.73m2.[†] • Currently taking part in another clinical trial that would interfere with the outcomes of the COBALT trial. • If in the opinion of the investigator, the patient would be unable to comply with the trial procedures or has difficulty taking oral medications. • Patients without a reliable caregiver/informant. **LFTs should be repeated if they were not carried out at screening and were abnormal in the last 6 months and/or, in the judgement of the local PI, are clinically relevant to check before deciding trial entry.*

	†U&Es should be repeated if they were not carried out at screening and were abnormal in the last 6 months and/or, in the judgement of the local PI, are clinically relevant to check before deciding trial entry. For example, a previous borderline eGRF <45 mL/min/1.73m2.
Number of Planned Participants:	372 total (186 DLB and 186 PDD)
Investigational product:	**Memantine**: Initial dose – 5mg per day, titrated up to 20mg per day by 4 weeks Week 1 = 5 mg per day Week 2 = 10 mg per day Week 3 = 15mg per day Week 4 and maintenance dose = 20mg per day Matched placebo
Statistical Methods:	Intention to treat analysis of the effect of memantine combined with AChEI versus AChEI alone on ADCS-CGIC at 26 weeks, adjusting for baseline disease severity. Statistical analyses will be performed separately for the two modules; COBALT-DLB and COBALT-PDD.
Subgroups:	n/a

2. GLOSSARY OF ABBREVIATIONS AND TERMS

Abbreviation	Description (using lay language)
Aβ	Amyloid beta
AChEI	Acetylcholinesterase Inhibitor
ADCS-CGIC	Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change
AE	Adverse Event
BMI	Body Mass Index
CACE	Complier Average Causal Effect
C/I CGIC	Carer/Informant Clinical Global Impression of Change
COBALT	COmBining memantine And cholinesterase inhibitors in Lewy body dementia treatment Trial
COBALT-DLB	COmBining memantine And cholinesterase inhibitors in Lewy body dementia treatment Trial – dementia with Lewy bodies group
COBALT-PDD	COmBining memantine And cholinesterase inhibitors in Lewy body dementia treatment Trial – Parkinson's disease dementia group
CRF	Case Report Form
CRO	Clinical Research Organisation
CSIR	Client Service Receipt Inventory
DAD	Disability Assessment for Dementia
eGFR	estimated Glomerular Filtration Rate
EQ-5D-5L	EuroQoL EQ-5D 5 Level
ESS	Epworth Sleepiness Scale
GCP	Good Clinical Practice
HADS	Hospital Anxiety and Depression Scale
IDMC	Independent Data Monitoring Committee
LBD	Lewy body dementias
MCID	Minimum Clinically Important Difference
MEDDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency (UK)

MIBG	Meta-Iodobenzylguanidine myocardial scintigraphy
MICE	Multiple Imputation by Chained Equations
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
NHS	National Health Service (UK)
NICE	The National Institute for Health and Care Excellence (UK)
NMA	National Mutual Acceptance (Aus)
NPI+	Neuropsychiatric Inventory Plus – a 12 item version of the NPI, original 10 items supplemented by 2 DLB/PDD relevant domains of sleep and cognitive fluctuations
PET	Positron Emission Tomography
PI	Principal Investigator
PID	Patient Identifiable Data
PIS	Patient Information Sheet
PPE	Personal Protection Equipment
PPIE	Patient and Public Involvement and Engagement
PSF	Pharmacy Site File
QA	Quality Assurance
QALY	Quality Adjusted Life Year
REDCap	Research Electronic Data Capture (Aus)
REM	Rapid Eye Movement
RGO	Research Governance Office (Aus)
RSI	Reference Safety Information (UK)
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDA	Source Data Agreement
SOC	System Organ Class
SPECT	Single-Photon Emission Computed Tomography

SSI	Significant Safety Issue
SUSAR	Suspected Unexpected Serious Adverse Reaction
TSC	Trial Steering Committee
TMG	Trial Management Group
UPDRS-III	Unified Parkinson's Disease Rating Scale
WHOQOL-BREF	World Health Organisation Quality of Life – Brief Version
USM	Urgent Safety Measure

3. INTRODUCTION &BACKGROUND INFORMATION

3.1. Lay Summary

Dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD) are related and complex illnesses with a wide range of distressing symptoms. People with DLB/PDD have worse quality of life, more complex symptoms, higher care costs, and are more sensitive to medications than people with Alzheimer's disease (AD). Acetylcholinesterase Inhibitor (AChEI) are commonly used medicines that can help people with DLB/PDD by improving day to day functioning and thinking abilities. Another drug which might help is Memantine. Memantine is a prescription drug used to treat moderate to severe confusion in Alzheimer's disease and may help to improve memory, awareness and the ability to perform daily functions. However, it is not clear if adding Memantine to AChEI is beneficial for people with DLB/PDD.

The aim of this trial is to find out if adding Memantine to AChEI improves overall health and functioning for people with DLB or PDD.

3.2. Introduction

Lewy body dementia (LBD) includes DLB and PDD and is the second commonest form of neurodegenerative dementia in older people. DLB and PDD are both devastating and progressive illnesses, and are associated with higher rates of morbidity, dependency, and mortality than AD. LBD remains one of the most challenging late life dementias in view of the combination of cognitive, neuropsychiatric, sleep, autonomic and motor features that people living with LBD experience.

This trial aims to determine the clinical and cost effectiveness of augmenting AChEI with memantine in patients with DLB and PDD.

COBALT is a multi-centre, parallel arm, double-blind, placebo-controlled, randomised trial to assess the clinical and cost effectiveness of memantine compared to placebo in patients with DLB (COBALT-DLB) and PDD (COBALT-PDD) on an AChEI.

DLB/PDD patients on a stable dose of AChEI will be randomised 1:1 to memantine or placebo for 52 weeks with an initial dose titration (to maximum tolerated dose of 20mg in 5mg increments over 4 weeks). Both trials are identical in procedure and conduct, with the only variation being the disease group. The primary outcome will be the Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change (ADCS-CGIC) scale at 26 weeks for both groups. Secondary and exploratory outcomes include a range of clinical, patient/caregiver focused, and health economic measures at 26 weeks and 52 weeks.

3.3. Background Information

LBD, neuropathologically characterised by the accumulation of abnormal alpha-synuclein proteins, is a common form of neurodegenerative disorder. DLB and PDD have many overlapping clinical and pathological features and have a wide range of distressing symptoms. LBDs, and in particular DLB, also share many clinical and pathological features with Alzheimer's disease (AD), with many patients having concurrent Alzheimer-related pathology (e.g. Amyloid beta (Aβ) and tau).[1, 2]

LBDs typically manifest as progressive cognitive and motor impairment. Diagnostic criteria exist for both DLB[3] and PDD,[4] and the two disorders are distinguished from each other on the basis of the onset of motor (parkinsonism) symptoms relative to cognitive dysfunction. Clinically, DLB is diagnosed when the onset of dementia either precedes or occurs at the same time as the motor symptoms, while PDD is diagnosed when cognitive decline/dementia occurs at least one year after the onset of idiopathic PD.[3]

DLB and PDD have a wide spectrum of cognitive, neuropsychiatric, sleep, motor, and autonomic features. As well as dementia, specific symptoms include motor parkinsonism, visual hallucinations, fluctuations in attention and alertness, and rapid eye movement (REM) sleep behaviour disorder.[3, 4] People with DLB/PDD have worse quality of life[30], experience more complex symptoms, have higher care costs, and are more sensitive to medications than people with AD.
Whilst there are significant clinical and pathological overlaps between DLB and PDD, there are also important differences:[5, 6]

- the level of co-existing abnormal proteins, for example, amyloid and tau. DLB often has greater Alzheimer's co-pathology than PDD
- the use of dopaminergic medications is often greater in PDD than in DLB
- the degree of neuropsychiatric symptoms is often greater in DLB than PDD
- the degree of parkinsonism is often greater in PDD than DLB.

Prior trials with memantine which combined DLB and PDD groups demonstrated inconsistent findings in terms of which symptoms improved, or whether DLB or PDD sub-groups benefited more from the drug.[7] Consequently, COBALT has two independently powered modules to evaluate the efficacy of memantine in DLB and PDD respectively (COBALT-DLB and COBALT-PDD) which will be conducted using the same protocol.

Pharmacological management of DLB/PDD is hugely challenging. Average care costs per patient are double those of AD reflecting the multi-morbidity associated with DLB/PDD and the significant unmet therapeutic needs.[8] DLB/PDD patients have higher rates of institutionalisation, worse quality of life and poorer survival than AD (on average 1.6 years less).[6, 9, 10] Almost 1 in 4 caregivers rate the DLB patient's health state as being equal to or worse than death.[6]
The multi-morbidity of DLB/PDD and the high likelihood of drug induced adverse events highlights the need for specific trials in DLB/PDD.[3, 11] AChEIs and memantine may delay institutionalisation, improve quality of life, and reduce care costs in DLB/PDD.[8, 12, 13]

Results from this trial will inform treatment guidelines and improve patient care internationally. If the trial result is positive, it will give a clear message to clinicians and regulatory authorities that adding memantine to AChEI in DLB/PDD is beneficial to patients and should be considered a part of standard clinical care.

3.3.1. Hypotheses

1) There will be a clinically significant difference in global outcomes between patients with DLB who receive memantine augmentation compared to those on placebo both in the short term (26 weeks) and longer term (52 weeks).

2) There will be a clinically significant difference in global outcomes between patients with PDD who receive memantine augmentation compared to those on placebo both in the short term (26 weeks) and longer term (52 weeks).

3) Memantine augmentation will be a cost-effective treatment for patients with DLB.

4) Memantine augmentation will be a cost-effective treatment for patients with PDD.

3.3.2. Risk Assessment

Memantine is a licenced medication for moderate to severe dementia in Alzheimer's disease and can be used in combination with acetylcholinesterase inhibitors (AChEI) in the UK and Australia. In Dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD) there have been previous trials using memantine, either alone or in combination with AChEI[32, 33]. In the UK, memantine is not licensed for DLB or PDD however it is recommended by NICE[34], if cholinesterase inhibitors are not tolerated or are contraindicated. Memantine has also been recognised as a potential treatment in

the recent NIHR Diamond Lewy management guideline[37,38] and is often used by clinicians off-license in the UK in these patient population groups. Given the low side effect, tolerability, and broad clinical awareness of the use, titration, and monitoring of this drug, we consider the COBALT trial to be a "Type A" Clinical Trial of an Investigational Medicinal Product (CTIMP) given the risk to the patient from the IMP would be considered to be no greater than that of standard medical care.

This trial is categorised as:

Type A = No higher than the risk of standard medical care

3.3.3. Covid-19

The COBALT protocol has been designed to allow flexibility, as far as possible, regarding face to face versus remote completion of trial related tasks, in order to allow both the central trial team and local trial teams the ability to effectively adapt should this be necessary due to COVID-19 i.e. the occurrence of additional waves, further local and/or national lockdowns, etc.

Possible delivery options for trial related tasks are described throughout section 7. Throughout this section the ideal way of delivering a task is outlined, with a remote back-up option available to sites and participants, should this be necessary. For any tasks that will continue to be carried out face to face, sites must ensure that they continue to follow local guidelines and policies, including in relation to COVID-19, for example, contacting participants prior to attendance at site in terms of COVID-19 related risk factors, the use of personal protection equipment (PPE) at site etc.

4. TRIAL AIMS AND OBJECTIVES

4.1. Aims

To determine the clinical and cost effectiveness of 12 months therapy with up to 20mg daily oral memantine in addition to Acetylcholinesterase inhibitor therapy in people with dementia with Lewy bodies (COBALT-DLB) and Parkinson's Disease Dementia (COBALT-PDD).

4.2. Objectives

Table 1 COBALT Trial Objectives

Clinical Objectives	Assessment
Primary	
To assess the impact of memantine on clinical global impression of change at 26 weeks compared to placebo in patients with DLB (COBALT-DLB) and PDD (COBALT-PDD) who are being treated with an Acetylcholinesterase Inhibitor (donepezil, rivastigmine or galantamine).	Global clinical change assessed using the Alzheimer's Disease Cooperative Study - Clinical Global Impression of Change (adapted ADCS-CGIC) scale at 26 weeks compared to baseline.
Secondary	
To assess the impact of memantine on Carer-based impression of global change compared to placebo in patients with DLB (COBALT-DLB) and PDD (COBALT-PDD) who are being treated with an Acetylcholinesterase Inhibitor (donepezil, rivastigmine or galantamine).	Change at 26 weeks compared to baseline for the Caregiver/Informant Impression of Change (C/I-CGIC) scale.
To assess the impact of memantine on changes in cognitive function compared to placebo in patients with PDD (COBALT-PDD) who are being treated with an Acetylcholinesterase Inhibitor.	Change at 26 weeks from baseline for the Montreal Cognitive Assessment (MoCA)
To assess the impact of memantine on changes in cognitive function compared to placebo in patients with DLB (COBALT-DLB) who are being treated with an Acetylcholinesterase Inhibitor.	Change at 26 weeks from baseline for the Mini-Mental State Examination (MMSE)
To assess the impact of memantine on neuropsychiatric symptom frequency and severity compared to placebo in patients with DLB (COBALT-DLB) and PDD (COBALT-PDD) who are being treated with an Acetylcholinesterase Inhibitor	Change at 26 weeks from baseline for the Neuropsychiatric Inventory Plus (NPI+)
To assess the impact of memantine on quality of life and function compared to placebo in patients with DLB (COBALT-DLB) and PDD (COBALT-PDD) who are being treated with an Acetylcholinesterase Inhibitor	Change at 26 weeks from baseline for the following assessments :- • EuroQol EQ-5D 5 Level (EQ-5D-5L) – patient • EQ-5D-5L – proxy
To assess the impact of memantine on clinical global impression of change at 52 weeks compared to placebo in patients with DLB (COBALT-DLB) and PDD (COBALT-PDD) who	Global clinical change assessed using the Alzheimer's Disease Cooperative Study - Clinical Global Impression of

are being treated with an Acetylcholinesterase Inhibitor (donepezil, rivastigmine or galantamine).	Change (ADCS-CGIC) scale at 52 weeks compared to baseline.
Exploratory	
To assess the impact of memantine on Carer-based impression of global change compared to placebo in patients with DLB (COBALT-DLB) and PDD (COBALT-PDD) who are being treated with an Acetylcholinesterase Inhibitor (donepezil, rivastigmine or galantamine).	Change at 52 weeks compared to baseline for the Caregiver/Informant Impression of Change (C/I-CGIC) scale.
To assess the impact of memantine on changes in cognitive function compared to placebo in patients with DLB (COBALT-DLB) who are being treated with an Acetylcholinesterase Inhibitor.	Change at 26 and 52 weeks from baseline for the Montreal Cognitive Assessment (MoCA)
To assess the impact of memantine on changes in cognitive function compared to placebo in patients with DLB (COBALT-DLB) who are being treated with an Acetylcholinesterase Inhibitor	Change a 52 weeks from baseline for the Mini-Mental State Examination (MMSE)
To assess the impact of memantine on changes in cognitive function compared to placebo in patients with PDD (COBALT-PDD) who are being treated with an Acetylcholinesterase Inhibitor.	Change at 26 and 52 weeks from baseline for the Mini-Mental State Examination (MMSE)
To assess the impact of memantine on changes in cognitive function compared to placebo in patients with PDD (COBALT-PDD) who are being treated with an Acetylcholinesterase Inhibitor.	Change at 52 weeks from baseline for the Montreal Cognitive Assessment (MoCA)
To assess the impact of memantine on neuropsychiatric symptom frequency and severity compared to placebo in patients with DLB (COBALT-DLB) and PDD (COBALT-PDD) who are being treated with an Acetylcholinesterase Inhibitor	Change at 52 weeks from baseline for the Neuropsychiatric Inventory Plus (NPI+)
To assess the impact of memantine on quality of life and function compared to placebo in patients with DLB (COBALT-DLB) and PDD (COBALT-PDD) who are being treated with an Acetylcholinesterase Inhibitor	Change at 52 weeks from baseline for the following assessments :- • EuroQol EQ-5D 5 Level (EQ-5D-5L) – patient • EQ-5D-5L – proxy Change at 26 and 52 weeks from baseline for the following assessments :- • Hospital Anxiety and Depression Scale (HADS) – Patient • Disability Assessment for Dementia (DAD) • The Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III -

	motor examination • Epworth Sleepiness Scale (ESS)
To assess the impact of memantine compared to placebo in patients with DLB (COBALT-DLB) and PDD (COBALT-PDD) on quality of life for the caregiver.	Change at 26 and 52 weeks from baseline for the following assessments :- • EQ-5D-5L - Caregiver/ informant • Zarit Burden Interview - Caregiver/ informant • WHO Quality of Life - BREF (WHOQOL-BREF) - Caregiver/ Informant • Hospital Anxiety and Depression Scale (HADS) - Caregiver/informant
To determine the long-term outcomes for patients with DLB (COBALT-DLB) and PDD (COBALT-PDD) who are being treated with an Acetylcholinesterase Inhibitor following treatment with memantine compared to placebo	*Optional long-term follow-up at 24 months:* • Significant medical events experienced • Current living situation • Current medications • Vital status
Health Economic Objectives	**Assessment**
Exploratory	
To assess the cost effectiveness of memantine compared to placebo in patients with DLB (COBALT-DLB) and PDD (COBALT-PDD) who are being treated with an Acetylcholinesterase Inhibitor.	Change at 26 and 52 weeks from baseline for the Client service receipt Inventory (CSRI)

4.3. Outcome Measures

Table 2. COBALT Trial outcome measures

Time point	Condition	Outcome	Assessment
26 weeks	PDD	Primary	Alzheimer's Disease Cooperative Study - Clinical Global Impression of Change (ADCS-CGIC)
		Secondary	Caregiver/Informant Impression of Change (C/I-CGIC) Montreal Cognitive Assessment (MoCA) Neuropsychiatric Inventory Plus (NPI+) EuroQol EQ-5D 5 Level (EQ-5D-5L) - patient EQ-5D-5L – proxy
		Exploratory	Mini-Mental State Examination (MMSE) Hospital and Depression Scale (HADS) Disability Assessment for Dementia (DAD) The Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III - motor examination Epworth Sleepiness Scale (ESS) Client service receipt Inventory (CSRI) EQ-5D-5L - Caregiver/informant Zarit Burden Interview - Caregiver/informant WHO Quality of Life - BREF (WHOQOL-BREF) - Caregiver/Informant Hospital and Depression Scale (HADS) - Caregiver/informant
	DLB	Primary	ADCS-CGIC
		Secondary	C/I-CGIC MMSE NPI+ EQ-5D-5L - patient EQ-5D-5L – proxy
		Exploratory	MoCA HADS DAD MDS UPDRS-III ESS CSRI Zarit Burden Interview - Caregiver/informant WHOQOL-BREF - Caregiver/informant HADS - Caregiver/informant EQ-5D-5L - Caregiver/informant
52 weeks		Secondary	ADCS-CGIC

	PDD and DLB	Exploratory	C/I-CGIC MMSE MOCA NPI+ EQ-5D-5L – patient EQ-5D-5L - proxy HADS DAD MDS UPDRS-III ESS CSRI Zarit Burden Interview - Caregiver/informant WHOQOL-BREF - Caregiver/informant HADS - Caregiver/informant EQ-5D-5L - Caregiver/informant
24 months (optional)	PDD and DLB	Exploratory	Significant medical events experienced Current living situation Current medications Vital status

