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The NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC), based at the University of Southampton, manages evaluation research programmes and activities for the NIHR

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Multi-centre UK Study of the Acetylcholinesterase Inhibitor Donepezil in Early Dementia Associated with Parkinson's Disease (MUSTARDD-PD)

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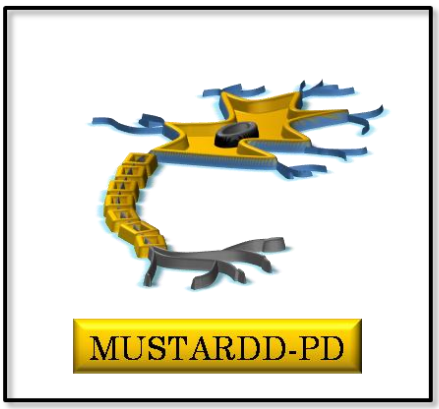

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2. Protocol Signature Page

2.1 Protocol Authorisation Signatories

Signature …… Date ……

Professor David J Burn, Chief Investigator

Signature …… Date ……

Dr Ian Nicholas Steen, Statistician

Signature …… Date ……

Sharon Erb, Trial Manager

2.2 Principal/Chief Investigator Signature

I confirm that I have read and understood protocol version 7.0, dated 22 August 2013. I agree to comply with the study protocol, the principles of GCP, research governance, clinical trial regulations and appropriate reporting requirements.

Signature …… Date ……

Print Name ……

Site Name/I.D. ……

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4. Glossary of Abbreviations

Abbreviation	***Definition***
AD	*Alzheimer's Disease*
ACE-R	*Addenbrooke's Cognitive Examination*
ADAS-cog	*Alzheimer's Disease Assessment Scale: Cognitive Subsection*
ADCS-CGIC	*Alzheimer's Disease Cooperative Study - Clinical Global Impression of Change*
AE	*Adverse Event*
BADLS	*Bristol Activities of Daily Living Scale*
BDI	*Beck Depression Inventory*
BPSD	*Behavioural and Psychological Symptoms of Dementia*
ChEI	*Cholinesterase inhibitor drugs*
CI	*Chief Investigator*
CRF	*Case Report Form*
CTA	*Clinical Trial Authorisation*
DBS	*Deep Brain Stimulation*
DeNDRoN	*Dementias and Neurodegenerative Diseases Research Network*
DLB	*Dementia with Lewy Bodies*
DMEC	*Data Monitoring and Ethics Committee*
DOB	*Date of Birth*
DSM-IV	*Diagnostic Statistical Manual IV*
ECG	*Electrocardiogram*
e-CRF	*Electronic Case Report Form*
GCP	*Good Clinical Practice*
HTA	*Health Technology Assessment*
IMP	*Investigational Medicinal Product*
IRAS	*Integrated Research Application System*
Mattis DRS-2	*Mattis Dementia Rating Scale*
MoCA	*Montreal Cognitive Assessment*
MHRA	*Medicines and Health Care Products Regulatory Agency*
MMSE	*Mini-Mental Status Examination*
MRC	*Medical Research Council*
MUSTARDD-PD	*Multicentre UK Study of the Acetylcholinesterase Inhibitor Donepezil in Early Dementia Associated with Parkinson's Disease*
NCTU	*Newcastle Clinical Trials Unit*
NICE	*National Institute for Health and Clinical Excellence*
NIHR	*National Institute for Health Research*
NPI-10	*10 item Neuropsychiatric Inventory*
PD	*Parkinson's Disease*
PD-CRS	*Parkinson's Disease Cognitive Rating*

	Scale
PDD	*Dementia associated with Parkinson's Disease*
PI	*Principal Investigator*
PSSRU	*Personal Social Services Research Unit*
QALY	*Quality-Adjusted Life Year*
RCT	*Randomised Controlled Trial*
SAE	*Serious Adverse Event*
SCOPA-COG	*SCales for Outcomes of PArkinson's disease-cognition*
SSRI	*Selective Serotonin Reuptake Inhibitor*
SOP	*Standardised Operating procedure*
SmPC	*Summary of Product Characteristics*
SUSAR	*Suspected, Unexpected Serious Adverse Reaction*
TMG	*Trial Management Group*
TSC	*Trial Steering Committee*
UPDRS	*Motor subsection of the new Unified Parkinson's Disease Rating Scale*

5. Responsibilities

Sponsor: Newcastle upon Tyne Hospitals NHS Foundation Trust will act as the sponsor for this study. Day-to-day responsibility for sponsor level activities will be delegated to the Chief Investigator and the Newcastle Clinical Trials Unit.