5. TRIAL DESIGN

5.1. Cobalt DLB Trial Flow diagram

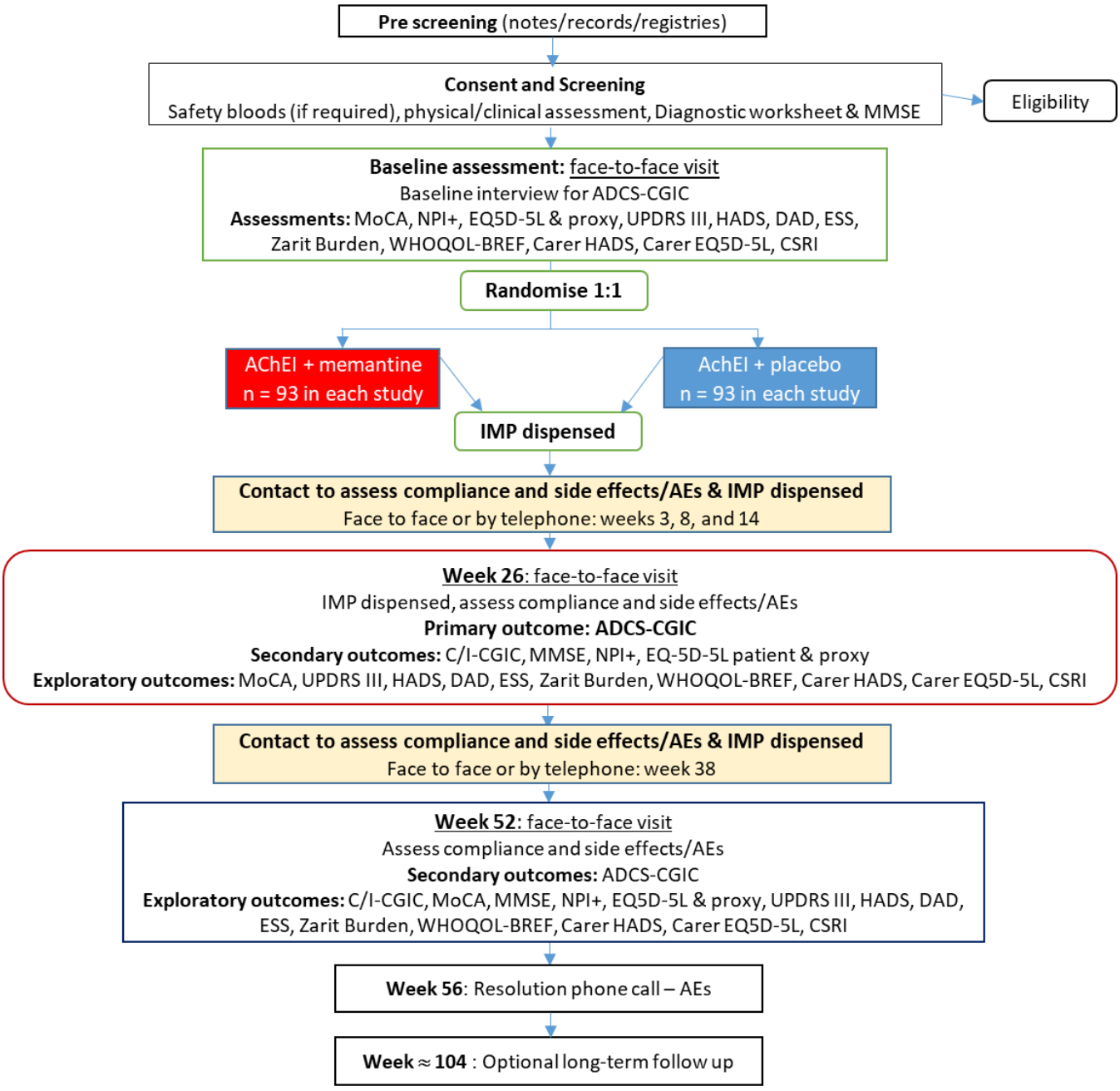

Figure 1. COBALT DLB Trial Flow Chart

5.2. Cobalt PDD Trial Flow diagram

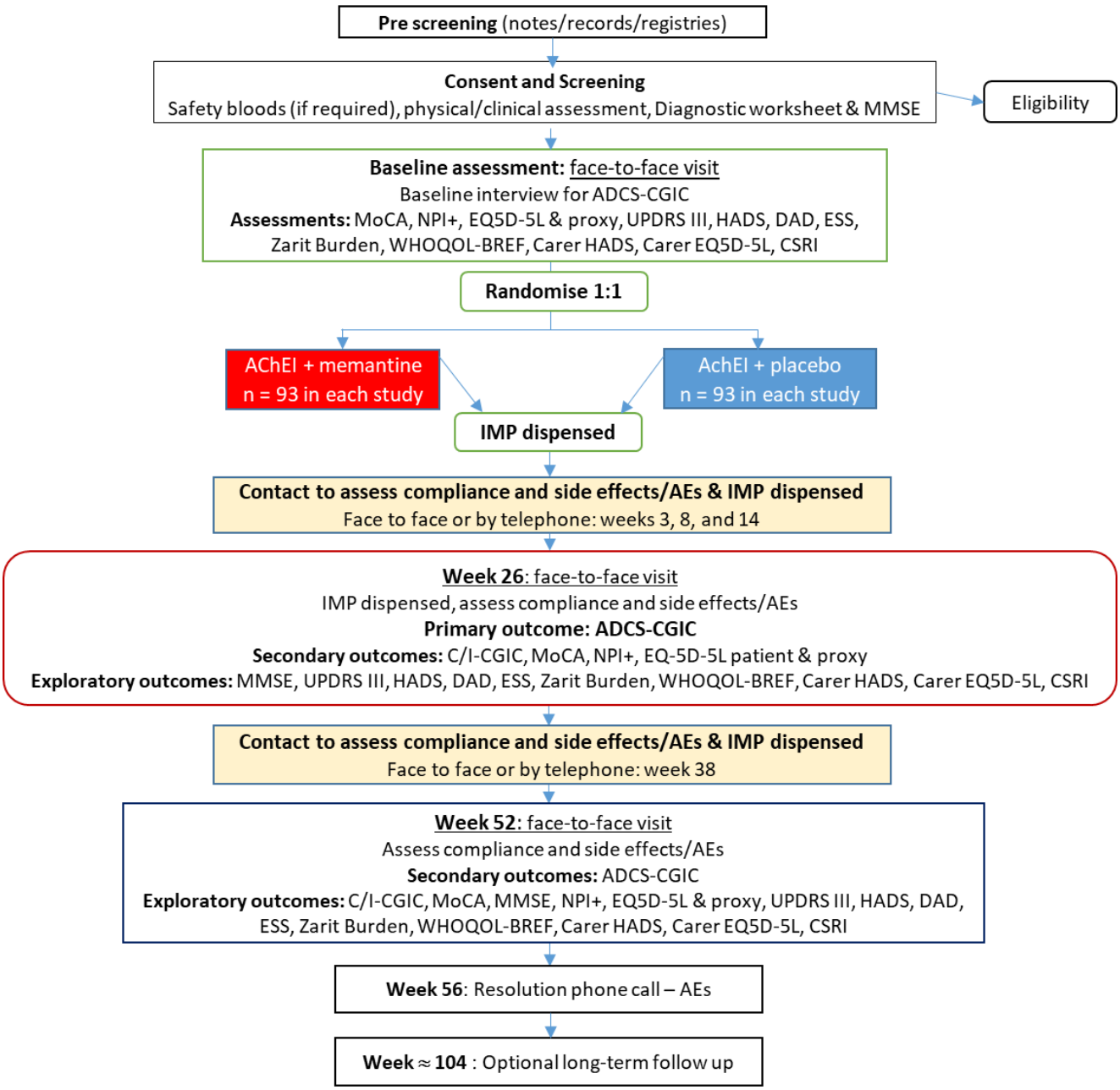

Figure 2. COBALT PDD Trial Flow Chart

5.2. Trial Design & Patient Population

The COBALT trial is a multi-centre, parallel arm double blind randomised controlled trial to assess the clinical and cost-effectiveness of memantine compared to placebo in patients with DLB (COBALT-DLB) and PDD (COBALT-PDD) on an AChEI (donepezil, rivastigmine or galantamine).

186 DLB and 186 PDD patients, aged 55 years and above, on a stable dose of AChEI, will be randomised 1:1 to memantine or placebo for 52 weeks with an initial dose titration (to maximum tolerated dose of 20 mg in 5mg weekly increments over 4 weeks).

The primary outcome will be the ADCS-CGIC scale at 26 weeks. Secondary and exploratory outcomes will include a range of clinical, patient- and caregiver-focused, as well as health economic measures. The assessment time point for the primary outcome will be at 26 weeks post baseline. Secondary/exploratory outcomes will be assessed at 26 and 52 weeks.

5.3. Trial Setting

Patients with a clinical diagnosis of probable DLB/PDD will be recruited from UK sites, which will include up to 25 NHS services in England and the Devolved Nations, and up to 5 Australian sites.

Given the trial population includes potentially older, frail participants, the option of home visits and virtual assessments will be available. This approach is strongly advocated by our Patient and Public Involvement and Engagement (PPIE) panel as well as by expert clinicians with prior experience in DLB/PDD clinical trials. This approach has significant impact on minimising drop-out from the trial given the high degree of frailty/motor disability in DLB/PDD and the practical challenge many participants face when travelling to assessment/clinical units. The location of trial assessments (i.e. home visit, site visit or remote) will be recorded, allowing the option for further future analysis whether assessment location has an impact on trial outcomes.

Ideally assessments for a particular participant will consistently be performed in the same setting across visits i.e., if assessed at baseline in the clinic the subsequent 26 week and 52 week assessments are also done in the clinic.

5.4. Trial Population

Patients with a diagnosis or clinical features consistent with established consensus criteria for probable DLB and probable PDD and their caregiver/informant.

DLB: patients must have dementia with at least two of the four core clinical features (cognitive fluctuations, parkinsonism, visual hallucinations, REM sleep behaviour symptoms); or one core clinical feature with at least one positive indicative biomarker (reduced dopamine transporter uptake in basal ganglia demonstrated by single-photon emission computed tomography (SPECT) or positron emission tomography (PET) imaging, reduced uptake on meta-iodobenzylguanidine myocardial scintigraphy (MIBG), or polysomnography confirmation of REM sleep without atonia) (see Appendix 1)[3].

PDD patients must have diagnosis of PD according to the Queen Square Brain Bank Criteria: dementia developing in the context of established PD, with a typical cognitive profile (impairment in at least two of the following domains: attention, which may fluctuate; executive function; visuospatial function; free recall, the presence of at least one behaviour symptom and absence of group III and IV features.) (See Appendix 2)[4].

DLB and PDD often have similar clinical profiles. To categorise participants for the purposes of the trial as either DLB or PDD, we will apply the one-year rule i.e., to make a diagnosis of PDD, the motor symptoms (if present) must precede the onset of dementia by at least one year whereas if the dementia develops within 1 year of the onset of motor symptoms then the diagnosis will be DLB.

At screening, it is likely that sites will identify patients with a broad range of other diagnostic labels e.g. Alzheimer's with Lewy body disease, Lewy body disease, Lewy body dementia, Parkinson's with cognitive impairment, Parkinson's with memory difficulties etc. In addition, some patients who have a clinically recorded diagnosis of PDD or DLB may end up having a diagnosis of the other after entry into the trial.

The onus will be on the site Principal Investigator (PI)/ sub-I to define the final diagnosis for the purposes of COBALT on basis of the consensus diagnostic criteria for DLB / PDD and the one who will decide which trial (PDD or DLB) the patient enters, rather than any a priori clinical diagnosis/label. This will be explained to the participant and caregiver/informant during the screening and consent process and that any variance between prior clinical diagnosis and the diagnosis used in the trial is done for ensuring that the participants meet the appropriate criteria for the right trial whether as a DLB or PDD.

The patient's caregiver/informant should be a person that is in regular contact with the patient (minimum once per week), who knows the patient well and is able to attend the trial follow-up visits as required. The caregiver/informant must have sufficient knowledge of the patient so that they are able to complete assessments relating to the patient's cognitive, emotional, and physical changes during the trial. The carer/informant should be identified during the screening process and is required to consent to participate in the trial. The term 'trial partner' is used to describe the caregiver/informant throughout the patient facing documentation.

6. Eligibility Criteria

6.1. Inclusion criteria

- Patients with a diagnosis or clinical features consistent with established consensus criteria for probable DLB or probable PDD (see appendix 1 and 2 respectively)
- aged ≥ 55 years (no upper limit)
- MMSE score ≥ 8 *
- Receiving a stable dose of AChEI for ≥12 weeks prior to baseline, with no expected plans for dose adjustment during the trial period; dose adjustment will be allowed during the trial, if clinically indicated, following discussion with PI and, if required, the central trial team.
- If receiving any antiparkinsonian treatment, antidepressants, anxiolytics, antipsychotics or other drugs with significant psychotropic effects then dose must be stable for a minimum of 4 weeks prior to enrolment with no expected plans for dose adjustment during the trial period; dose adjustment will be allowed during the trial if clinically indicated and will be documented. †
- Patients who lack capacity to consent will be included in the trial to ensure that the sample is representative of the population that is likely to benefit. Patients who lack capacity will be required to have a personal/professional nominated representative who is able to give informed consent on the patient's behalf.
- Females must be postmenopausal and not receiving IVF treatment or have undergone permanent sterilisation††
- Patients with sufficient knowledge of the English language or support to understand the Patient Information Sheet and complete the trial assessments

**Evidence of mild, moderate, or moderate to severe cognitive impairment on similar global cognitive scales previously completed by their clinical care team (e.g. Addenbrooke's Cognitive Examination, Mini-Addenbrooke's Cognitive Examination, Montreal Cognitive Assessment) can be used to pre-screen the patient, prior to approach.*

†If a change in medication with psychotropic effects is required, this decision can be made by the treating clinician (e.g. starting an antidepressant in clinic) without consultation with the CI. In some instances the clinician may feel it is appropriate/relevant to discuss this with the PI prior to prescribing, for example, if the clinician feels that the medication change may have an impact on the trial and/or trial medication.

Any changes should however be documented in the patient's concomitant medications electronic Case Report Form (eCRF).

[††]Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

6.2. Exclusion Criteria

- Atypical clinical features or course that might suggest an alternative dementia diagnosis.
- Any clinically relevant concomitant disease that will affect ability to participate in the trial including, but not limited to, chronic renal disease stage 5, history of acute or chronic pancreatitis, epilepsy or former history of convulsions, patients with recent myocardial infarction (within last 6 months), uncompensated congestive heart failure (NYHA III-IV), or uncontrolled hypertension.
- Patients with severe hepatic impairment based on known history and/or significant abnormalities identified in blood liver function tests (for example, levels in liver function tests that are 2-3 times higher than the upper limit of normal), which in the judgement of the local PI would exclude the patient from the trial.*
- Patients taking memantine, amantadine, ketamine, or dextromethorphan.
- Any neurological or major psychiatric diagnosis that may be contributing to cognitive impairment above and beyond that caused by the patient's DLB/PDD.
- Renally impaired patients with eGFR <35 mL/min/1.73m2.[†]
- Currently taking part in another clinical trial that would interfere with the outcomes of the COBALT trial.
- If in the opinion of the investigator, the patient would be unable to comply with the trial procedures or has difficulty taking oral medications.
- Patients without a reliable caregiver/informant.

**LFTs should be repeated if they were not carried out at screening and were abnormal in the last 6 months and/or, in the judgement of the local PI, are clinically relevant to check before deciding trial entry.*

[†]U&Es should be repeated if they were not carried out at screening and were abnormal in the last 6 months and/or, in the judgement of the local PI, are clinically relevant to check before deciding trial entry. E.g., a previous borderline eGRF <45 mL/min/1.73m2.

UK only:

NB: Enrolling a patient onto the trial who does not meet the inclusion/exclusion criteria is considered a protocol waiver and is in breach of Regulation 29 (SI 2004/1031) of the Medicines for Human Use (Clinical Trials) Regulations 2004. PROTOCOL WAIVERS ARE NOT PERMITTED.

To maximise recruitment and ensure the generalisability and impact of the findings, the inclusion criteria are broad, and the exclusion criteria are limited while ensuring patient safety.

7. TRIAL PROCEDURES

7.1. Recruitment

Recruitment will take place across a large network of centres widely geographically distributed in the UK and Australia.

We will raise awareness of the trial at local clinics such as secondary care movement disorder, neurology, geriatric, memory clinics, care home settings and psychiatric services and, where identified, patients who

have been discharged back to primary care, from local secondary care services. Trial posters or pamphlets may be displayed in waiting rooms and clinics.
Patients may be identified on review of clinical databases, review of medical records, clinical trial registries, societies, websites, social media, subject to local guidelines. Patients may then be referred to a trial site for further information or to see if they are eligible to join the trial. If preferred the patient invitation letter may be provided by trial sites to referring clinicians that they can then send to patients who they think may be interested in hearing about the trial.

UK only:

In addition to the above, patients may be identified by Participant Identification Centres (PICs) and from registers such as Join Dementia Research. This service connects registered volunteers with dementia researchers across the UK who are looking for people to participate in trials.

Australia only:
In addition to the above, the trials will be listed on platforms such as Dementia Australia or Step Up for Dementia where patients can search for trials that they may be suitable for and/or register their interest, and/or contact trial sites directly.

Recruitment will be reviewed as part of an internal 12 month pilot. Screening to recruitment conversion rate will be monitored during this time and a stop-go milestone has been agreed with the UK funder.

7.1.1. Patient identification and Provision of trial Information

The PIs at each site will promote the trial to their fellow clinicians. Suitable patients will be identified by clinicians or clinical research network staff at sites using patient clinic lists and databases, and/or research registers. Each site can also accept self-referrals from interested patients or their GPs.

UK only:

Recruitment will be supported by local Clinical Research Network staff and both locally and regionally through the Parkinson's UK 'Take Part' Hub, and the Parkinson's Disease Nurse Specialist Association (PDNSA) website, as well as other patient advocacy groups/charities including for example, the Lewy Body Society.

An MMSE score of ≥8 is not a prerequisite for approach, as this assessment will be completed at screening to confirm eligibility. Evidence of mild, moderate, or moderate to severe cognitive impairment on similar global cognitive scales (e.g., Addenbrooke's Cognitive Examination, Mini-Addenbrooke's Cognitive Examination, Montreal Cognitive Assessment) previously completed by the patient's clinical care team, can be used to pre-screen the patient, prior to approach.

All patients pre-screened and formally screened at site will be documented on a screening log. Reasons for patient ineligibility will be documented on the log as will reasons given by the patients or their nominated representative for those who decline, if known, to avoid re-approach.
Initial contact can be made through a variety of routes, including, for example, informing patients about the trial at one of their standard clinical visits, contacting potential participants by telephone or sending the COBALT trial invitation letter including the patient information sheet.

All patients and their caregivers/informants will be given a minimum of 24 hours to consider participation to ensure they understand what the trial involves and the risks for them. Patients will be encouraged to ask questions about the trial and consider whether they wish to participate.

A member of the local trial team will contact the patient and if the patient and caregiver/informant both wish to proceed, a consent/screening visit will be arranged to take place at a location convenient to them. This could be at the clinic where the patient would be attending a standard clinic appointment, at another

clinical facility that is part of the research site, or at the patient's home or via telephone/teleconference or videoconference.

Routine care will continue for all patients alongside trial participation.

7.1.2. Consent

Written informed consent from the patient and their caregiver/informant will be received by the **investigator**, after discussing the trial and answering any questions the patient has to their satisfaction. Informed, written consent will be sought prior to conducting any trial procedures, including any screening assessments. The **investigator** taking consent will be GCP trained, suitably qualified, experienced and will have been delegated this duty by the site PI on the Delegation of Duties Log.

UK only:

Investigators taking consent in the UK must be GMC registered.

For this trial, written informed consent needs to be obtained from:

- the participant (or nominated representative if the participant has impaired capacity to consent – see section 7.1.2.1)
- the participant's Caregiver/Informant

In some circumstances, the Caregiver/Informant may also be the participant's **nominated representative** (for example, next of kin). In this instance they would be required to sign each applicable consent form.

7.1.2.1. Impaired Capacity to Consent

For the purposes of inclusivity and on the principle of equity in research access, participation in the trial is open to people who may lack capacity to consent given participants with dementia or cognitive impairment may not have capacity to consent for themselves.

However, investigators should also bear in mind that even without full capacity participants may have some understanding of the trial as well as the benefits and burdens of participation. Participants with reduced capacity should therefore be involved in the discussion and decision making; however, a **nominated representative** to provide informed consent on their behalf should be identified. A Personal Legal representative will used in the first instance i.e., someone who knows the participants thoughts and wishes. It is important to note that any advanced decisions made by the participant will be respected. All sites will be required to adhere to the local and national regulations regarding who a nominated representative may be.

UK only:

A nominated representative in the UK is referred to as a personal/professional legal representative.

Australia only:

A nominated representative in Australia is referred to as a Medical Treatment Decision Maker.

For patients lacking capacity we will seek their agreement to participate and will check their level of understanding. If the patient is lacking capacity but still appears to be willing, an opinion will be sought from their nominated representative. The nominated representative **must not** be a person connected with the conduct of the trial, for example a trial investigator, a member of the local trial team, or a person who provides health care under the directions or control of a local trial team member regardless of whether it is in relation to the trial or not. If the patient regains capacity during the trial, they will be asked whether they wish to continue taking part.

If a patient has capacity and consents to the baseline assessment, but loses capacity during the trial, then opinion will be sought from their **nominated representative** and the patient would only continue to be included in the trial if they appear willing and the nominated representative agrees. Any advanced decisions made by the participant will be respected. This decision process should be clearly documented in the participant's medical records. The nominated representative will be required to complete and sign a consent form.

If at the time of consent the participant appears unwilling to be included, then they will not be included. If at any point throughout the trial the participant appears unwilling to continue to take part they will be withdrawn after discussion with the nominated representative.

In the case of protocol amendments or information becoming available which may affect any of the parties willingness to continue in the trial, it may be necessary to re-consent using an updated consent form (after necessary ethical approvals have been obtained).

7.1.2.2. Consent Process

Reflecting the challenges of COVID-19 and to maximise opportunity for trial participation we have delineated a number of consent process options depending on the prevailing circumstances and COVID-19 rules/legal frameworks. A summary of these is found in Table 3. These processes may also be used for reconsenting throughout the trial.

For those participants who have capacity to consent for themselves, they must personally print their name, sign and date the latest approved version of the Informed Consent Form. In cases where the participant is physically unable to print their name or date the consent form due to their condition or physical disability, this can be completed by another person (e.g., a family member, in the presence of the patient at their request). The consent process must be fully documented in the participant's medical records and in the event that a participant is assisted to complete the consent form (e.g. to print participant's name or date), a file note should be attached to the consent form, detailing that another person has assisted with completion of the consent form on behalf of the participant and the reason why this was necessary. The consent form however **cannot** be signed on behalf of the patient; the patient must always add their own signature.

Option A: In-person consent

The consent process can take place in clinic or at the participant's home if necessary, with the investigator visiting the participant to carry out in-person consent. This consent visit should take place following appropriate local policies regarding face-to-face patient contact including any local COVID-19 policies. Consent must be received prior to any trial specific assessments.

Step 1: The current, approved version of the information sheet and consent forms should be provided in advance so that the participant, nominated representative (if applicable and as described in section 7.1.2.1), and caregiver/informant have adequate time to read the information and to discuss with their local doctor and/or family member/s if they wish. They should be advised to **not** sign the forms prior to the in-person visit.

Step 2: The participant's capacity to consent must be assessed. Members of the local trial team who will assess capacity should have experience working with vulnerable patients and those with cognitive impairment and will be delegated to assess the participant's capacity to consent.

Step 3: The Investigator gives a verbal explanation of the trial to the participant/nominated representative and caregiver/informant, and they will be given the opportunity to ask questions. The voluntary nature of this trial, and the right to withdraw from the trial at any stage, will be made clear to all parties without their decision having an impact on the participant's ongoing clinical care.

Step 4: The consenting parties will then be invited to sign and date the consent form/s in the presence of the investigator. The investigator will also sign and date the form. A signed copy of the original will be given back to the participant and caregiver/informant, a copy will be filed in the participants medical records and the original will be filed in the Investigator Site File. The consent process should be documented in the participants medical records.

UK only:

A copy of the completed consent forms should be sent to NCTU within 5 working days using the COBALT trial confidential inbox: **nctu.cobalt.conf@nhs.net**

Option B: Remote consent discussion, followed by in-person visit for signing the consent form

This consent option allows for preliminary consent discussion to occur via telephone or videoconference which is followed by an in-person visit where all parties sign the informed consent form in each other's presence.

This approach may be preferential for some individuals or useful if for example due to safety reasons (e.g. COVID-19 risk), face-to-face contact time needs to be minimised. It allows ample time for the investigator, participant/nominated representative, and their caregiver/informant to discuss the trial and respond to any questions via telephone/videoconference prior to the visit, so that on the day of the visit a brief summary of the consent discussion can be provided before all parties sign the consent form in each other's presence.

Step 1: Same process as Step 1, Table 3.

Step 1a: A consent discussion via phone or video conference should be scheduled at a mutually convenient time between the investigator, member of the local trial team, the participant/nominated representative and their caregiver/informant. The date of discussion and who was present should be documented in the participant's medical records.

Step 2: Same process as Step 2, Table 3.

Step 3: Same process as Step 3, Table 3. In addition, an in-person visit is scheduled after the consent discussion (ideally within 2 weeks) for the consenting parties. They should be advised to **not** sign the consent form prior to the in-person visit.

Step 4: Same process as Step 4, Table 3. The consenting parties will sign and date the consent form/s in the presence of the investigator at the scheduled in-person visit. The investigator will also sign and date the form. A signed copy of the original will be given back to the participant/nominated representative and caregiver/informant, a copy will be filed in the participants medical records and the original will be filed in the Investigator Site File. The consent process should be documented in the participants medical records.

UK only:

A copy of the completed consent forms should be sent to NCTU within 5 working days using the COBALT trial confidential inbox: **nctu.cobalt.conf@nhs.net**

Australia only:

Option C: Remote consent via telephone or videoconference

Ideally, obtaining consent in person should always be the chosen option wherever possible. However, a remote consent alternative via videoconference or speakerphone has been provided for instances where

COVID-19 disruptions may impact in-person visits or there are other extenuating circumstances affecting the participant's ability to attend clinic for an in-person consent visit. Examples of such circumstances may be (but not limited to) increased participant/caregiver burden to travel to the site, living at a distance from the site, and participant frailty.

If the remote consent process is followed, it is important to note that the phone call/videoconference should include a delegated investigator who will assess capacity and obtain consent, the participant/ nominated representative (if applicable) and the caregiver/informant, and at least one other member of the local trial team who will observe the process. *Please note this team member is not the same as an independent witness. If an independent witness is required (for example, if a person cannot read for themselves) then the independent witness cannot be a member of the local trial team.*

When remote consent is utilised, the consent form will be signed on different days. The reason for this should be clearly documented in the participant's records as detailed below.

Step 1: Same process as Step 1, Table 3. In addition, the Investigator or delegate should ascertain whether the consenting parties have the capability for speakerphone or videoconferencing and schedule the date and time for the consent call.

Step 1a: At the pre-determined date and time, the Investigator, the participant/nominated representative and their caregiver/informant, and another member of the local trial team should join the consent discussion by speakerphone or videoconference.

Step 2: Same process as Step 2, Table 3

Step 3: Same process as Step 3, Table 3

Step 4: The participant/nominated representative, and caregiver/informant will sign and date the consent form/s whilst on the call. They will return the signed forms via post in the pre-paid envelope provided. After the consent forms have been signed, the participant is considered enrolled in the trial and trial assessments may proceed. The process of obtaining consent should be documented in the participant's records by the Investigator. For example, "The protocol was discussed with [participant/nominated representative, caregiver/informant] via telephone/video conference today [DD/MM/YYYY]. The investigator and local trial team member who was present should then initial and date the entry.

Step 5: Once the original, signed consent form has been received back at the trial site, the investigator who obtained consent should sign and date the consent form with the date that it has been reviewed. In addition, the investigator should document the following in the participant's records "the original consent form signed by the participant on [DD/MMM/YYYY], was received in hard copy and signed by me the consenting investigator, dated today DD/MMM/YYYY]".

Step 6: A signed copy of the original consent form should be sent back to the participant/nominated representative and caregiver/informant, and the original should be filed in the ISF. The consent process should be documented in the participants medical records.

UK only:

Option C: Remote consent via telephone or videocall

Ideally, obtaining consent in person should always be the chosen option wherever possible. However, a remote consent alternative via videocall or telephone (using speakerphone) has been provided for instances where COVID-19 disruptions may impact in-person visits or there are other extenuating circumstances affecting the participant's ability to attend clinic for an in-person consent visit. Examples of such circumstances may be (but not limited to) increased participant/caregiver burden to travel to the site, living at a distance from the site, participant frailty.

NB. The local trial team member is not the same as an independent witness. If an independent witness is required (for example, if a person cannot read for themselves) then the independent witness cannot be a member of the local trial team.

If the remote consent process is followed, it is important to note that the telephone/video call should include a delegated investigator who will assess capacity and obtain consent, the participant/ nominated representative (if applicable) and the caregiver/informant, and at least one other member of the local trial team who will carry out initial capacity assessment, facilitate the telephone/video call, observe at the patient's home and countersign the consent form as a witness. This double check of capacity will be conducted due to the remote nature of this option.

When remote consent is utilised, the investigator taking consent remotely will also sign a consent interview declaration form.

Step 1: Same process as Step 1, Table 3. In addition, the investigator or delegate should ascertain whether the consenting parties have the capability for speakerphone or videoconferencing and schedule the date and time for the consent call.

Step 1a: At the pre-determined date and time, the Investigator, the participant/nominated representative and their caregiver/informant, and another member of the local trial team (present at the participants home) should join the consent discussion by speakerphone or videoconference.

Step 2: Same process as Step 2, Table 3

Step 3: Same process as Step 3, Table 3

Step 4: The participant/nominated representative, and caregiver/informant will sign and date the consent form/s whilst on the call. The member of the local trial team present at the participants home will countersign the consent form. The investigator will sign a **consent interview declaration form** on the call to confirm consent has been received and that they are happy for the patient to be enrolled.

After the consent forms have been signed, the participant is considered enrolled in the trial and trial assessments may proceed. The process of obtaining consent should be documented in the participant's medical records by the Investigator. For example, "The protocol was discussed with [participant/nominated representative, caregiver/informant] via telephone/video conference today [DD/MMM/YYYY]. The investigator and local trial team member who was present should then initial and date the entry.

Step 5: Once the original, signed consent form has been received back at the trial site, the Investigator who obtained consent should sign and date the consent form with the date that it has been reviewed. In addition, the investigator should document the following in the participant's records "the original consent form signed by the participant on [DD/MMM/YYYY], was received in hard copy and signed by me, the consenting investigator, dated today DD/MMM/YYYY]".

Step 6: A signed copy of the original consent form should be sent back to the participant/nominated representative and caregiver/informant, the original should be filed in the Investigator Site File (ISF) and a copy filed in the participants medical records. The consent process should be documented in the participants medical records.

A copy of the completed consent forms and consent interview declaration form should be sent to NCTU within 5 working days using the COBALT trial confidential inbox: **nctu.cobalt.conf@nhs.net**

Table 3. Consent Process Summary

	Option A In-Person Consent	**Option B Remote consent discussion, followed by in-person visit for signing**	**Option C Remote consent via telephone or videoconference**
Step 1 Provide information sheet and consent form in advance and allowing adequate time for consideration by the participant before taking part	✓	✓	✓
Step 1a - Schedule a consent discussion call - Record date of discussion and who was present in the participant's trial records	n/a	✓	✓
Step 2 Assess participant's capacity	✓	✓	✓
Step 3 Investigator explains trial and provides opportunity for questions	✓	✓ In addition, schedule an in-person visit (ideally within 2 weeks) for the consenting parties.	✓
Step 4 Sign the consent form	✓	at the scheduled in-person visit	- Participant and Caregiver/informant sign and date the consent form/s whilst on the call **Australia only**: - Return the signed forms to site **UK only:** - local trial team member countersigns consent form - Investigator signs consent interview declaration form - Participant is considered enrolled and trial assessments may proceed

	Option A In-Person Consent	Option B Remote consent discussion, followed by in-person visit for signing	Option C Remote consent via telephone or videoconference
Step 5 - original, signed consent form received back at the trial site	n/a	n/a	✓
Step 6 - signed copy of the original given back to the participant/nominated representative and caregiver/ informant. Original copy and other copies filed as required	✓	✓	✓

7.1.3. Screening

The screening assessment may occur at the same visit as consent is received. Written informed consent will be obtained (section 7.1.2), and the following assessments performed to check eligibility and confirm which trial the patient will be entered into (DLB or PDD).

- MMSE*
- Blood sample for eGFR and Liver Function Tests (total protein, bilirubin, GGT, AST and/or ALT & ALP), if no result available or accessible to the local trial team in the last 6 months. †
- DLB or PDD clinical diagnostic worksheet.

**MMSE which has been completed at screening (day -14 to 0) does not need to be repeated at the baseline visit (day 0) given it occurs no later than 14 days after the screening assessments.*

†If in the opinion of the PI, the available results are abnormal/clinically relevant, the tests should be repeated.

The DLB or PDD clinical diagnostic worksheet must be completed for every patient to confirm that they are eligible to be randomised as part of the COBALT-DLB or COBALT-PDD trial. The initial screening diagnosis can be completed by an experienced delegated member of the local trial team. However, final diagnosis sign-off on the diagnostic worksheet, before randomisation/prescribing, should be made by someone medically qualified and who is familiar with DLB and PDD diagnostic criteria (e.g. PI or sub-PI).

If the patient meets all Inclusion/Exclusion criteria they will be randomised to receive either memantine or placebo.

UK only:

A copy of the completed eligibility checklist should be sent to NCTU within 5 working days using the COBALT trial confidential inbox: **nctu.cobalt.conf@nhs.net**

If the patient is found to be ineligible to participate (for example, too low an MMSE score due to cognitive fluctuations on that day or acute intercurrent illness which precludes their immediate involvement etc.), they can be re-screened at least 2 weeks after the initial screening assessment date if, in the opinion of

the investigator, they may have become eligible. Patients can be re-screened once only. If they are found to be ineligible at the second screening assessment, they will not be re-screened.

7.2. Randomisation

For each trial (COBALT-DLB; COBALT-PDD), a web-based interactive randomisation system will assign participants to active or placebo treatment in a 1:1 ratio. Randomisation will be stratified by severity of dementia (using MMSE 8-19 for moderate/severe; ≥20 for mild) and country.

Participants who fulfil the eligibility criteria and for whom informed consent has been obtained, will be randomly allocated to receive either memantine or matched placebo by delegated and trained members of the local trial team.

UK only:
The Sealed Envelope randomisation system (a central, secure, 24-hour web-based randomisation system with concealed allocation) will be used. Participants will be randomised in a ratio of 1:1 (placebo: intervention). The allocation sequence will be computer-generated, using a random permuted blocks design.

Local research staff delegated the randomisation task on the delegation log, will be provided with a login and password for the randomisation system.

Site will allocate a unique participant trial identifier and the system will allocate a medication number to be dispensed to the participant.

Randomisation system URL:
https://www.sealedenvelope.com/access/
This system is available 24 hours a day, seven days a week

In the event that the online system is not accessible at site, NCTU can liaise with Sealed Envelope Support to investigate the cause. Site staff should contact NCTU Database Support during normal working hours:
Email: nctu.database.support@newcastle.ac.uk
Telephone: 0191 208 8211

Australia only:

A central randomisation schedule will be generated by an independent statistician. The randomisation schedule will be programmed into an electronic case report form (eCRF) system which will be housed on a RedCAP platform. Randomisation will be performed by an independent, central, unblinded delegate who is not a member of the local trial team. The unblinded delegate will require a password protected log in. Participants will be randomised in a ratio of 1:1 (placebo:intervention).

7.2.1. Blinding/masking

This is a double-blind trial, meaning participants, caregivers, and the local trial team involved in providing intervention and conducting assessments will be blinded/masked to treatment allocation. Participants, caregivers and the investigator/assessor completing the CGIC at the visit will be asked at 26 weeks and 52 weeks whether they think the participant is on active or placebo treatment and this will be documented on the treatment allocation worksheet.

The central trial team, including the Senior Statistician, will be fully blinded to the treatment allocations, with the exception of the Data Manager and Trial Statistician. The Trial Statistician will be partially blinded as they will prepare reports and perform the data analysis for the Independent Data Monitoring Committee (IDMC) reports. For the IDMC closed report, the unblinded Data Manager will provide the Trial Statistician the data with the treatment allocation identified by codes, so that the Trial Statistician remains

partially blinded. In emergency situations, some clinical TMG members may be unblinded to individual patients under their care.

7.2.2. Emergency Unblinding

Unblinding should only occur for valid medical or safety reasons where it is necessary for the treating clinician to know which treatment the participant has been receiving. **When treating a participant, and to avoid any unnecessary unblinding, it should be assumed that the participant is on active treatment within the trial.** The participants will be given a safety card that they will be instructed to give to treating medical staff should they present at any hospital or treatment facility. The safety card will state that the patient is participating in a clinical trial of memantine and include the contact details for the local trial team and an out of hours contact number to be used by medical staff in case of emergency. It is likely that if unblinding occurs it will be for one of the following reasons:

- In the event of a potential Suspected Unexpected Serious Adverse Reaction (SUSAR)
    - see section 10 for reporting details
    - This will be undertaken in accordance with the regulatory requirements for safety reporting in CTIMPs.
- At the request of a senior clinician responsible for the care of the trial participant
    - Such requests are likely to occur only in the case of an SAE and are expected to be rare.

Participants will not routinely be unblinded once they have completed trial treatment.

Unblinding will only be performed by the PI or another medically qualified trial member delegated this task on the delegation log.

The PI should be notified as soon as practically possible of any unblinding, if not performed by themselves, **but should not be told what arm the participant had been allocated to**. Details provided in the unblinding will only be communicated to certain individuals assigned to receive this information and must not be shared unless required in the emergency setting. The details of the unblinding will be documented in the ISF, TMF and participant's medical records and include the following details:

- Participant ID
- Who broke the code
- When the code was broken
- Reason for unblinding

Where a trial participant's treatment allocation has been unblinded, the participant will be withdrawn from treatment in the trial. They may remain in the trial to be followed up as per protocol (see section 7.6 for withdrawal information).

UK only:

Unblinding will be performed by accessing the 24-hour web-based randomisation system, Sealed Envelope.

It is responsibility of the PI (or delegated Sub-I) to inform the CI, Sponsor and NCTU of any unblinding as soon as practicably possible by emailing **nctu.cobalt.conf@nhs.net** and must include the following information:

- Participant ID number*
- Date and time of unblinding*
- Name of person performing unblinding*
- Reason for unblinding*

*A full audit trail of any unblinding performed on Sealed Envelope is recorded and includes this information.

The notification email should not include the treatment arm of the unblinded participant. The CI, Sponsor and NCTU trial management team must remain blinded to the participants allocated treatment unless the participant is unblinded due to a SUSAR (see section 10 for reporting details).

The CI and NCTU trial managers will be kept informed of all instances of unblinding but remain blind to treatment allocations themselves wherever possible.

Code break envelopes will not be utilised for this trial. In the event of an emergency, participants will be treated as if they are on trial treatment until they are unblinded using the Sealed envelope randomisation system.

Australia only:

Blinding/unblinding process

The unblinded randomisation schedule will only be accessible by the independent, central, unblinded delegate. If a participant requires unblinding, the site PI and Australian CI must be notified.

7.3. Trial Assessments

Participants and their caregivers/informants will be interviewed by the local trial team to collect measures of cognition, clinical and neuropsychiatric symptoms, function, mood, quality of life, caregiver burden, and health economics using standardised tools as summarised below:

Cognition:

Our justification for the use of two cognitive scales is the differential use of these scales in clinical practise (MMSE in dementia services; MoCA in PD clinics), and that both scales have been used in previous clinical trials in LBD.[23, 24]

- The MoCA is a short validated cognitive measure that has more weighting towards executive/attentional function (a domain postulated to be improved by memantine in DLB/PDD).[14, 25]
- MMSE is a short validated cognitive measure that has the advantage that it can track progression in DLB/PDD.[15, 26]

Clinical Symptoms and Function:

- MDS-UPDRS part III[16] will assess the impact of memantine on motor function in participants given that it may have theoretical dopamine D2 receptor agonism[27] and anecdotally improve parkinsonism in DLB/PDD.
- ADCS-CGIC is a systematic method for assessing clinically significant change in a clinical trial as viewed by an independent, suitably qualified person . The ADCS-CGIC focuses on observations of change in the patient's cognitive, functional, and behavioural performance since the beginning of a trial with participants scored on a 7-point scale (ranging from 1 = very much worse to 7 = very much better, with 4 = no change). It relies on both direct examination of the patient and interview of their Caregiver/informant[28]. Given the focus on Lewy body dementia, the ADCS-CGIC has been adapted with Lewy body related probes. In addition caregiver/informants will complete an adapted care-giver global impression of change assessment (C/I-CGIC)[29] with subscoring of different domains.
- DAD is conducted with the Caregiver/informant and evaluates the participant's functional abilities in activities of daily living[20].

Neuropsychiatric Symptoms:

- NPI+ is the NPI-12 version of the NPI; original 12 items supplemented by an extra domain covering cognitive fluctuations and sleep as well as a sub-section on hallucination modality (given original scale does not specify the frequency/severity/distress of which hallucination) and sleep subscores which relate to DLB/PDD-relevant domains of sleep. This scale will be conducted with the Caregiver/informant.[19]
- The ESS is a short scale that asks the patient to rate their probability of falling asleep on a scale of increasing probability from 0 to 3 for eight different situations to assess daytime sleepiness.
- The HADS[17] is a 14- item scale: Seven of the items relate to anxiety and seven relate to depression. The HADS will be conducted with both participants and caregiver/informants to determine levels of anxiety and depression.