Funder:

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Michael J Fox Foundation. Contact: Jamie L. Eberling, PhD, Associate Director, Research Programs, The Michael J. Fox Foundation for Parkinson's Research.
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Trial Management: A Trial Management Group (TMG) will be appointed and will be responsible for overseeing the progress of the trial. The day-to-day management of the trial will be co-ordinated by the MUSTARDD-PD Trial Manager.

Chief Investigator: The Chief Investigator (Professor David Burn) will have overall responsibility for the conduct of the study as a whole.

Principal Investigator: The Principal Investigator will have overall responsibility for the conduct of the study at a particular trial site.

Trial Management:
The following functions falling under the responsibility of the sponsor will be delegated to Professor Burn as Chief Investigator:

- Authorisation and Ethics Committee Opinion (including CTA request, research ethics committee opinion, notification of protocol amendments and end of trial, site specific assessment and local approval).
- Good Clinical Practice (GCP) and Trial Conduct (including GCP arrangements, management of Investigational Medicinal Product (IMP), data monitoring, emergency and safety procedures).
- Pharmacovigilance (including defining and recording adverse events/reactions, reporting SUSARs, notifying investigators of SUSARs, ensuring SAEs are reviewed by an appropriate committee for safety monitoring, annual listings and safety report).
- Administration of the study budget.

Trial Conduct at Each Site:
Principal Investigator (PI) responsibilities:

- Study conduct and the welfare of study subjects.
- Familiarity with the use of the investigational medicinal product as described in the product information, appropriate storage, and administration according to the protocol and drug accountability. Ensuring investigational medicinal product is not used for any purposes other than the conduct of the study.
- Compliance with the protocol, documentation of any protocol deviations and reporting of all serious adverse events.
- Screening and recruitment of subjects.
- Ensuring all trial-related medical decisions are made by a qualified physician, who is an investigator or co-investigator for the trial.
- Provision of adequate medical care in the event of an adverse event.
- The PI should be qualified by education, training and experience to assume responsibility for the proper conduct of the trial. The PI shall provide a current signed and dated curriculum vitae as evidence for the Trial Master File and a copy kept at local site.
- Obtaining relevant local approvals and abiding by the policies of Research Governance.
- Compliance with the Principles of GCP, Research Governance Framework and any national legislation implementing the EU Clinical Trials Directive (2001/20/EC) and subsequent amendments.
- Ensuring no participant is recruited into the study until all relevant regulatory permissions and approvals have been obtained.
- Obtaining written informed consent from participants prior to any study specific procedures.
- Ensuring that Study Site team members are appropriately qualified by education, training and experience to undertake the conduct of the study.
- Being available for Investigator meetings, monitoring visits and in the case of an audit.
- Maintenance of study documentation and compliance with reporting requirements:
    - Maintaining an Investigator Site File, including copies of study approval, list of subjects and their signed informed consent forms.
    - Documenting appropriate delegation of tasks to study personnel e.g. Pharmacist, Research Nurse, Investigator(s).
    - Ensuring data collected is accurate and complete.
    - Providing updates on the progress of the trial.
    - Ensuring subject confidentiality is maintained during the project and archival period.
    - Ensuring archival of study documentation for a minimum of 15 years following the end of the study, unless local arrangements require a longer period.