Quality of Life:

- EQ-5D-5L and EQ-5D-5L proxy comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression[18]. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The patient is asked to indicate their health state by ticking the box next to the most appropriate statement in each of the five dimensions. There are no optimised scales of QOL for DLB/PDD and given DLB/PDD patients may be less able to self-report QOL compared to AD patients with similar cognitive performance[30] we include both a patient QOL measures (EQ-5D-5L) and an informant version (Proxy EQ-5D-5L).

Caregiver Burden:

To assess the impact of memantine augmentation therapy on caregiver QOL, depression, and carer burden, assessments include:

- HADS is a self-rating scale developed to assess psychological distress in non-psychiatric patients. It consists of two subscales, Anxiety and Depression.
- Zarit burden Interview[21, 31] is a self-report measure consisting of 22 items rated on a 5-point Likert scale that ranges from 0 (never) to 4 (nearly always) with the sum of scores ranging between 0–88. Higher scores indicate greater burden.
- WHOQOL-BREF[22] is a 26-item quality of life assessment designed to measure the impact of disease and impairment on daily activities and behaviour, perceived health, disability and functional capacity. The caregiver/informant will complete the WHOQOL-BREF relating to themselves.
- EQ-5D-5L completed by the carer relating to their own quality of life. EQ-5D-5L of caregiver/informant quality of life which will be incorporated into secondary analyses of quality adjusted life years (QALYs) in the health economic evaluation.

Health Economic Measures:

- Client service receipt Inventory (CSRI) - The participant will complete information regarding their use of services and care required, with help from their caregiver/informant. As part of the CSRI (section F) the caregiver/informant will complete information on day-to-day caring tasks to allow us to monetise their input.

Participants will also undergo the following assessments and investigations summarised below:

Physical examination: (including brief neurological examination) – This should be carried out by a medic

- The Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III - motor examination
- General appearance
- Behaviour
- Skin
- Cardiovascular
- Respiratory
- Abdomen
- Neurological
- Musculoskeletal
- Myoclonus
- Autonomic symptoms in previous 6 months (change in sense of smell or taste, constipation, excessive sweating, double vision, urination frequency and light headedness)
- Height (arm span if patient unable to stand)
- Weight

Vital signs:

- Blood pressure (sitting and standing)
- Pulse
- Temperature
- Respiration rate

Eligibility Bloods: (taken at screening if no results available from previous 6 months)

- Urea and Electrolytes including -
  - eGFR calculation
  - Sodium
  - Potassium
  - Creatinine
  - Urea
- Liver Function Tests including -
  - Total Protein
  - Total Bilirubin
  - Aspartate aminotransferase (AST) and/or Alanine aminotransferase (ALT)
  - Alkaline Phosphatase (ALP)

Demographics and medical history:

- Demographics (DOB, Sex, Ethnicity, Education level & Years in education)
- Past clinical history
- Concomitant medications
- Postcode – used to obtain deprivation score from Office of National Statistics area records (where available). Postcode data will not be shared or reported.

7.4. Trial Visits

7.4.1. Screening/Baseline Visit (V1) – day -14 to day 0

The screening and baseline assessments can occur at the same visit if randomisation can be completed and IMP can be dispensed on the same day. The MMSE must be completed at the screening visit to confirm eligibility and to provide the randomisation stratification variable for dementia severity. A blood

sample should be taken from the patient at screening, after consent, to assess eGFR and liver function to confirm eligibility if no results are available from the patients' medical records within the last 6 months or, if in the opinion of the PI, the available results are abnormal/clinically relevant. (see section 7.3 - Eligibility Bloods).

If baseline is a separate visit, the MMSE and Eligibility bloods (if applicable) may be conducted at screening and do not need to be repeated at baseline. All baseline assessments must be carried out within 2 weeks of the screening assessment (Visit 1, day-14 to day 0).

The screening/baseline visit/s can occur at the trial site or at the patient's home, if preferred. The visit assessments should take approximately 2 hours but may take longer if additional breaks are required. Adequate rest breaks and light refreshments will be provided if the visit occurs at the trial site. If the patient/caregiver requests an extended break, the assessment can be paused but must be resumed within 7 days of the initial visit. Splitting of assessments must be recorded in the patient's medical records and eCRF. It is however preferred that all cognitive assessments are carried out in one sitting and that assessment are conducted in the order listed below.

At baseline, demographics, past clinical history, and concomitant medications will be obtained. Participants will undergo a brief physical and neurological examination, including vital signs (postural blood pressure, pulse, temperature, respirations), height and weight (to calculate Body Mass Index).

Australia only:
At selected trial sites, participant consent will be obtained to collect and store approximately 60mL of blood for future research including for example, genomics, transcriptomics and blood-based biomarker development. Blood may be collected at up to 3 timepoints throughout the trial, i.e. screening/baseline, week 26 and week 52.

UK only:

If participants are being recruited in an area which is geographically close/covered by the national Bioresource, participants will be asked if they wish to provide samples. If they agree, we will share their contact details with Bioresource who will contact and consent participants using their established and approved processes. Therefore, this process will be separate and outwith of the COBALT trial although we will seek consent in COBALT that we are able to, at a future point access any acquired bioresource data and conversely share trial data (e.g. assessment outcomes) with bioresource and other national and international data repositories subject to current data protection regulatory frameworks and governance processes.

ADCS-CGIC

Participants and their Caregiver/informant will undergo a semi-structured interview to provide baseline information for subsequent ADCS-CGIC assessments. The ADCS-CGIC at baseline is a clinical record with no score attributed to the interview.

This will take approximately 20- 60 minutes to complete. This assessment will be conducted by an assessor who has undergone training and has familiarity with DLB/PDD. This assessment should be completed first and signed off, ideally by an independent 'blind' assessor who does not conduct any other paper assessments or telephone reviews with the patient. The blind assessor can however conduct the baseline physical examination of the patient. **The ADCS-CGIC must not be altered on the basis of subsequent assessments.**

In exceptional circumstances the ADCS-CGIC assessor can carry out the caregiver/informant assessments, only after the ADCS-CGIC has been completed and signed.

Participant related measures - completed with the participant, will take approximately 60 minutes to complete. Please carry out the assessments in the order that they are listed below:

1. Baseline interview for Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change (ADCS-CGIC)
2. Mini Mental State Examination (MMSE) –completed at screening
3. Montreal Cognitive Assessment (MoCA)
4. Hospital Anxiety and Depression Scale (HADS)
5. Epworth Sleepiness Scale (ESS)
6. EuroQol-5 Dimension-5 Level (EQ-5D-5L)
7. Client Service Receipt Inventory (CSRI) adapted for DLB/PDD

Participant related measures - completed with the Caregiver/informant either in person or virtually (e.g. video conference or telephone); will take approximately 60 minutes to complete.

Please carry out the assessments in the order that they are listed below:

1. Neuropsychiatric Inventory Plus (NPI+)
2. Disability Assessment of Dementia (DAD)
3. EQ-5D-5L proxy

Caregiver related measures - completed with the Caregiver/informant either in person or virtually (e.g. video conference or telephone); will take approximately 30 minutes to complete.

Please carry out the assessments in the order that they are listed below:

1. Zarit Burden Interview
2. Caregiver/informant HADS
3 WHO Quality of Life-BREF (WHOQOL-BREF)
4. EQ-5D-5L specifically asking about caregivers' health related quality of life

Following completion of all baseline assessments, IMP will be dispensed in line with the IMP schedule.

Participants will also be given a Participant Diary – Part 1 and instructed on how to complete it, including how to record missed dose/s, adverse events, changes in current medication and any contacts with healthcare services. They will be instructed to bring the Participant Diary to each visit. It is expected that the patient's caregiver/informant will assist them with the completion of the diary and so they should also be present when instructions are given.

Participants will be provided with a safety card to present to medical staff, should they attend a hospital or other medical treatment facility. The card will state that the patient is participating in a clinical trial of memantine and also give the contact details of the local trial team and an out of hours number to be used in case of emergency. Participants must be reminded to carry their safety card at all times.

Participants will be instructed to finish the trial medication packs that they have, per dosing schedule, before they begin a new pack and will be instructed to return them at a trial visit, after they have been finished.

UK only:
Participants can be provided with a pre-paid envelope to return the empty IMP packs, if the site has a Royal Mail click and drop account.

Local trial teams will send out the GP letter provided to notify the patients' General Practitioner of their involvement in the study.

7.4.2. Visit 5 (week 26)

The in-person assessments should occur at the same location as the baseline visit (i.e. at the trial site or in the participant's home) where possible. We have given the option for some of the assessments to be carried out over the telephone or, if essential, completed and returned by post to reduce the burden on the patient and caregiver/informant and to accommodate any COVID-19 circumstances.

All assessments can occur face to face in clinic or in the patient's home if this is preferred. If the patient/caregiver requests an extended break, the assessment can be paused but must be resumed within 7 days of the initial visit. It is however preferred that all cognitive assessments are carried out in one sitting and carried out in the order listed below.

As noted in section 7.4.1, the ADCS-CGIC should be completed first and signed off, ideally by an independent assessor who does not conduct any other assessments with the patient and by the same assessor who conducted the baseline ADCS-CGIC assessment. The ADCS-CGIC must not be altered on basis of subsequent assessments conducted as part of the assessment visit.

If required, the ADCS-CGIC assessor can carry out the caregiver/informant assessments, only after the ADCS-CGIC has been first completed and signed.

In-person Assessments, completed with the participant (approx. 120 mins).
Please carry out the assessments in the order that they are listed below:

1. ADCS-CGIC performed by a trained assessor – ideally same person who performed the baseline visit.
2. MMSE
3. MoCA
4. MDS UPDRS-III
5. Vital Signs

Assessments completed by participant either in person or virtually (e.g. video conference or telephone) with assessor with help from caregiver/informant (approx. 30 mins).

Please carry out the assessments in the order that they are listed below:

1. HADS
2. ESS
3. EQ-5D-5L
4. CSRI adapted for DLB/PDD
5. Medication adherence
6. Adverse events
7. Changes in concomitant medications
8. Treatment allocation worksheet

Assessments completed by the caregiver/informant either in person or virtually (e.g. video conference or telephone) with assessor (approx. 25 – 75 mins).

Please carry out the assessments in the order that they are listed below:

1. C/I - CGIC interview– ideally with different assessor to person performing patient ADCS-CGIC
2. NPI+
3. EQ-5D-5L proxy
4. DAD
5. EQ-5D-5L - caregiver related
6. HADS - caregiver related
7. Zarit Burden Scale - caregiver related

8. WHOQOL Bref - caregiver related
9. Treatment allocation worksheet

The investigator/assessor completing the CGIC will also be asked by the second assessor to confirm which treatment arm they believe the patient has been randomised to. This should be documented in the treatment arm allocation worksheet along with the patient and carer/informant's responses.

New trial medication packs will be dispensed in line with the IMP schedule. Participants will be asked to present their safety card to ensure that they are carrying this with them. If the participant does not have their safety card, they will be given a new card at the visit and should be reminded that they must carry the card at all times.

UK only:
If a participant cannot attend face-to-face visits, and if their caregiver is unable to collect IMP from site, medication may be posted to participant by Royal Mail 'track and trace' delivery or by sponsor approved courier. Site staff will be required to complete the IMP postage Log and to document postage and confirmation of receipt in the participant's medical records. IMP may also be delivered by local pharmacy or the local research team to the participant's home.

Participants will be instructed to return the empty IMP packs at a trial visit.

UK only:
Participants can be provided with a pre-paid envelope to return the empty IMP packs, if the site has a Royal Mail click and drop account.

Part 1 of the patient diary will be collected and retained at site for monitoring purposes. Part 2 of the patient diary will be given to the participant for completion. The dose table in part 2 of the diary must be completed by a member of the local trial team **before** it is given to the patient.

7.4.3. Visit 7 (week 52) or Early Withdrawal

The in-person assessments should occur at the same location as the baseline visit (i.e. at the trial site or in the participant's home) where possible. We have given the option for some of the assessment to be carried out over the telephone or, if essential, to be completed and returned by post to reduce the burden on the patient and caregiver/informant. All assessments can occur face to face in clinic or in the patient's home if this is preferred. If the patient/caregiver requests an extended break, the assessment can be paused but must be resumed within 7 days of the initial visit. It is however preferred that all cognitive assessments are carried out in one sitting and carried out in the order listed below.

As noted above, the ADCS-CGIC should be completed first and signed off, ideally by an independent assessor who does not conduct any other assessments with the patient and by the same assessor who conducted the baseline ADCS-CGIC assessment. The ADCS-CGIC must not be altered on basis of subsequent assessments at the assessment visit. The ADCS-CGIC assessor can carry out the caregiver/informant assessments, only after the ADCS-CGIC has been completed and signed.

In-person Assessments, completed with the participant (approx. 120 mins).
Please carry out the assessments in the order that they are listed below:

1. ADCS-CGIC performed by a trained assessor – ideally same person who performed the baseline visit.
2. MMSE
3. MoCA

4. MDS UPDRS - Part III
5. Vital Signs

Assessments completed by patient either in person or virtually (e.g. video conference or telephone) with assessor with help from caregiver/informant (approx 30 mins).

Please carry out the assessments in the order that they are listed below:

1. HADS
2. ESS
3. EQ-5D-5L
4. CSRI adapted for DLB/PDD
5. Medication adherence
6. Adverse events
7. Changes in concomitant medications
8. Treatment allocation worksheet

Assessments completed by the caregiver/informant either in person or virtually (e.g. video conference or telephone) with assessor (approx. 25 – 75 mins).

Please carry out the assessments in the order that they are listed below:

1. C/I - CGIC interview– ideally with different assessor to person performing patient ADCS-CGIC
2. NPI+
3. EQ-5D-5L proxy
4. DAD
5. EQ-5D-5L - caregiver related
6. HADS - caregiver related
7. Zarit Burden Interview - caregiver related
8. WHOQOL Bref - caregiver related
9. Treatment allocation worksheet

Patient Diary – Part 2 and any unused trial medication will be collected for drug accountability monitoring. The investigator/assessor completing the CGIC will also be asked to confirm which treatment arm they believe the patient has been randomised to. This should be documented in the treatment arm allocation worksheet.

7.4.4. Visit 2 (week 3), Visit 3 (week 8), Visit 4* (Week 14) and visit 6* (week 38)

These visits may occur at the local trial site, in the participant's home or by telephone and will assess the following:

- Medication adherence
- Adverse events
- Changes in concomitant medications

Participants must also be reminded to carry their safety card at all times. If the participant indicates that they have misplaced their safety card, a new card must be sent to them by the local trial team.

*At Visits 4 and 6 new trial medication will be dispensed. If these visits are conducted over the telephone, the trial site must be able to facilitate the delivery of medication to the participants.

UK only:
If a participant cannot attend face-to-face visits, and if their caregiver is unable to collect IMP from site, medication may be posted to the participant by Royal Mail 'track and trace' delivery or by sponsor

approved courier. Site staff will be required to complete the IMP postage Log and to document postage and confirmation of receipt in the participant's medical records. IMP may also be delivered by local pharmacy or local research team to the participant's home.

Participants will be instructed to finish the trial medication packs that they have, per dosing schedule, before they begin the new packs and will be instructed to return the empty IMP packs the following trial visit.

UK only:
Participants can be provided with a pre-paid envelope to return the empty IMP packs, if the site has a Royal Mail click and drop account.

These visits will take approximately 15 - 30 minutes.

7.4.5. Visit 8 (Week 56) or Early Withdrawal

A Resolution Call will be made to participants at week 56 to document any adverse events they have experienced following the week 52 visit. Initiation of memantine post trial will be a treating clinician led decision. Any memantine prescribed after the patient has finished the trial at week 56 will be done so outwith the trial and as per normal titration schedule, as patients and their treating clinicians will not be unblinded when the patient completes the trial.

7.4.6. Optional Long-Term Follow-up (24 Months)

Participants are given the option to consent to a long-term follow up 12 months after the end of their participation in the trial. This can either be by review of the medical records or by speaking to someone from the local or central trial team, depending on what the participant agrees to. The purpose of this additional follow-up is to understand the long-term outcomes for patients with DLB and PDD following treatment with memantine. This will include information on significant medical events experienced, current living situation (e.g., home/residential care facility), current medications and vital status. The participants are also given the option to consent to allow the trial team to review their medical records up to 10 years after they finish the trial. This will give us an opportunity to follow up a proportion of consenting patients at the 24 month point, as well as potentially even longer follow-up e.g., 3 years or more. It is important to note that this extended follow up is outwith of the COBALT trial and will be a separately funded activity and therefore an independent follow-on study. If funding is not secured within the 10-year time window to support this, then all identifiable records linking the patient to the trial would be destroyed.

7.5. Schedule of Events

Visit number	V1 Screening /Baseline	V2	V3	V4	V5	V6	V7 or E/W	V8	**Optional** long-term follow up
Time (weeks)	(Day -14 – Day 0)	3 wks – day 21 (+/- 5 days)	8 wks – day 56 (+/- 5 days)	14 wks – day 98 (+/- 5 days)	26 wks – day 182 (+/- 5 days)	38 wks – day 266 (+/- 5 days)	52 wks - Day 364 (± 14 days)	56 wks – day 378 (± 14 days)	Week 104 (± 28 days)
Visit Type*	Face-to-face + Medication pick up/drop off	Phone Call	Phone Call	Phone Call + Medication pick up/drop off	Face-to-face + Medication pick up/drop off	Phone Call + Medication pick up/drop off	Face-to-face	Resolution phone call	Phone Call and/or Review of medical records
Informed Consent	✓								
DLB/PDD clinical diagnostic worksheet	✓								
Inclusion/exclusion criteria	✓								
Demographics	✓								
Clinical History	✓								
Concomitant Medications	✓	✓	✓	✓	✓	✓	✓		
Adverse Events		✓	✓	✓	✓	✓	✓	✓	
Vital Signs	✓				✓		✓		
Physical Examination	✓								
Height and Weight	✓				✓		✓		
Eligibility Bloods†	✓								
Randomisation	✓								
ADCS-CGIC	✓#				✓		✓		
C/I – CGIC					✓		✓		
MoCA	✓				✓		✓		
MMSE	✓				✓		✓		
NPI+	✓				✓		✓		
UPDRS III	✓				✓		✓		
HADS	✓				✓		✓		

DAD	✓				✓		✓		
EQ-5D-5L	✓				✓		✓		
EQ-5D-5L proxy	✓				✓		✓		
Client Service Receipt Inventory	✓				✓		✓		
ESS	✓				✓		✓		
Zarit Burden Interview (carer)	✓				✓		✓		
WHOQOL-BREF (carer)	✓				✓		✓		
Caregiver HADS	✓				✓		✓		
EQ-5D-5L carer	✓				✓		✓		
Australia only -Research Bloods	✓				✓		✓		
Drug Adherence Check		✓	✓	✓	✓	✓	✓		
Treatment Allocation worksheet					✓		✓		
Optional Long-term follow-up									✓

**Face-to-face visits may be conducted at trial site, or in participant's home, where local set up permits.*

[†] Results from up to 6 months prior to screening visit can be used

[#] Baseline assessment – no score

7.5.1. IMP Schedule

Visit number	V1 Screening /Baseline	V2	V3	V4	V5	V6	V7 or E/W
Time (weeks)	(Day -14 – Day 0) (+ 5 days)	3 wks (+/- 5 days)	8 wks (+/- 5 days)	14 wks – day 98 (+/- 5 days)	26 wks – day 182 (+/- 5 days)	38 wks – day 266 (+/- 5 days)	52 wks – day 364 (± 14 days)
Visit Type	Face-to-face	Phone Call	Phone Call	Phone Call	Face-to-face	Phone Call	Face-to-face
Drug Dispensing	✓ Dispense Initiation Pack (for titration)#(1) and Maintenance packs (2, 3, 4)			✓ Dispense Maintenance Packs 5, 6, 7, 8*	✓ Dispense Maintenance packs, 9, 10, 11*	✓ Dispense Maintenance packs 12, 13, 14*	
Drug Reconciliation				✓	✓	✓	✓

**Patients will receive a reduced number of packs, should their maximum tolerated dose be less that 20mg.*

 # Patients who have missed doses may require additional initiation packs (used to titrate participants onto memantine). See section 8.8.

NB. IMP packs only to be returned to site once participant has completed the pack with exception of the final pack which should be returned at week 52 or E/W. Reconciliation should occur when the participant has completed and returned all empty packs from the previous dispensing visit and so the timing may not align exactly with the date of the participant's visit.

7.5.2. Titration schedule

Timepoint	Week 1	Week 2	Week 3	Week 4
Dose	5mg	10mg	15mg	20mg

7.6. Withdrawals

Participants have the right to withdraw from the trial at any time without having to give a reason. The local trial team should try to ascertain the reason for withdrawal and document this reason within the eCRF, and participant's medical records.

The Investigator may withdraw a participant from the trial at any time if the Investigator considers it necessary for any reason including, for example:

- Significant and unexpected symptomatic deterioration,
- Unacceptable toxicity,
- Participant withdrawal of consent,
- Significant protocol deviation or non-compliance,
- PI's/Sub PI's discretion that it is in the best interest of the participant to withdraw,
- An adverse event, including a drop in renal function, that requires discontinuation of the trial, medication or renders the participant unable to continue in the trial,
- Termination of the clinical trial by the sponsor.

If a trial participant withdraws from the trial, all data collected to the point of withdrawal will be retained. Consent will have been sought to allow this. The participant and their trial partner will also complete an end of trial visit (see section 7.4.3), if they are willing.

Australia only
Samples held for future use can be withdrawn upon the participant's request, however if samples have already been included in batches for analysis these will not be destroyed.

Should a participant decide to withdraw from the trial, or should their nominated representative believe that it is in the participants best interest to withdraw from the trial, they will be asked to complete and sign a withdrawal form. The original signed form should be filed in the ISF and a copy should be filed in the patient records. A copy should also be given to the participant or their nominated representative.

UK only

A copy of the completed withdrawal form should also be sent to the NCTU from a secure NHS email account to **nctu.cobalt.conf@nhs.net.**

It should be noted that a participant can choose to stop taking trial medication but remain in the trial and continue to complete trial visits/contacts and assessments as per protocol, up until Week 52. The local trial team should try to ascertain the reason for IMP discontinuation and document this reason within the eCRF, and participant's medical records.

UK only

The participant will be asked to complete a trial IMP discontinuation form. If the patient lacks capacity, their nominated representative can also make this decision on their behalf if they believe that it is in the participants best interest to discontinue the IMP. In this case, the nominated representative will be asked to complete and sign the IMP discontinuation form. The original signed IMP discontinuation form should be filed in the ISF and a copy should be filed in the patient medical records. A copy should also be given to the participant or their nominated representative.

A copy of the completed form should also be sent to the NCTU from a secure NHS email account to **nctu.cobalt.conf@nhs.net.**

As per section 7.2.2 where it has been necessary to unblind a participant, the participant should stop taking trial medication but as above they may remain in the trial and be followed up as per protocol, if they wish.

7.7. Participant Replacements

Withdrawn DLB and PDD participants will not be replaced. The sample size calculation has been powered for 20% participant attrition due to lost to follow up/discontinuation at 26 weeks.

If the patient's caregiver/informant is unable to continue as a participant in the trial or wishes to withdraw, a replacement will be sought. The replacement caregiver/informant should be a person that is in regular contact with the patient (minimum once per week), who knows the patient well and is able to attend the trial follow-up visits as required. The replacement caregiver/informant must have sufficient knowledge of the patient so that they are able to complete assessments relating to the patient's cognitive, emotional, and physical changes during the trial. They will be required to complete all assessments relating to the patient but will not complete the Zarit Burden Interview, WHOQOL BREF, EQ-5D-5L or HADS relating to themselves. The replacement caregiver/informant will be required to consent to their participation. If no replacement caregiver/informant can be found the DLB/PDD participant will be withdrawn from the trial.

7.8. End of Trial

The definition of the end of trial is the last patient, last visit (LPLV) date. At baseline we will seek consent from participants (consent from nominated representatives where capacity is lacking) to examine future medical records of participants after the end of the trial (up to 10 years). This is in alignment with our commissioning brief, where follow-up beyond the trial will be sought to understand longer term outcomes including for example, rates of residential aged care admissions, hospital admissions, and death. This will also give us an opportunity to follow up a proportion of consenting patients at the 24 month point (see section 7.4.6), as well as potentially even longer follow-up e.g., 3 years or more. It is important to note that this extended follow up is outwith of the COBALT trial and will be a separately funded activity and therefore an independent follow-on study. If funding is not secured within the 10-year time window to support this, then all identifiable records linking the patient to the trial would be destroyed.

8. Trial Medication

8.1. Name and Description of IMP

For the purposes of this trial Memantine will be classed as IMP. Memantine is currently licensed for the treatment of moderate to severe dementia in Alzheimer's disease and is used off-licence in the UK for treatment of other dementias including DLB and PDD.

IMP:

Memantine 10mg tablets: Registered in the UK (PL 36687/0114) by Torrent Pharma (UK) Ltd

Memantine 5mg tablets: Registered in Germany (87847.00.00) by neuraxpharm Arzneimittel GmbH

Placebo:

Matching placebo tablets for memantine 5mg and 10 mg tablets will be manufactured and classed as an IMP for this trial.

8.2. Reference Safety Information

UK only:

The Memantine Torrent 10mg SmPC, section 4.8 will be used as the Reference Safety Information (RSI) for this trial. The IMP manufacturers may update the SmPC during the trial. The CI, Sponsor and NCTU will monitor and review these updates during a scheduled annual review, to consider the impact on the trial. An updated version of the SmPC may be used as RSI in the future with other relevant documentation updated, but only once approval is given form the competent authority, as required.

Serious Adverse Reactions (SARs) that are thought to have a causal relationship with memantine must be assessed for expectedness against the RSI outlined above only.

Category	Definition
Expected	An adverse event which is consistent with the information about the IMP listed in section 4.8 of the SmPC - see below
Unexpected	An adverse event which is not consistent with the information about the IMP listed in section 4.8 of the SmPC - see below

In the event of a SAR, which is thought to have occurred due to a reaction with the IMP, please also ensure to check section 4.5 'Interaction with other medicinal products and other forms of interaction' of the approved Memantine SmPC for the COBALT Trial.

Australia only:
The COBALT Investigator Brochure (IB), section 4.8 will be used as the RSI for this trial.

8.3. Drug Storage and Supply

The storage conditions are "Store in the original package in order to protect from light."

Australia only:

IMP to be stored under 30˚C.

IMP will be supplied as tablets of either 5mg or 10mg memantine. Placebo will be supplied as tablets matched to both doses of IMP.

Returned and unused trial medication will be disposed of in accordance with local pharmacy requirements following approval by Sponsor. Records of trial medication disposal must be kept in line with GCP requirements.

UK only:

At each visit requiring medication allocation, a medication ID for that participant will be generated by the Sealed Envelope system. These medication IDs must be included on trial prescriptions. Prescriptions should be sent to site Pharmacy as soon as possible following generation.

Australia only:

Medication ID allocation: At dispensing visits, the next medication ID kit number will be obtained from REDCap. If medication is stored at a site's pharmacy, then local processes between sites and pharmacy should be followed (e.g. prescriptions).

8.4. Preparation and Labelling of IMP

The IMP manufacturing, packaging, and QP release will be arranged by MODEPHARMA. All memantine and placebo tablets will be blister packed and IMP will be labelled to comply with Annex 13 Good Manufacturing Practice (GMP) guidelines. Further details can be found in the IMP dossier.

8.5. Dosage Schedule & Modifications

All participants will receive an initial 4-week initiation pack (used to titrate participants onto memantine) with clear instructions stated in the participant diary (part 1) dose instructions table. This table must be completed by the local trial team and the participant must be in receipt of the diary prior to starting the IMP. The 4-week titration schedule will start at 5mg daily in a single dose, taken in the morning. Thereafter, the dose will be increased by 5mg every week. The target dose will be 20mg/day, taken in the morning but titration will be based on tolerability and response. Refer to sections 7.5.1 and 7.5.2 for dosing and titration schedules.

Memantine tablets should be administered orally, once a day and should be taken at the same time every day (for example, morning), with or without food.

No tapering down is required if a particpant wishes to stop taking trial medication.

AEs and potential side effects of the IMP will be reviewed throughout the treatment phase by the local trial teams.

In the event of any non-serious AE or new onset side effect that is at least possibly related to the IMP and deemed intolerable or presents a clear risk to the participant's health and well-being, the dose of trial medication can be reduced as per dose modification column in **table 4**.

Table 4. Dose modification for mild to moderate AEs

Current Dose	Dose Modification for AEs
20mg once a day	Mild: Consider maintaining at 20 mg but monitor closely or reduce to 10 mg once a day and continue this dose. Moderate: Reduce to 10 mg once a day and continue this dose. Monitor closely. If worsening, consider withholding treatment.
In titration phase or maintenance phase and on 10 mg once a day	Mild: Consider increasing IMP dose as per normal titration plan if in titration phase and monitor closely; if in maintenance phase consider holding IMP at 10 mg dose and monitor closely. Moderate: Consider holding IMP at 10mg or withholding treatment.
In titration phase and currently on 5 mg	Mild: Consider increasing IMP dose as per normal titration plan and monitor closely. Moderate: Consider increasing IMP dose as per normal titration plan and monitor closely. If worsening, consider withholding treatment.

In titration phase and currently on 15 mg	Mild: Consider increasing IMP dose as per normal titration plan if in titration phase and monitor closely. Moderate: Reduce to 10 mg once a day and continue this dose. Monitor closely. If worsening, consider withholding treatment.

The participant may remain at this lower dose of IMP for the remainder of the trial. The patient's diary must be updated to reflect this change in dose. At the following dispensing visit, the amount of IMP dispensed should be informed by the participant's current maintenance dose.

In the event of **related** serious adverse events (SAEs), the IMP should either be withheld and only restarted if remedial action has been taken to mitigate risk to the participant and is in the participant's best interest in the investigator's judgment. This should be undertaken in discussion with the participant or their nominated representative, if the patient lacks capacity.

8.6. Known Drug Reactions and Interactions

Due to the pharmacological effects and the mechanism of action of memantine the following interactions may occur:

The mode of action suggests that the effects of L-dopa, dopaminergic agonists, and anticholinergics may be enhanced by concomitant treatment with NMDA-antagonists such as memantine. The effects of barbiturates and neuroleptics may be reduced. Concomitant administration of memantine with the antispasmodic agents, dantrolene or baclofen, can modify their effects and a dose adjustment may be necessary.

Concomitant use of memantine and amantadine should be avoided, owing to the risk of pharmacotoxic psychosis. Both compounds are chemically related NMDA-antagonists. The same may be true for ketamine and dextromethorphan. There is one published case report on a possible risk also for the combination of memantine and phenytoin.

Other active substances such as cimetidine, ranitidine, procainamide, quinidine, quinine and nicotine that use the same renal cationic transport system as amantadine may also possibly interact with memantine leading to a potential risk of increased plasma levels.

There may be a possibility of reduced serum level of hydrochlorothiazide (HCT) when memantine is co-administered with HCT or any combination with HCT.

In post-marketing experience, isolated cases with international normalized ratio (INR) increases have been reported in patients concomitantly treated with warfarin. Although no causal relationship has been established, while not part of the trial protocol, close monitoring of prothrombin time or INR is advisable for patients concomitantly treated with oral anticoagulants. Coagulation clinics should be made aware that the patient is participating in this trial.

8.7. Assessment of Compliance

Participants will be taking trial medication for up to a maximum of 54 weeks. Regular telephone contact, face to face visits (clinic or home, depending upon local arrangements) and medication compliance checks will be carried out by delegated local research personnel and will include pill counts and checks of medication adherence. Participants will also complete a diary to record any missed doses and the reasons that they were missed. The local trial team will work with patients to improve compliance if any issues arise. (e.g. set alarm on phone as reminder to take IMP).

Unused medication will be returned to the local trial team. All returned medication will be compared against site accountability records.

UK only:
Returned medication will be monitored by the Trial Managers and compared against the site accountability records. If satisfied (with sponsor delegation) approval for secure destruction will be confirmed. Trial technicians/pharmacy teams at sites will complete paperwork to document details of the IMP/placebo returned, document when it has been destroyed, and retain copies of these records in the Pharmacy Site File (PSF). Detailed information will be provided to sites in a Pharmacy Manual.

Australia only:

Returned medication will be monitored by the Sponsor delegate and compared against the site accountability records. Local destruction of any used, partially used or expired IMP must be authorised by the Sponsor delegate prior to destruction, and after verification of the IMP Accountability log. Detailed information will be provided to sites in an IMP Manual.

8.8. Missed doses and Re-titration

If a participant does not take IMP for 3 consecutive days or less, they can continue at the previous dose they were taking without any re-titration.

For those participants missing over 3 consecutive days but less than 7 days, and previously on 20 mg, should restart at 10 mg for 7 days and then, on second week go up to 20 mg. This can be done for participants who have previously tolerated memantine medication up to this dose.

For those participants missing over 3 consecutive days but less than 7 days, and previously on 10 mg, should restart at 10 mg and remain at this dose. This can be done for participants who have previously tolerated memantine medication up to this dose.

If a participant has missed or had IMP held due to AE for more than 7 consecutive days, the local trial team should notify the CI as soon as they become aware. The TMG would make a decision as to how this participant would be managed within the trial i.e., whether they are re-titrated from, for example, 5 mg (as per normal titration of 5 mg week 1; 10 mg for week 2; 15 mg for week 3; and 20 mg for week 4) or have IMP discontinued.

UK only:

For those participants who have missed for ≥7 consecutive days, the local trial team should notify the CI and NCTU by contacting **nctu.cobalt.conf@nhs.net** as soon as they become aware of the missed doses.

If a participant misses a dose, and it is almost time for the next dose, they should be instructed to take the next dose at the scheduled time. They should not take a double dose to make up for the dose that was missed. These instructions are stated in the participant diary.
Participants will be instructed to document any missed doses in their participant diary and the number of doses reported as missed will be recorded in the eCRF at each follow up appointment. If a participant has missed more than 3 consecutive doses, the diary instructions state that they should contact the local trial team using the contact details in their diary.

8.9. Overdose

Relatively large overdoses (for example, as has been reported previously, 200 mg and 105 mg/day for 3 days, respectively) have been associated with symptoms of tiredness, weakness and/or diarrhoea or no symptoms. Overdoses less than 140mg or unknown dose, reported symptoms have been related to

central nervous system (confusion, drowsiness, somnolence, vertigo, agitation, aggression, hallucination, and gait disturbance) and/or gastrointestinal (vomiting and diarrhoea) system.

8.9.1. Treatment of Overdose

In the event of overdose, treatment should be symptomatic. No specific antidote for intoxication or overdose is available. Standard clinical procedures to remove active substance material, e.g. gastric lavage, carbo medicinalis (interruption of potential entero-hepatic recirculation), acidification of urine, forced diuresis should be used as appropriate.

In case of signs and symptoms of general central nervous system (CNS) overstimulation, careful symptomatic clinical treatment should be considered.

8.10. Special Precautions

Moderate to severe dementia usually causes impairment of driving performance and compromises the ability to use machinery. Memantine has minor to moderate influence on the ability to drive and use machines, such that participants should be warned to take special care if continuing to drive or operate machinery.

9. Risk Management & Safety

Memantine is well tolerated in DLB/PDD with adverse events (AEs) reported in 10% of patients (comparable to placebo).[32, 33] The most frequently occurring adverse reactions are dizziness, headache, constipation, somnolence, and hypertension.

9.1. Adverse Event Reporting

- Adverse events including Serious Adverse Events (SAEs) resulting in trial discontinuation and Suspected Unexpected Serious Adverse Reactions (SUSARs) will be assessed from the time of first drug dose until completion or withdrawal. Safety data will be collected by local research personnel and PIs. The site PI, or appropriately qualified delegate, will assess all AEs for severity, causality and seriousness.
- All SAEs should be followed up until resolution, or until the condition has stabilised.
- Planned hospital admissions (e.g. for elective surgery or respite) or institutionalisation are not required to be reported as a Serious Adverse Event, unless the planned admission results in a separate Serious Adverse Event (e.g. prolongation of hospitalisation, death).
- **UK only:** SAEs and SUSARs will be reported to the Sponsor, Cumbria, Northumberland Tyne and Wear NHS Foundation Trust (CNTW) within 24 hours of the research team becoming aware of the event (see section 10.4).
- **Australia only:** SAEs and SUSARs will be reported to the Sponsor-delegated CRO Neuroscience Trials Australia (NTA) within 24 hours of the research team becoming aware of the event (see section 10.4).
- SUSARS will undergo expedited reporting to the local Research Ethics Committee and the originating country's specific reporting agency. In the UK this is the Medicines Healthcare Products Regulatory Agency (MHRA) and in Australia the Therapeutic Goods Administration (TGA).
- All events will be reviewed by the Trial Management Group (TMG), by the Independent Data Monitoring Committee (IDMC) and the Trial Steering Committee (TSC), as part of their ongoing assessment of safety.

Please see Pharmacovigilance section 10 for full details regarding adverse events reporting requirements.

9.2. Memory testing and health related questionnaires

At some visits the questionnaires and memory testing may take 1-2 hours. Participants may find the questions tiring, tedious or embarrassing. Participants may choose not to answer any specific questions or do any test at any time. The local trial team will ensure there are adequate rest breaks, however participants or their caregiver/informant can also request a break at any time. If the patient or their caregiver/informant requests an extended break, the assessment can be paused but must be resumed within 7 days of the initial visit. It is however preferred that all cognitive assessments are carried out in one sitting.

9.3. Blood Sampling

Having a blood sample taken may cause some discomfort, bruising, minor infection or bleeding. Some people feel dizzy or faint after a blood test. If any of these happen, they can be easily treated.

9.4. Good Clinical Practice

Each PI will be responsible for ensuring that the trial is conducted in accordance with the protocol, local ethical and regulatory approval/s, and Good Clinical Practice (GCP); as well as safeguarding the well-being of participants at their sites.

10. PHARMACOVIGILANCE

10.1. Definitions

Table 5. Safety event definitions

Term	Definition
Adverse Event (AE)	An untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. **AEs can 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 at baseline) • continuous persistent disease or a symptom present at baseline that worsens following administration of the trial treatment
Adverse Reaction (AR)	An untoward or unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase “response to an investigational medicinal product” means that a causal relationship between a trial medication and an AE is at least a reasonable possibility i.e., the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions
Australia only: NHMRC	National Health and Medical Research Council of Australia

Australia only: Product Information (API)	The information contained in either an investigator's brochure or an approved Australian Product Information (or another country's equivalent) that contains the information used to determine what adverse reactions are to be considered expected adverse reactions and on the frequency and nature of those adverse reactions. [Equivalent to RSI in UK].
UK only: Reference Safety Information (RSI)	The RSI is a list of medical terms detailing the ARs that are expected for an IMP and must be referred to when assessing a SAR for expectedness. The Memantine Torrent 10mg SmPC will be used as RSI for the purpose of expectedness review.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • Results in death • Is life-threatening* • Requires inpatient hospitalisation or prolongation of existing hospitalisation • Results in persistent or significant disability/incapacity • Other important medical events that jeopardise the participant or require intervention to prevent one of the above consequences * life-threatening refers to an event in which the participant was at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. *N.B. The natural progression of DLB or PDD is not reportable as an SAE unless the PI/Sub-I assesses the event to be related to the IMP.*
Serious Adverse Reaction (SAR)	A serious adverse event deemed to be causally related to any dose of IMP. Causality of serious adverse event against IMP will be assessed by a medically qualified investigator.
Australia only: Significant Safety Issue (SSI)	Safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial. This may be because of the seriousness and potential impact on the benefit-risk balance of the investigational medicinal product, which could prompt regulatory action and/or changes to the overall conduct of the clinical trial, including the monitoring of safety and/or the administration of the investigational medicinal product.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	**Australian definition:** An adverse reaction that is both serious and unexpected.
	UK definition: A serious adverse reaction, the nature and severity of which is not consistent with the approved Reference Safety Information.

10.2. Non-Reportable Adverse Events

For the purposes of this trial the PI is responsible for recording all Adverse Events, regardless of their relationship to the IMP. However, due to the nature of the study population (high risk older patients with multiple co-morbidities) only serious adverse events which are causally (possible, probable or definitely) related to the study medication will be reported. Further, the natural progression of DLB or PDD is not reportable as an SAE unless the PI/Sub-I assess the event as being related to the IMP.

The following SAEs will be recorded on the AE log within the eCRF, but not reported immediately to the Sponsor, and not reported using the SAE form:

- Any death or hospitalisation due to new cardiovascular event
- Any death or hospitalisation due to new major cerebrovascular event (e.g. transient ischaemic attack, cerebrovascular accident)
- Any death or hospitalisation due to new diagnosis or treatment of cancer
- Any death or hospitalisation due to fall or fracture
- Any death or hospitalisation due to infection
- Any death or hospitalisation due to delirium
- Any hospitalisation due to reduced mobility
- Any death or hospitalisation due to exacerbation of an existing medical condition
- Any admission for elective or planned investigation or treatment
- Any hospitalisation due to nausea, vomiting, constipation or diarrhoea
- Any falls related soft tissue injury, which require medical attention

To re-emphasise **the above exceptions to immediate SAE reporting refer only to SAEs where the study medication is not deemed to be causally related to the event by the local PI**. Where study medication is deemed to be causally related (SAR or SUSAR) by the local PI, immediate reporting of the event should proceed to the Sponsor using the SAE form.

The following adverse events (AEs) do not require reporting:

- Pre-existing disease or conditions that are present at screening and do not deteriorate
- Medical or surgical procedures where the condition that leads to the procedure is the adverse event
- Overdose of medication without signs or symptoms
- Abnormal laboratory values unless deemed clinically significant by the PI and documented as such.

10.3. AEs of special interest in relation to clinical management and dose modification

Based on the reference safety information (RSI) and previous trials of memantine, the AEs in **table 6** will be monitored by the local trial team and reported as per standard (see section 10.4), with dose modification made as per the recommendation in the dose modification table (see section 8.5). In addition to the safety monitoring specified in the protocol, follow up of emergent AEs will be at the discretion of the PI, based on severity, tolerability, and risk.
Dose modifications should be considered only if, in the opinion of the PI/Sub-I, that there is a probable or possible causal relation between the AE and with the prescribing of memantine.

Table 6. AEs of special interest

Common, Uncommon and Infrequent AEs	**Severity**	**Clinical Management and Dose Modification recommendations**
Dizziness Balance disorders Somnolence Increased hallucinations Increased confusion	Mild – occasional or intermittent	If in titration phase: Consider increasing IMP dose as per normal titration plan If in maintenance phase: Consider holding IMP at current dose
	Moderate – persistent and requiring treatment	If in titration phase: Consider dose reduction as per Dose Modification Table

Hypertension Dyspnoea Constipation Nausea and vomiting Headache Fatigue		If in maintenance phase: Hold IMP at current dose. If no improvement, or becomes intolerable, reduce dose as per recommendation in the Dose Modification table.
	Severe – impacting ADLs and requiring treatment	Withhold/stop IMP and only restart if remedial action has been taken to mitigate risk to the participant and is in the participant's best interest in the investigator's judgment. In such cases consider whether maximum dose should be 10 mg.
Hypersensitivity	New onset or acute worsening of respiratory symptoms (wheeziness) or other symptoms including swelling of lips, urticarial rash (pink or white raised itchy areas of skin)	Stop IMP and refer for acute medical attention for further assessment. Unless another cause is identified (e.g., respiratory infection, allergy to skin products, or other medications), do not recommence IMP
Cardiac failure	New onset or acute worsening of pre-existing cardiac failure	Stop IMP and refer for medical attention for further assessment with urgency contingent on severity. Unless another cause is identified do not recommence IMP
Venous thrombosis/thromboembolism	New onset	Stop IMP and refer for urgent medical attention for further assessment. Unless another cause is identified do not recommence IMP.
Rare or unknown level of frequency		
Neuropsychiatric reactions e.g. psychosis, agitation, and/or new depression / anxiety	Mild – occasional or intermittent	If in titration phase: Increase IMP as per protocol. If in maintenance phase: Hold IMP at current dose.
	Moderate – persistent	If in titration phase: Increase IMP as per protocol to 10 mg and consider holding at this dose. If in maintenance phase: Hold IMP at current dose. If no improvement, or becomes intolerable, consider reducing dose as per recommendation in the dose modification table.
	Severe – persisting and impacting ADLs and/or leading to suicidal	Withhold/stop IMP and only restart if remedial action has been taken to mitigate risk to the participant and is in the participant's best

	risk/ideation or other significant risks.	interest in the investigator's judgment. In such cases consider whether maximum dose should be 10 mg.
Seizures*	Participants with no previous history of seizures	Rule out other symptoms which can be mistaken for a seizure (e.g. syncope, marked cognitive fluctuation). If there is certainty about the diagnosis, consider stopping IMP, depending on the participant's wishes and a careful consideration of the risks and benefits. If seizures continue, discontinue the IMP and record any ongoing seizures.
Pancreatitis†	New onset	Stop IMP and refer for acute medical attention for further assessment. Unless another cause is found do not recommence IMP.
Elevated liver function tests	New onset	If severe stop IMP and refer for acute medical attention for further assessment. In this circumstance unless another cause is found do not recommence IMP.
Decline in renal function	eGFR <35 mL/min/1.73m2	If renal function declines during the trial, the decision will be made locally whether to reduce IMP dose or to withdraw patient
Hepatitis	New onset	Stop IMP and refer for acute medical attention for further assessment. Unless another cause is found do not recommence IMP.

***** Pre-existing epilepsy or history of seizure is an exclusion criterion for the trial.
† Prior history of pancreatitis (acute or chronic) is an exclusion criterion for the trial.

10.4. Recording and Reporting AEs and SAEs

10.4.1. UK specific safety event reporting

All AEs and ARs occurring from the start of administration of IMP through to 1 month post last dose of trial medication must be recorded in the participant's eCRF as well as the participant's medical records. The documentation of each AE/AR should include a description of the event, event duration (start and stop dates), details of any action taken or treatment in response to the event, and results of any assessments conducted in relation to the event. Each AE must also be assessed for **severity (10.4.1.1), seriousness (10.4.1.2)** and for **causality (10.4.1.3)** as described below.

10.4.1.1. Assessment of Severity

The PI, or delegated clinician, should make an assessment of severity for each AE according to the following criteria:

Grade 1	Minor adverse event, not requiring medical intervention. May be asymptomatic and is likely to be a clinical or diagnostic observation only; or may be a symptomatic but minor, or transient event, with no necessity for medical intervention. This might include asymptomatic laboratory or radiographic findings. A minor adverse event is likely to have only marginal clinical relevance.
Grade 2	An adverse event which may require some medical intervention (local/non-invasive) and which is symptomatic to patient. May affect activities of daily living.
Grade 3	Significant symptoms reported, requiring medical intervention and possibly requiring hospitalisation. Medically significant and likely to be significantly affecting activities of daily living.
Grade 4	An adverse event that requires urgent intervention or may have life-threatening consequences.
Grade 5	Death related to the adverse event.

10.4.1.2. Assessment of Seriousness

The PI, or delegated clinician, should assess seriousness against the standard definition in the Safety Event Definitions table (table 5, section 10.1).

10.4.1.3. Assessment of Causality

The relationship between the use of IMP and the occurrence of each AE must be assessed and categorised by the PI or delegated clinician using clinical judgement to determine the causal relationship. Other factors such as medical history of underlying diseases, concomitant therapy and any other relevant risk factors should be considered. The PI should also consult the current version of the RSI.

Yes (related)	The event is considered related to the IMP
Probable	It is probable that the event is related to the IMP
Possible	It is possible that the event is related to the IMP
Unlikely	It is unlikely that the event is related to the IMP
No	The event is not considered related to the IMP
Unable to Determine	After review of the information the PI/delegated clinician is unable to determine if the event is related to the IMP or not

10.4.1.4. Reporting SAEs/SARs

Where an AE is assessed as serious, as well as recording in the participant's medical records and the eCRF as described above, it must also be reported as an SAE. All SAEs occurring from the start of administration of IMP to 1 month post last dose of trial medication must be reported to NCTU on the COBALT SAE form.

In addition, all SARs occurring from first participant's dose of IMP to the last participant's end of follow-up must be reported to NCTU on the COBALT SAE form and also recorded in the eCRF and participants medical records. Following this defined active monitoring period for SARs, investigators are still required to report any SARs or SUSARs they become aware of.

All SAEs/SARs must be reported to NCTU within 24 hours of research staff becoming aware of the event.

Please send completed COBALT SAE report forms via secure email to:
nctu.cobalt.sae@nhs.net

nctu.cobalt.sae@nhs.net is a trial specific distribution list created to ensure that the NCTU trial management team are informed of the event in a timely manner. The NCTU trial management team will then forward this information to sponsor and CI for review.

All confirmed SAEs will be allocated a unique SAE number and a confirmation of receipt returned to the sender. SAEs will be recorded by trial management personnel on the trial's safety database.

Preliminary reporting to NCTU via email is acceptable in order to meet the 24-hour reporting timeline, where circumstances do not allow for immediate completion of the SAE form. However, the SAE form should be completed and submitted as soon as possible after the initial notification in order to comply with reporting timelines.

For each SAE the following information will be collected:

- Full details in medical terms and case description
- Event duration (start and end dates, if applicable)
- Severity
- Action taken
- Outcome
- Seriousness criteria
- Causality in the opinion of the investigator

Any change of condition or other follow-up information must be reported to NCTU on a COBALT SAE Follow-up Form and submitted to the NCTU via secure email **nctu.cobalt.sae@nhs.net** as soon as it is available or at least within 24 hours of the information becoming available at site. Events will be followed up until the event has resolved or a final outcome has been reached.

The assessment of causality will undergo documented review by the CI for each SAE.

10.4.1.5. Assessment of Expectedness

All SARs (SAEs determined as having a reasonable suspected causal relationship to IMP) will be assessed for expectedness by the CI only, using the current MHRA approved RSI.

10.4.1.6. Recording and reporting SUSARs

All SARs assessed as unexpected, in accordance with the approved RSI, occurring from first administration of IMP up to 4 weeks following the participants last dose must be reported to the MHRA and REC as SUSARs. Reporting will be performed by the trial Sponsor.

SUSARs which are determined as fatal and life-threatening must be sent to the MHRA within 7 calendar days of notification to the Sponsor (with a further 8 days for follow up information).

Non-fatal SUSARs must be reported to the MHRA no later than 15 calendar days after the Sponsor has first knowledge of the event. Any relevant follow-up information should be sought and reported as soon as possible after the initial report.

As soon as a member of the local trial team suspects that a SAR may be a SUSAR they must contact the CI, sponsor representative and the trial manager immediately. Information should be submitted via secure email to **nctu.cobalt.sae@nhs.net**.

The reporting timeframe starts at day 0 when the Sponsor is in receipt of the minimum set of information as follows:

- Sponsor trial reference (RES-20-041) and trial name (COBALT)
- EudraCT number (2021-003232-88)
- Patient trial number and date of birth
- Name of IMP
- Date of notification of the event
- Medical description of the event
- Date and time of the onset of the event (including event end date if applicable)
- Causality assessment (both PI and CI assessment)
- Seriousness of the event, particularly if life threatening or fatal
- An identifiable reporter (e.g., Principal Investigator)

This information must be provided on the COBALT SAE form. The site is expected to fully cooperate with the NCTU and Sponsor in order that a full and detailed report can be submitted to the MHRA and REC within the required timelines.

Following confirmation that the CI and PI consider the event to be a SUSAR, site must unblind the participant and inform NCTU trial management team of the treatment allocation via secure email to **nctu.cobalt.sae@nhs.net**. The Trial Manager will ensure all trial PIs will be informed of any SUSARs that occur in relation to the trial IMP. For a life threatening SUSAR sites will be informed within 2 working days and non-life threatening within 5 working days from the date the initial report has been submitted to the MHRA.

10.4.1.7. Notification of Deaths

AEs that result in death will meet the criteria for seriousness as defined in section 10.1 and be reported accordingly as SAEs.

10.4.1.8. Reporting Urgent Safety Measures

An Urgent Safety Measure (USM) is an action that the Sponsor or an Investigator may take in order to protect the subjects of a trial against any immediate hazard to their health or safety. Upon implementation of an USM by an Investigator, the Sponsor, CI and NCTU must be notified immediately and details of the USM given. The Sponsor must inform the MHRA and the NHS REC within 3 days of the USM taking place in accordance with the Sponsor' standard operating procedures.

10.4.1.9. Principal Investigator responsibilities

- Checking for AEs and ARs when participants attend for treatment or follow-up
- Using medical judgement in assigning seriousness and causality.
- Ensuring that all SAEs and SARs, including SUSARs, are recorded and reported to the Sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available.
- Ensuring that AEs and ARs are recorded and reported to the Sponsor in line with the requirements of the protocol.
- Ensuring all AEs and ARs are recorded in the eCRF

10.4.1.10. Chief Investigator responsibilities

- Clinical oversight of the safety of trial participants, including an ongoing review of the risk/benefit.
- Using medical judgement in assigning seriousness, causality of SAEs where it has not been possible to obtain local medical assessment.
- Using medical judgement in assigning causality and expectedness to SARs in line with the RSI.

- Immediate review of all SUSARs, within 24 hours.
- Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol.
- Review/assignment of Medical Dictionary for Regulatory Activities (MedDRA) or body system coding for all AEs, ARs, SAEs and SARs.
- Preparing the clinical sections and final sign off of the DSUR.
- Reviewing RSI at least annually
- Notifying PIs of any required updates to the RSI (delegated to NCTU)

10.4.1.11. Sponsor responsibilities

- Data collection and verification of AEs, ARs, SAEs, SARs and SUSARs onto a database (may be delegated to NCTU).
- Reporting safety information to the independent oversight committees for the ongoing assessment of the risk/benefit ratio throughout the life of the trial (may be delegated to NCTU).
- Assessment of expectedness of any SUSARs (may be delegated to the CI)
- Expedited reporting of SUSARs to the CA and REC within required timelines
- Reviewing RSI at least annually
- Preparing tables and other relevant information for the DSUR in collaboration with the CI and ensuring timely submission to all appropriate Competent Authorities (including MHRA) and RECs, as required (may be delegated to NCTU)

10.4.2 Australia specific safety event reporting

It is the responsibility of the Sponsor, CRO, Investigators, institutions and their delegates conducting this trial to comply with the reporting requirements of the NHMRC.

Adverse events must be assessed to determine each of the following:

1. Seriousness
2. Relatedness (i.e. causal relationship)
3. Expectedness

10.4.2.1. Site Principal Investigator Reporting Procedures

The Site Principal Investigator/delegate is responsible for recording all safety events in the source document. A trial specific CRF will be used to record adverse events, which will capture the onset, duration, date of resolution; severity; seriousness; action taken; outcome; and causality. Adverse events will be followed until adequate resolution or if not expected to resolve, until stabilised where possible.
The Investigator is responsible for expedited reporting (within 24 hours of becoming aware of the event) to the Sponsor or delegate the following local safety events:
USMs
SUSARs

The Site Principal Investigator is responsible for reporting SAEs (including SUSARs) to the Sponsor or delegate as soon as possible but within 24 hours of the first knowledge of the event. These reports should be submitted using the trial specific Expedited Safety Report Form provided by the Sponsor/delegate.

The Site Principal Investigator is also responsible for reporting SSIs, local USMs and local SUSARs to their research governance office within 72 hours of becoming aware of the event and in accordance with their local governance authorisation.

10.4.2.2. Sponsor/delegate Reporting Procedures

The Sponsor/delegate must assess and categorise the Expedited Safety Reports received from Investigators and report these to all Site Principal Investigators, the approving HREC and TGA in accordance with the NHMRC's 'Safety monitoring and reporting in clinical trials involving therapeutic goods' (November 2016) and any additional requirements of the approving HREC. All safety reports must clarify the impact of the safety event on participant safety, trial conduct and trial documentation.
The Sponsor/delegate is responsible for the following reporting to PIs, the HREC(s) and TGA:
All SSIs that meet the definition of a USM within 72 hours of becoming aware of the issue.
All other SSIs within 15 calendar days of instigating or becoming aware of the issue
For SSIs leading to an amendment of trial documentation:
Submit details of the SSI without undue delay and no later than 15 calendar days of becoming aware of the issue.

Submit amendment to the HREC without undue delay.

For SSIs leading to temporary halt or early termination of a trial for safety reasons:

Communicate reasons, scope of halt, measures taken, further actions planned without undue delay and no later than 15 calendar days of decision to halt.

For a temporary halt, notify the PIs, HREC and TGA when the trial restarts, including evidence that it is safe to do so.

The Sponsor/delegate will also report SUSARs to the TGA as follows:

Fatal or life-threatening SUSARs immediately, but no later than 7 calendar days after being made aware of the issue (follow up info within a further 8 calendar days)

All other SUSARs no later than 15 calendar days of being made aware of the issue

The Sponsor/delegate is responsible for providing the additional safety information to the approving HREC:

Provide an annual safety report, including a summary of the evolving safety profile of the trial

Provide any updated Product Information for the investigational products

The Sponsor/delegate is also responsible for providing any updated Product Information to Investigators.

10.5. Sharing safety data

In line with the General Data Protection Regulations 2018 (GDPR) explicit consent must be obtained via the informed consent form from each trial participant to allow data sharing to occur. Pseudonymised safety data will be shared between UK and Australia for the purposes of independent review by the Data Monitoring Committee. The SUSAR's reported will be shared with the other country within 24 hours of being made aware of the occurrence. The Trial Manager will share the details of the SUSAR occurring in their country to the Trial Manager in the other country. The CI's will review the SUSAR's from the other country and make the decision as to whether these should be reported to the site PI's. SSI's occurring in Australia will also be reported to the UK.

Australia only:
The trial manager will send all SUSARs and SSIs to the UK safety inbox nctu.cobalt.sae@nhs.net within 24 hours of being made aware of the occurrence.

UK Only:
The trial manager will send all SUSARs and SSIs to the Australian Trial Manager within 24 hours of being made aware of the occurrence.

11. STATISTICAL METHODS

11.1. Sample Size Estimation & Justification

The sample size has been calculated on the basis of a pre-defined minimum clinically important difference (MCID) for the primary outcome (ADCS-CGIC) of 0.7 points. This value has been derived using a tripartite approach considering what is clinically meaningful to (a) patients/caregiver-givers; (b) clinicians experienced in the treatment of DLB/PDD; and (c) a similarly reported 0.7 improvement in the ADCS-CGIC in the only prior clinical trial in DLB/PDD that included patients on AChEIs.[32]

Patients on our PPIE panel felt that even small incremental improvements in any symptom domain would be important to them, particularly if side effects were limited. Caregivers on the panel set a higher bar but felt that even if changes were only 'modest' that this would still be of impact. On consensus discussion the PPIE panel felt that somewhere between no improvement and mild improvement was meaningful particularly if side effects were limited. Our clinical experts, in consensus, proposed that AChEIs have clinically meaningful impacts on patients with DLB/PDD and given that 0.7 difference was viewed in the clinical trials with AChEI as clinically meaningful that an MCID of this level was appropriate.[7] In addition, clinicians also agreed that even small changes, particularly global, or indeed no worsening of symptoms could be clinically meaningful. Finally, similar or smaller symptomatic improvements have been reported in AD with memantine augmentation[34] and this has led memantine to be accepted by NICE as being the NHS standard of care for AD, further reinforcing the MCID choice.

11.1.1. Power Calculations

Sample size calculation was conducted for the two independent modules (COBALT-DLB and COBALT-PDD). The calculation was based on a standard deviation (SD) of ≈1.3 points on the ADCS-CGIC at 6 months relative to baseline and derived from previous DLB/PDD trials.[7, 32, 33] To detect a MCID of 0.7 points (a standardised effect size of 0.54) with 90% power and alpha=0.05 will require the following participant numbers:

- COBALT-DLB module: 74 active vs 74 placebo
- COBALT-PDD module: 74 active vs 74 placebo

Allowing for a conservative 20% loss to follow up/discontinuation at 26 weeks (in alignment with previous published trials in DLB/PDD with memantine), we will require 93 participants per trial arm, or a total sample size of 186 for COBALT-DLB and 186 for COBALT-PDD (372 in total).

11.2. Statistical Methods to be Undertaken

11.2.1. Primary outcome analyses

Statistical analyses will be performed separately on the two modules; COBALT-DLB and COBALT-PDD. The primary analysis will be an intention to treat analysis of the effect of memantine combined with AChEI versus AChEI alone on ADCS-CGIC score at 26 weeks, adjusting for the stratification factors; baseline disease severity (dichotomised, MMSE <20, ≥20) and country (UK, Australia). Separate mixed-effect generalised linear models with treatment centres as random effects, will be fitted for each module and the corresponding estimated treatment effects will be reported separately accompanied by a 95% confidence interval and p-value. Patients who have died before 26 weeks will be excluded from the primary analysis.

We also express the primary outcome analysis in terms of the estimand framework. The primary analysis will be conducted on all participants who complete an ADCS-CGIC score at 26 weeks. This

will be a principal stratum analysis limited to those participants who have not died prior to 26 weeks. Participants will be analysed by the group they were randomised to regardless of treatment received. The primary estimand will be the regression coefficient for the allocated/ randomised group, i.e. the adjusted difference between the two treatment groups. Mixed effect regression models will be used with centre as a random effect and the stratification factors (county and severity) as fixed effects.

The proportions of patients who have died before 26 weeks will be compared between arms. If the raters appear different, a composite outcome and alternative analysis may be considered.

As a first sensitivity analysis for the primary estimand, the missingness at random assumption will be evaluated for any patient or system related intercurrent events preventing the collection of the primary outcome.

The primary outcome will also be further analysed in a number of secondary analyses. These will include analysing the outcome with ordinal logistic regression and the generalised odds ratio. A per protocol analysis may also be performed.

11.2.2. Secondary outcome analyses

The effect of augmentation with memantine on secondary outcomes at 26 weeks and 52 weeks will be assessed using analogous methods. No multiplicity correction is planned to contain Type I error for secondary outcomes. The aim of secondary outcomes is to provide a more complete characterisation of the treatment effect and these outcomes will be interpreted in this context.

We will also conduct mixed effects modelling to analyse secondary outcome data (excluding ADCS-CGIC 52 week data given the ADCS-CGIC is a change score measure) from both 26 and 52 week follow up times simultaneously in a single model; this is a parsimonious analysis approach which can also account for missing data under the missing at random assumption. Longitudinal modelling with interactions will examine trajectory and determine the impact of treatment-by-time interaction. In this context we will fit separate generalised linear mixed effects models for each secondary outcome (aside from the week 52 CGIC) in each diagnostic group (DLB and PDD). The response variable will be the secondary outcome data from all time points (baseline, 26 weeks and 52 weeks for other outcome measures), with treatment (memantine combined with AChEI versus AChEI alone), time and the interaction between treatment and time as the main explanatory variables, which will enable the treatment effects at 26 weeks and 52 weeks to be estimated from the same model.

Models will adjust for baseline severity (stratification factor), and country (UK vs. Australia), will specify random effects of site (to account for correlations between patients within site) and participant where appropriate (to account for repeated measures on individuals over time), and will constrain the estimated value of the outcome at baseline to be the same in both treatment groups, which is equivalent to adjusting for the baseline measure of the outcome.

11.2.3. Exploratory outcome analyses

We will assess effect of augmentation with memantine on exploratory outcomes at 26 weeks and 52 weeks. Prespecified exploratory subgroup analyses will investigate whether the treatment effect on the primary outcome differs according to dementia severity (based on MMSE scores of 8-19 for moderate/severe; ≥20 for mild), age (<74 vs ≥75) and gender.

11.2.4. Treatment of Missing Data

Loss to follow up and missing outcome data will be summarised separately by trial arm. Subject to the validity of missing-at-random assumption, all analyses will follow the intention to treat strategy[35] by conducting the complete case analysis that will be followed by sensitivity analyses to examine treatment effect for plausible departures from missing-at-random assumption. Predictors of missingness will be identified and included as covariates in modelling the estimated treatment effect.

11.2.5. Medication Adherence

Adherence to medication will be summarised by trial arm. If appropriate, we will consider a complier average causal effect (CACE) analysis as a sensitivity analysis to investigate the effect of non-adherence.

11.2.6. Adverse events

Adverse events will be summarised by trial arm, using MedDRA System Organ Class (SOC) classifications.

11.2.7. Interim Analyses and Criteria for the Premature Termination of the Trial

There is no planned interim analysis. Recruitment will be reviewed as part of an internal 12-month pilot. Screening to recruitment conversion rate will be monitored during this time and a stop-go milestone has been agreed with funder.

11.3. Health economic analysis

We will evaluate the cost-effectiveness of memantine combined with AChEI vs. AChEI alone over 12-months in patients with DLB and PDD separately and in an analysis where the two diagnostic groups are combined.

The primary analysis will report the mean incremental cost per quality adjusted life year (QALY) gained calculated using the EQ-5D-5L proxy and relevant UK tariff from a health and social care cost perspective in line with NICE guidance (www.nice.org.uk/process/pmg9/chapter/foreword). Caregivers will also complete the EQ-5D-5L asking about their own health related quality of life, and hence the choice of the EQ-5D-5L facilitates addition across these two groups given both use the same algorithm.

Secondary analyses will calculate (i) costs from a societal perspective including out of pocket costs as well as cost impact on caregivers and addition of their QALYs as calculated using the EQ-5D-5L; (ii) using patient completed EQ-5D-5L to calculate QALYs from a health and social care cost-perspective; and (iii) mean incremental cost per point improvement on ADCS-CGIC from a health and social care and societal cost perspective.

The intervention and control costs will include the cost of memantine and AChEI plus any costs associated with treatment monitoring. Data for the 12 month analysis will be collected at 6 and 12 months asking about the last 6 months using a modified version of the CSRI adapted for DLB and PDD and our experience of using the CSRI in similar populations.

The health care component of the questionnaire will focus on specialist secondary care services, inpatient admissions, social care and institutionalisation. We will also include questions about impact on caregivers (time spent on caring activities for paid and unpaid caregivers and employment for unpaid caregivers), out-of-pocket costs and caregiver health and social care resource use. Given the long recall time (6 months) we will give caregivers a health care resource use diary to collect the relevant information to

facilitate recall. Unit costs will be applied to resource use based on published UK sources. Unpaid caregivers will be costed at the same rate as paid caregivers to reflect that these are likely to be substitutes.

We will report a range of descriptive statistics for resource use, costs and caregiver impact, including means and standard deviations. Bootstrapping and adjustment for stratification variables will be used to calculate the difference in costs between arms for broad cost categories (e.g. specialist services, institutionalisation, caregiver costs) and total mean costs for the two different cost perspectives (health and social care and societal). Results will be reported by DLB, PDD and for the two diagnostic groups combined. Separate sub-group analyses for the Australian cohort will also be conducted.

Responses to the EQ-5D-5L proxy and relevant English tariff will be used to calculate QALYs as the area under the curve adjusting for baseline and stratified variables.[36] These analyses will also be repeated for patient completed EQ-5D-5L and adding caregiver EQ-5D-5L responses. Means and standard errors will be reported for each time point and total QALYs, with between group differences calculated using bootstrapping and adjusting for baseline and stratification variables. Separate Australian sub-group analyses will also be conducted. Missing data will be addressed using multiple imputation by chained equations (MICE). Using the bootstrap adjusted and MICE results we will construct cost-effectiveness acceptability curves and cost-effectiveness planes for all primary and secondary analyses.

12. Storage of Blood & Tissue Samples

Blood samples for routine safety analysis will be collected and analysed at the local trial site. This blood will not be stored.

UK only:

UK sites may have ongoing programmes of biobanking. An example of this is the UK Bioresource. Whilst out with of the present trial, participants will have the option to consent to be approached if they would like to be part of any of these initiatives and we would seek consent that if individuals did participate in biobanking studies, we can approach the biobanks for their data for future analysis. Information giving, consent and blood sampling for these purposes would be done out with and separate to the COBALT Trial.

Australia only:

Up to 60mL (approximately 3 tablespoons) of blood will be obtained from participants at screening/baseline visit, visit 5 and visit 7. These samples are for routine laboratory tests, genetic testing, biomarker and other research tests. Serum and whole blood samples will be stored at -80°C after fractionation and aliquoting. Blood samples will be collected and stored at the local trial site/s before being batch-transferred for long term storage and analysis at the Walter and Eliza Hall Institute of Medical Research or at other specialised laboratories. Samples will be stored de-identified.

Participants can choose to have samples stored for future use (unspecified consent). These samples will only be released to projects that have been ethically approved by a Human Research Ethics Committee. These samples may be requested by other specialised laboratories in Australia or overseas.

13. Data Security & Handling

13.1. Data sharing between Australia and UK

Whilst many aspects of COBALT will be operationalised separately in the two countries, data collection, validation and storage procedures will be harmonised with an ethos of free data sharing between countries. Consent will be sought from all participants (at the point of trial enrolment) to transfer their

pseudonymised data to the other country for the purpose of central trial staff in the other country to use these data.

AE coding will be done using MedDRA in both countries, with the same version of MedDRA used. SUSARs reported in one country will immediately be copied to the other country (see section 10.6). A UKIDMC will consider the overall safety evidence from the trial.

After trial closure, UK and Australian data will be combined for analysis.

UK only:
Records will be securely stored for a minimum of 10 years.

Australia only:
Records will be securely stored for a minimum of 15 years.

13.2. Data handling and storage

UK only:

The Clinical Data Management System (CDMS) used for the electronic case report forms (eCRFs) in this trial is fully compliant with all regulatory frameworks for research of this nature. The CDMS is Sealed Envelope's Red Pill, in summary:

- Registered as a data controller with the Information Commissioner's Office (ICO) and has been inspected by the MHRA, the UK clinical trials regulator
- Certified as meeting Cyber Essential requirements (a UK Government led and industry –backed scheme) by a CREST accredited security company
- It has an inbuilt daily back-up facility, stored redundantly at two sites, which is encrypted
- It uses a secure web-based interface for data entry, no data is stored on computers at site
- Users are assigned role-based permissions specific to their site and trial role

The NCTU trial management team will continually monitor completeness and quality of data recording in eCRFs and will correspond regularly with site staff with the aim of capturing any missing data where possible and ensuring continuous high quality of data.

Participants, caregivers/informants and investigators/assessors will complete paper assessment tool(s) (i.e. questionnaires) as required. The tools will also only be identified using the participant ID. Data will be entered at sites onto corresponding eCRF in Red Pill, with the paper originals remaining at site.

Data Collection Tools and Source Document Identification

Clinical and safety data for all trial participants will be collected by the PI or their delegated nominees and recorded in the relevant eCRFs of the CDMS (Red Pill) and on relevant trial specific worksheets. Participant identification on the eCRFs and paper documentation will be by a unique participant number only. A Patient Identification Log linking the patient's name to the participant ID will be held within the ISF stored in a lockable filling cabinet within a secure room at site and is the responsibility of the PI. As such, patients cannot be identified from eCRFs. Patients can choose to consent to be followed up, by review of their medical records or by telephone contact, approximately 12 months after their participation in the trial has ended.

The CDMS will collate data from multiple sources, including patient medical records, paper Assessments and questionnaires (see section 7).

A Source Data Agreement (SDA) will be completed prior to each site opening to screening and recruitment activity; this will document agreed sources of data.

Data Handling and Record Keeping

Overall responsibility for data collection lies with the CI. Data will be handled, computerised, and stored in accordance with the General Data Protection Regulations 2018. Paper copies of trial-related documentation will be annotated, signed, and dated, and filed in the medical records.

The overall quality and retention of trial data is the responsibility of the CI. All trial data will be retained in accordance with the latest Directive on GCP (2005/28/EC) and local policy.

Access to Data during trial

Staff involved in the conduct of the trial, including the PIs, trial management team and NHS staff involved in screening and intervention will have access to the ISF.

The trial data and patient medical records may be looked at during monitoring by NCTU or auditing personnel from a Research Ethics Committee (REC), Medicines and Healthcare products Regulatory Agency (MHRA), the Sponsor or NCTU.

Clinical information will not be released without the written permission of the participant, except as necessary for monitoring and auditing by the Sponsor, its designee, Regulatory Authorities, the Trial Steering Committee (TSC) or the REC. The PI and trial site staff involved with this trial may not disclose or use for any purpose other than performance of the trial, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the trial. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

Password limited access to the trials database within Red Pill will be granted to site PIs and delegated data entry personnel, access is restricted to the individuals trial role and site. NCTU trial management team will have access the trial database for monitoring purposes.

Fields containing data which may be personally identifiable such as postcode and date of birth will be marked as such in the trial database set-up and will have 'reduced visibility'. This means that users with data entry permissions can enter data into and view data contained within these fields at their own site, but data in these fields are not visible to other user roles, and do not appear in any downloads of data from the database. The database manager can decrypt and then view encrypted fields in downloaded data files using the Red Pill decryption tool and password.

Archiving

Trial data will be archived for a minimum of 10 years. . Archiving will be authorised by the Sponsor following submission of the end of trial report.

NCTU does not have its own archiving facility, therefore the archiving facility designated by the Sponsor will be used for storage of the Trial Master File (TMF), which contains the essential documents that individually and collectively permit the evaluation of the data produced.

Electronic data from the trial database will be provided for the sponsor TMF and to sites in an appropriate format (to be determined at the time in accordance with latest guidance and SOPs).

Each individual trial site is responsible for archiving their trial Investigator Site File (ISF).

Authorisation will be requested from the Sponsor to destroy the documentation at the end of the archiving period.

Australia only:

REDCap (Research Electronic Data Capture) is a secure web application used exclusively to support data capture for research studies.

REDCap provides:

An intuitive interface for validated data entry (with data validation);
- 256-bit encryption between the data entry client and the server;
- Individual access to the database via secure login;
- An audit trail for tracking data manipulation and export procedures;
- Automated export procedures for data downloads to common statistical packages (SPSS, SAS, Stata, R et.);
- Procedures for importing data from external sources; and
- Advanced features such as branching logic, calculated fields, and data quality checks.

Data collection and storage will comply with all applicable requirements including ethical and governance approvals and applicable Australian state and federal legislation including privacy legislation.

Trial participants will be allocated a unique trial code and identifiers will not be used in the trial database. Documents linking the study participant to their unique trial code will be stored separately in a locked filing cabinet. REDCap provides individual access to the database via secure login to the REDCap portal as well as audit trails for tracking data manipulation and export procedures.

13.3. Confidentiality and security

All trial participants will be assigned a non-identifiable trial ID number. All data collected will be stored using the trial ID.
All necessary steps will be taken to protect participants safety and confidentiality. All individually identifiable information will be only accessible to key trial and administrative staff and will be stored in a secure database. Any written documentation will be stored in secure and locked facilities at the trial site/s. All trial analyses will be performed on pseudonymised data.

14. Monitoring Audit & Inspection

14.1. Trial Management Group

The trial will be co-ordinated by a Trial Management Group, consisting of the grant holders, Co applicants, Trial Managers, Trial Statisticians, NCTU trial management team, Sponsor, Sponsor Pharmacy representative, local PIs, local research personnel and a lay (PPIE) representative. The group will meet monthly. Invitations will be sent to the Funder and Sponsor to send representatives.

14.2. Trial Steering Committee

A Trial Steering Committee (TSC) will be established to provide overall independent oversight of the trial and will oversee trial conduct and progress. The Chair will be an independent clinician, and the committee will include one lay member. The TSC will have at least one Australian representative. Members of the Trial Management Group (TMG) will attend these meetings. At the first meeting, the TSC will agree on its charter of operation. The committee will meet at least annually for the duration of the trial.

14.3. Independent Data Monitoring Committee

An independent Data Monitoring Committee (IDMC) will be established to oversee the safety of trial participants. The IDMC will include, at minimum, an independent statistician, and two independent clinicians. This committee will monitor efficacy, safety and clinical outcomes. At the first meeting, the IDMC will agree on its charter of operation, and discuss and advise on the inclusion of an interim analysis

and possible adoption of a formal stopping rule for efficacy or safety. The committee will meet at least annually for the duration of the trial. The IDMC will have at least one Australian representative.

UK only:

Monitoring

A COBALT trial monitoring plan will be developed, based upon the trial risk assessment, and agreed by the Trial Management Group, NCTU QA representative and the Sponsor.

All monitoring activity will be detailed in the COBALT monitoring plan. Monitoring of trial conduct and data collected will be performed by a combination of central review and off- and on-site monitoring visits to ensure the trial is conducted in accordance with GCP and appropriate regulations. Trial site monitoring will be undertaken by NCTU Trial personnel as indicated in the monitoring plan.

All monitoring findings will be reported and followed up with the appropriate personnel in a timely manner. Sites will be expected to assist the Sponsor in monitoring the trial e.g. hosting monitoring visits, providing information for on- and off-site monitoring and responding to monitoring findings within the timeframes requested, wherever possible.

Inspection

The trial may be subject to audit by representatives of the host trial site, Sponsor, Funder, MHRA or HRA. Each Investigator site will permit trial-related monitoring, audits and regulatory inspection including access to all essential and source data relating to the trial.

Australia only:

Trial site monitoring will be conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol and amendment(s), good clinical practice and applicable regulatory requirements.

Full details of trial site monitoring will be documented in the Clinical Monitoring Plan (CMP). The CMP will describe in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

Monitoring for this trial will be performed by Neuroscience Trials Australia. Monitoring visits will be conducted both on-site and remotely.

The trial sites will provide direct access to all trial related source data/documents and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities as required.

15. Ethical & Regulatory Considerations

15.1. Ethical and Regulatory Considerations for UK only

Research Ethics Committee Review and Reports

NCTU trial management team will obtain a favourable ethical opinion from an NRES Committee (REC) prior to the start of the trial. All parties will conduct the trial in accordance with this ethical opinion.

NCTU will notify the REC of all required substantial amendments to the trial and those non-substantial amendments that result in a change to trial documentation (e.g. protocol or Participant Information

Sheet). Substantial amendments that require a REC favourable opinion will not be implemented until this REC favourable opinion is obtained. NCTU will notify the REC of any serious breaches of GCP or the protocol or Urgent Safety Measures (USMs). Sponsor will notify the REC of any SUSARs that occur during the trial.
An annual progress report will be submitted each year to the REC by NCTU until the end of the trial. This report will be submitted within 30 days of the anniversary date on which the original favourable ethical opinion was granted.

NCTU will notify the REC of the early termination or end of trial in accordance with the required timelines.

Peer Review

The trial has undergone rigorous peer review through the process of grant application and funding award by the NIHR HTA Panel.

Regulatory Compliance

The trial will be conducted in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments. All parties must abide by these regulations and the ICH GCP guidelines.

NCTU trial management team will apply for a Clinical Trial Authorisation (CTA) from the MHRA, on behalf of the sponsor, prior to the start of the trial and will notify the MHRA of any substantial amendments that require review by the competent authority. These substantial amendments will not be implemented until the MHRA has issued an acceptance of the amendment.

The sponsor will notify the MHRA of any serious breaches of GCP or the protocol, urgent safety measures or SUSARs that occur during the trial.

The Development Safety Update Report will be submitted each year to the MHRA by NCTU , until the end of the trial.

NCTU will notify the MHRA of the early termination or end of trial in accordance with the required timelines.

Protocol Compliance

It is the responsibility of the CI to ensure that the clinical investigation is run in accordance with GCP and the protocol. Trial tasks may be delegated to a suitably qualified or experienced member of the research team but the CI and PI will retain overall responsibility for adherence to protocol and GCP. The trial will be monitored by NCTU , to measure protocol compliance and manage deviations. The local trial team are responsible for compliance with the protocol in their everyday trial activities, and must report anything that they feel constitutes an AE, SAE, SUSAR, protocol deviation, serious breach, anything that requires an USM, or anything else that should be reported and documented between monitoring visits.

Protocol deviations, non-compliances or breaches are departures from the approved protocol. Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used.

Deviations from the protocol and GCP occur in clinical trials and the majority of these events are technical deviations that are not serious breaches. These events must be documented on the trial deviation log, including the relevant Corrective and Preventive Actions (CAPA) required.
Deviations that are found to frequently recur at a site are not acceptable and could be classified as a violation or serious breach.

Notification of Serious Breaches to GCP and/or the Protocol

Any violations must be reported to NCTU by emailing cobalt.study@newcastle.ac.uk within 3 days of awareness. The trial manager will notify the sponsor of all violations as soon as they become aware of them. Violations will be reviewed to determine if they meet the criteria for a serious breach. Where a serious breach has been identified, it is the responsibility of the Sponsor to notify the REC and MHRA within **7 calendar days** of determining that a serious breach has occurred.

A serious breach is a breach which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the subjects of the trial, or
(b) the scientific value of the trial

Data Protection and Patient Confidentiality

The trial will be run in accordance with the Data Protection Act 2018, to maintain the confidentiality of trial participants and trial data integrity.

Indemnity

The Sponsor will provide indemnity in the event that trial participants suffer negligent harm due to the management of the trial provided under the NHS indemnity arrangements for clinical negligence claims in the NHS.

The substantial employers of the protocol authors will provide indemnity in the event that trial participants suffer negligent harm due to the design of the trial.

The trial sites will provide indemnity in the event that trial participants suffer negligent harm due to the conduct of the trial at their site. For NHS Organisations this indemnity will be provided under the NHS indemnity arrangements for clinical negligence claims in the NHS. NHS Organisations must ensure that site staff without substantive NHS contracts hold honorary contracts to ensure they can access patients and are covered under the NHS indemnity arrangements. Trial staff without NHS contracts e.g. General Practitioners or Dentists will provide their own professional indemnity.

Amendments

It is the responsibility of the Sponsor to determine whether an amendment is substantial or not and trial procedures must not be changed without the mutual agreement of the CI, Sponsor and Trial Management Group.

Substantial amendments will be submitted to the HRA, REC and/or MHRA (as appropriate) and will not be implemented until this approval is in place. It is the responsibility of NCTU to submit substantial amendments to HRA, REC and/or MHRA (as appropriate) and to send to sites following approval.

Non-substantial amendments will be submitted to the Health Research Authority (HRA) and will not be implemented until authorisation is received. NCTU will notify sites when authorisation is received.

Substantial amendments and those minor amendments which may impact sites will be submitted to the relevant NHS R&D Departments for notification, to determine whether the amendment affects the NHS permission for that site. Amendment documentation will be provided to sites by NCTU.

Access to the Final Trial Dataset

In accordance with Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust, Government and NIHR policies, non-identifiable research data may be shared with researchers in other Universities and organisations (including those in other countries), for research in health and social care. If there is a need to share identifiable information, explicit consent will be sought from participants. Appropriate

safeguards will be in place where any patient identifiable data (PID) is transferred to other countries, in particular those countries with different data protection laws to the UK. All fields in the database that collect PID can be encrypted which includes DOB and Ethnicity.

We are committed to sharing pseudonymised individual level data, where a rigorous research question may be answered by those data. The central trial team, including NCTU and the CI, will consider proposals from researchers as long as there is no constraint due to:

- Ethical approval and informed consent
- The NIHR contract
- The request does not require the data prior to publication of the main trial findings
- The request for data does not extend beyond that which is needed to answer the specific research question.

The CI is nominated by the sponsor to take responsibility, as custodian of the data.

15.2. Ethical and Regulatory Considerations for Australia only

Research Ethics Approval & Local Governance Authorisation

This protocol and the informed consent document and any subsequent amendments will be reviewed and approved by a National Mutual Acceptance (NMA) Human Research Ethics Committee (HREC) prior to commencing the research. A letter of approval by HREC will be obtained prior to the commencement of the trial, as well as approval for other trial documents requiring HREC review.
Each participating institution will also obtain institutional governance authorisation for the research and associated HREC-approved documents. A letter of authorisation will be obtained from the Research Governance Office (RGO) prior to the commencement of the research at that institution. Institutional governance authorisation for any subsequent HREC-approved amendments will be obtained prior to implementation at each site.

Amendments to the protocol

This trial will be conducted in compliance with the current version of the protocol. Any change to the protocol document or Informed Consent Form that affects the scientific intent, trial design, participant safety, or may affect a participant's willingness to continue participation in the trial is considered an amendment, and therefore will be written and filed as an amendment to this protocol and/or informed consent form. All such amendments will be submitted to the HREC and RGO, for approval prior to being implemented.

Protocol Deviations and Serious Breaches

All protocol deviations will be recorded in the participant record (source document) and on the CRF and must be reported to the Site Principal Investigator, who will assess for seriousness.

Those deviations deemed to affect to a significant degree rights of a trial participant or the reliability and robustness of the data generated in the clinical trial will be reported as serious breaches. Reporting will be done in a timely manner (Site Principal Investigator to report to the Sponsor/delegate within 72 hours and to the Site RGO within 7 day; Sponsor/delegate to review and submit to the approving HREC within 7 days).

Where non-compliance significantly affects human participant protection or reliability of results, a root cause analysis will be undertaken and a corrective and preventative action plan prepared.

Where protocol deviations or serious breaches identify protocol-related issues, the protocol will be reviewed and, where indicated, amended.

Data and Information Management

National guidelines (National Statement on Ethical Conduct in Human Research [NHMRC, 2007 updated 2018; The Australian Code for the Responsible Conduct of Research 2007, updated 2018) require that the Principal Investigator maintains (during the trial and retains for the minimum, mandatory archive period) appropriate research records along with a record of their location.

The Principal Investigator is responsible for maintaining adequate and accurate source documents that include all key observations on all participants at their site. Source data will be attributable, legible (including any changes or corrections), contemporaneous, original, accurate, complete, consistent, enduring and available. Changes to source data (hardcopy and electronic) must be traceable, must not obscure the original entry, and must be explained where this is necessary.

Any person delegated to collect data, perform data entry or sign for data completeness will be recorded on the delegation log and will be trained to perform these trial-related duties and functions.

Data for this trial will be collected and entered using hardcopy and electronic data collection forms which will be completed by the participant, caregiver and researchers.

The data will be used for the analyses specified in the protocol and Statistical Analysis Plan.
Following the completion and analysis of the trial, the data will be retained long-term following the mandatory archive period for use in future research projects.

Hard copy data will be stored by the Site in a locked cabinet in a secure location, accessible to the research team only.

Electronic data will be securely stored in REDCap database system, hosted at the Melbourne Brain Centre (MBC), Royal Melbourne Hospital. Files containing private or confidential data will be stored only in locations accessible only by appropriate designated members of the research team.

REDCap maintains an audit trail of data create/update/delete events that is accessible to project users who are granted permission to view it. Access to REDCap will be provided via a REDCap user account created by the MBC REDCap system administrator. The permissions granted to each user within each REDCap project will be controlled by, and will be the responsibility of, the trial team delegated this task by the Principal Investigator. REDCap has functionality that makes adding and removing users and managing user permissions straightforward. All data transmissions between users and the REDCap server are encrypted. The instructions for data entry to REDCap must be read and the training log signed prior to personnel commencing data entry on REDCap.

Authorised representatives of the sponsoring institution as well as representatives from the HREC, Research Governance Office and regulatory agencies may inspect all documents and records required to be maintained by the Investigator for the participants in this trial. The trial sites will permit access to such records.

The trial protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the trial, or the data will be released to any unauthorised third party, without prior written approval of the sponsoring institution. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the HREC, Research Governance Office or regulatory agencies.

Data confidentiality

Participant confidentiality is strictly held in trust by the Site Principal Investigator, participating investigators, research staff, and the sponsoring institution and their agents. This confidentiality is

extended to cover testing of biological samples in addition to the clinical information relating to participating participants.

To preserve confidentiality and reduce the risk of identification during collection, analysis and storage of data and information, the following will be undertaken:

(1) The number of private/confidential variables collected for each individual has been minimised. The data collected will be limited to that required to address the primary, secondary and exploratory objectives.
(2) Participant data and samples will be identified through use of a unique participant trial number/code assigned to the trial participant ("re-identifiable"). The Site Principal Investigator is responsible for the storage of a master-file of names and other identifiable data with the participant ID; access to this document will be restricted to the site trial team and authorised persons. The master file should be stored securely, and separately, from trial data in locked/ password-protected databases with passwords kept separately.
(3) Separation of the roles responsible for management of identifiers and those responsible for analysing content. The data will be analysed by the statistician, who will be provided with pseudonymised data identified only by the unique participant trial ID.

15.3. Public and Patient Involvement and Engagement

Patient and Public Involvement and Engagement (PPIE) has informed proposed trial plans from the start, including during the grant application process. Utilising workshops with DLB/PDD patients and caregivers brought together by our PPIE panel, the group have contributed to the definition of the primary outcome (and other secondary outcomes), the benefits of home visits versus clinic visits within this patient group, provided advice on participant burden and how this is managed, reviewed the acceptability of the trial methods and provided input regarding the lay summary.

Ongoing PPIE will consist of regular meetings of the PPIE Panel to review progress and provide advice on the trial going forward. PPIE members from both the UK and Australia will be able to attend TMG meetings to oversee and input on the running of the trial. The PPIE panel will also collect participant feedback and organise events to publicise the findings.

16. Dissemination Policy

16.1. End of Trial Reporting

We will use traditional methods of publications and conference presentations to share the results with other researchers, clinicians and people living with DLB/PDD and their families.

A final report of the trial will be provided to the Sponsor, REC and the trial funder within 1 year of the end of the trial.

16.2. Authorship Policy

Ownership of the data arising from this trial resides with the trial team and their respective employers. On completion of the trial, the trial data will be analysed and tabulated, and a clinical trial report will be prepared.

Authorship eligibility for each manuscript arising from this trial will be determined by the Trial Management Group. All co-applicants, plus the senior trial manager, trial managers, data manager and trial statisticians, will be eligible for authorship on papers reporting the protocol and main trial results,

subject to fulfilling the ICMJE authorship criteria. Authorship for other conference abstracts and scientific papers arising from this work will be decided by the Trial Management Group.

All outputs from this programme of work will acknowledge the NIHR Health Technology Assessment Programme and NHMRC-NIHR Collaborative Research Grant as funders, the NIHR Newcastle Biomedical Research Centre and will specifically acknowledge the Newcastle Clinical Trials Unit, Newcastle University, University of Melbourne, and Cumbria, Northumberland Tyne and Wear NHS Foundation Trust as Sponsor.

16.3. Publication

We will publish our findings in high impact peer-reviewed academic journals, ensuring that all publications are open access. We will publicise our results at national and international conferences irrespective of the results, as it is important even for negative results to be in the public domain. We will present at a range of conferences across a number of medical specialties (Psychiatry, Neurology, Geriatrics, Primary Care) to ensure that the results are widely publicised.

We anticipate that the results will have a major impact on clinical practice. If negative, it would give a clear message to clinicians that adding memantine to an AChEI in DLB/PDD cases has no benefit to patients and healthcare systems and should not be part of clinical care. If positive, it will give a clear message to clinicians that adding memantine to an AChEI is beneficial.

We plan to present our findings to clinical commissioning groups, in order to ensure that the clinical and economic worth of adding memantine to an AChEI is made known. We will advocate that the results are accurately reflected in future NICE guidelines. Given the international context of our proposed trial and its generalisability, scale and scope, our findings will also have significant implications in helping inform clinical care guidelines for dementia internationally.

16.4. Making Results Publicly Available

The trial will be prospectively registered on the ISRCTN trial database prior to enrolment of the first participant.

16.5. Access to Final Data Set

Until publication of the trial results, access to the full dataset will be restricted to the Trial Management Group and to authors of the publication.

Anonymised or Pseudonymised data from this trial may be available to the scientific community in accordance with ethical approval obtained for the trial. Requests for data should be directed to the lead author/Chief Investigator and NCTU in line with any applicable data sharing policies.

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18. APPENDICES

18.1. Appendix 1 – DLB Diagnostic Criteria

Table 1 **Revised[1,2] criteria for the clinical diagnosis of probable and possible dementia with Lewy bodies (DLB)**

Essential for a diagnosis of DLB is dementia, defined as a progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational functions, or with usual daily activities. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention, executive function, and visuoperceptual ability may be especially prominent and occur early.

Core clinical features (*The first 3 typically occur early and may persist throughout the course.*)

Fluctuating cognition with pronounced variations in attention and alertness.
Recurrent visual hallucinations that are typically well formed and detailed.
REM sleep behavior disorder, *which may precede cognitive decline.*
One or more spontaneous cardinal features of parkinsonism: these are bradykinesia (defined as slowness of movement and decrement in amplitude or speed), rest tremor, or rigidity.

Supportive clinical features

Severe sensitivity to antipsychotic agents; postural instability; repeated falls; syncope or other transient episodes of unresponsiveness; severe autonomic dysfunction, e.g., constipation, orthostatic hypotension, urinary incontinence; hypersomnia; hyposmia; hallucinations in other modalities; systematized delusions; apathy, anxiety, and depression.

Indicative biomarkers

Reduced dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET.
Abnormal (low uptake) ^{123}iodine-MIBG myocardial scintigraphy.
Polysomnographic confirmation of REM sleep without atonia.

Supportive biomarkers

Relative preservation of medial temporal lobe structures on CT/MRI scan.
Generalized low uptake on SPECT/PET perfusion/metabolism scan with reduced occipital activity ± the cingulate island sign on FDG-PET imaging.
Prominent posterior slow-wave activity on EEG with periodic fluctuations in the pre-alpha/theta range.

Probable DLB can be diagnosed if:

a. Two or more core clinical features of DLB are present, with or without the presence of indicative biomarkers, or

b. Only one core clinical feature is present, but with one or more indicative biomarkers.

Probable DLB should not be diagnosed on the basis of biomarkers alone.

Possible DLB can be diagnosed if:

a. Only one core clinical feature of DLB is present, with no indicative biomarker evidence, or

b. One or more indicative biomarkers is present but there are no core clinical features.

DLB is less likely:

a. In the presence of any other physical illness or brain disorder including cerebrovascular disease, sufficient to account in part or in total for the clinical picture, although these do not exclude a DLB diagnosis and may serve to indicate mixed or multiple pathologies contributing to the clinical presentation, or

b. If parkinsonian features are the only core clinical feature and appear for the first time at a stage of severe dementia.

DLB should be diagnosed when dementia occurs before or concurrently with parkinsonism. The term Parkinson disease dementia (PDD) should be used to describe dementia that occurs in the context of well-established Parkinson disease. In a practice setting the term that is most appropriate to the clinical situation should be used and generic terms such as Lewy body disease are often helpful. In research studies in which distinction needs to be made between DLB and PDD, the existing 1-year rule between the onset of dementia and parkinsonism continues to be recommended.

Table taken from Mckeith et. al, 2017

18.2. Appendix 2 – PDD Diagnostic Criteria

TABLE 1. *Features of dementia associated with Parkinson's disease*

I. Core features

1. Diagnosis of Parkinson's disease according to Queen Square Brain Bank criteria
2. A dementia syndrome with insidious onset and slow progression, developing within the context of established Parkinson's disease and diagnosed by history, clinical, and mental examination, defined as:
   - Impairment in more than one cognitive domain
   - Representing a decline from premorbid level
   - Deficits severe enough to impair daily life (social, occupational, or personal care), independent of the impairment ascribable to motor or autonomic symptoms

II. Associated clinical features

1. Cognitive features:
   - Attention: Impaired. Impairment in spontaneous and focused attention, poor performance in attentional tasks; performance may fluctuate during the day and from day to day
   - Executive functions: Impaired. Impairment in tasks requiring initiation, planning, concept formation, rule finding, set shifting or set maintenance; impaired mental speed (bradyphrenia)
   - Visuo-spatial functions: Impaired. Impairment in tasks requiring visual-spatial orientation, perception, or construction
   - Memory: Impaired. Impairment in free recall of recent events or in tasks requiring learning new material, memory usually improves with cueing, recognition is usually better than free recall
   - Language: Core functions largely preserved. Word finding difficulties and impaired comprehension of complex sentences may be present
2. Behavioral features:
   - Apathy: decreased spontaneity; loss of motivation, interest, and effortful behavior
   - Changes in personality and mood including depressive features and anxiety
   - Hallucinations: mostly visual, usually complex, formed visions of people, animals or objects
   - Delusions: usually paranoid, such as infidelity, or phantom boarder (unwelcome guests living in the home) delusions
   - Excessive daytime sleepiness

III. Features which do not exclude PD-D, but make the diagnosis uncertain

- Co-existence of any other abnormality which may by itself cause cognitive impairment, but judged not to be the cause of dementia, e.g. presence of relevant vascular disease in imaging
- Time interval between the development of motor and cognitive symptoms not known

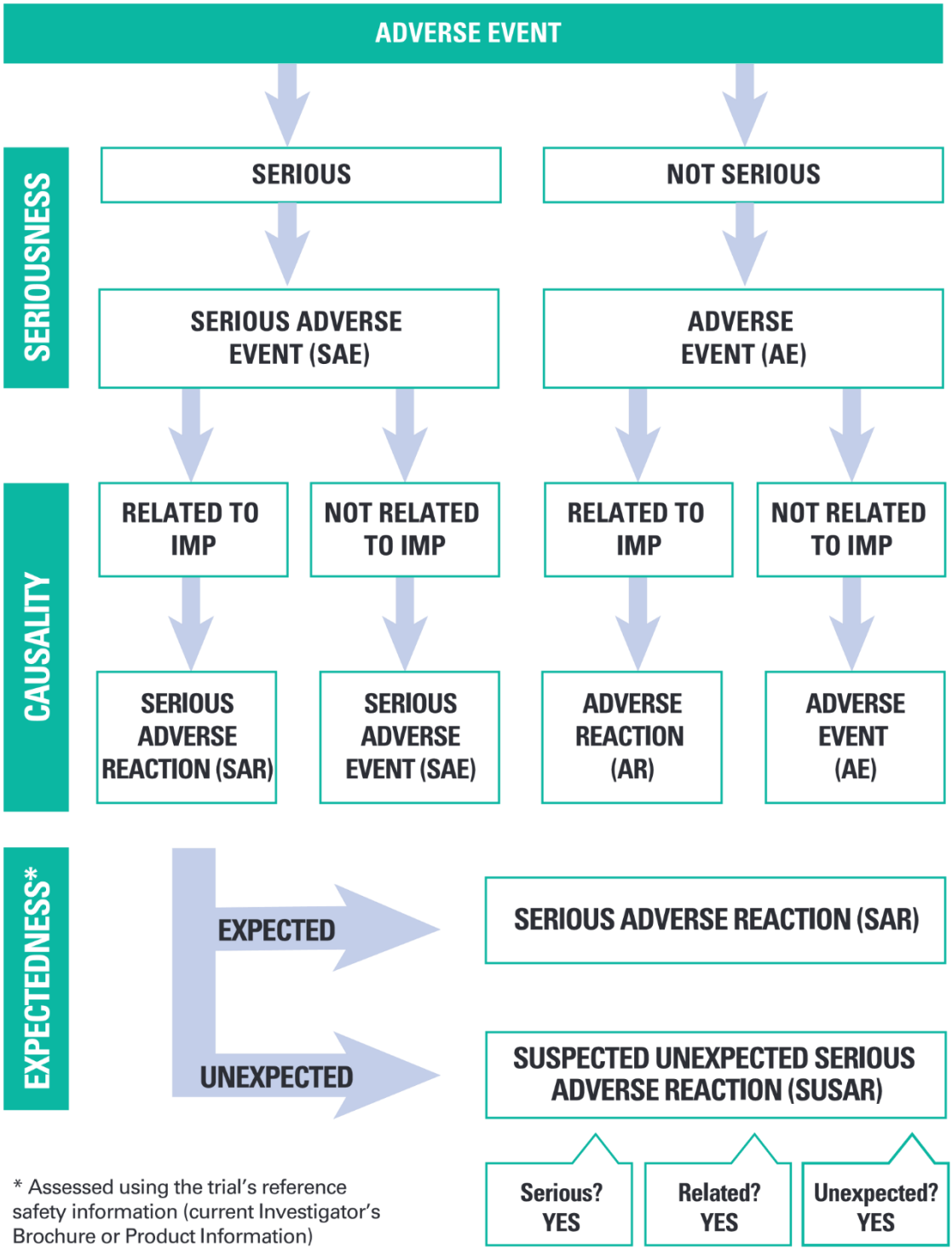
IV. Features suggesting other conditions or diseases as cause of mental impairment, which, when present make it impossible to reliably diagnose PD-D

- Cognitive and behavioral symptoms appearing solely in the context of other conditions such as:
  Acute confusion due to
  a. Systemic diseases or abnormalities
  b. Drug intoxication
  Major Depression according to DSM IV
- Features compatible with "Probable Vascular dementia" criteria according to NINDS-AIREN (dementia in the context of cerebrovascular disease as indicated by focal signs in neurological exam such as hemiparesis, sensory deficits, and evidence of relevant cerebrovascular disease by brain imaging AND a relationship between the two as indicated by the presence of one or more of the following: onset of dementia within 3 months after a recognized stroke, abrupt deterioration in cognitive functions, and fluctuating, stepwise progression of cognitive deficits)

Table taken from Emre et. al, 2007

18.3. Appendix 3 - Safety Reporting Flow Diagram

B. Safety Reporting Assessment Flowchart: IMP Trial



Adapted from the NIHR Clinical Trials Toolkit

18.4. Appendix 4 – Amendment History

Amendment Number	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
SA01	3.0		TS and SD	All references to titration pack changed to initiation pack so that it is consistent with the IMP labels. Minor typographical change made.