6. Protocol Summary

Short title:	Donepezil in Early Dementia Associated with Parkinson's Disease
Protocol version:	7.0
Protocol date:	22 August 2013
Chief Investigator:	Professor David J Burn
Sponsor:	The Newcastle upon Tyne Hospitals NHS Foundation Trust
Funder:	NIHR Health Technology Assessment Programme and the Michael J Fox Foundation
Study design:	Randomised, double-blind, placebo-controlled study
Study Intervention:	Donepezil hydrochloride versus placebo (1:1 ratio)
Primary objective:	To demonstrate the superiority of donepezil hydrochloride over placebo in improving cognitive function, neuropsychiatric burden and functional ability in people with Parkinson's disease and mild dementia after 24 months of treatment.
Secondary objectives:	To demonstrate the superiority of donepezil hydrochloride over placebo in improving patient and carer quality of life and to establish the cost-effectiveness of donepezil hydrochloride. To determine the instrument most suitable for evaluating change in cognition in people with Parkinson's disease and mild dementia.
Primary outcomes:	Mattis Dementia Rating Scale (DRS-2), Neuropsychiatric Inventory and Bristol Activity of Daily Living Scale.

Number of study sites: 22

Study population/size: 500 people with Parkinson's disease and mild dementia

Study duration: 60 months

7. Background

Parkinson's disease (PD) is a chronic neurodegenerative disease that places a substantial burden on the patient, their family and carers, as well as on society as a whole. PD affects 1% of the population over 65 and 2% over 80 years of age. In a UK community-based incidence study 36% of people with PD had evidence of cognitive impairment [1]. At a mean of 3.5 years from diagnosis, 10% of these patients had developed dementia, corresponding to an annual dementia incidence of 30.0 (95% confidence interval 16.4-52.9) per 1000 person-years [2]. A recent systematic review suggested that 24 to 31% of people with PD have dementia (PDD), and that 3 to 4% of the dementia in the general population is due to PDD [3]. The estimated prevalence of PDD in the general population aged 65 years and over is thus 0.2 to 0.5%, while from community-based longitudinal studies the cumulative incidence of dementia in PD may be as high as 80% [4, 5].

Dementia in PD is associated with increased mortality, greater likelihood of hospitalisation and nursing home placement, and constrains effective management of the motor features of the disorder. Nearly 90% of people with PDD also experience troublesome neuropsychiatric symptoms, with depression, apathy, anxiety and hallucinations being most frequent [6]. The carers of demented PD patients are more likely to experience higher levels of stress and depression compared to carers of non-demented PD patients [7].

In June 2006 the NICE Guidelines for the Diagnosis and Management of PD included a review of the treatment of dementia associated with PD [8]. The guidelines state that there is evidence from randomised placebo-controlled trials for the effectiveness and safety of cholinesterase inhibitors in the treatment of PDD and that these agents ware effective in treating both cognitive decline and psychosis in this context. This statement was tempered by the recognition that not all patients with PDD respond to cholinesterase inhibitors, and that further research is recommended. Indeed, PDD was identified as a research priority within the NICE guidelines, particularly with respect to evaluating efficacy and cost-effectiveness.

Existing Research

The pharmacological treatment of dementia may be considered in three categories: preventative strategies, disease-modifying treatment and symptomatic treatment. From a literature search, we are not aware of any trials of preventative or disease-modifying approaches in dementia associated with Parkinson's disease (PDD). Multiple convergent lines of evidence from clinical, neuroimaging, pathological and neurochemical studies indicate a profound loss of cholinergic neurotransmission in PDD, in excess of that found in Alzheimer's disease (AD) [9-11]. This loss underpins several core features of the dementia syndrome associated with PD. Cholinesterase inhibitor drugs (ChEIs) act to improve cholinergically-mediated cognitive and neuropsychiatric symptoms in PDD by reducing enzymatic breakdown of acetylcholine. There is therefore a sound scientific rationale for the use of these agents in the symptomatic management of PDD.

Just two adequately sized randomised controlled trials (RCTs) have been performed for the use of ChEIs in PDD and only one of these (EXPRESS study of rivastigmine, n=541) has fully reported [12], with the other (EDON study of donepezil, n = 549), published only in abstract form [13]. The other three trials have been very small, recruiting a total of 52 patients between them [14-16]. Both the EXPRESS and EDON studies recruited PD patients with mild to moderate dementia, with a treatment duration of 24 weeks. EXPRESS study participants were also offered the chance to enter an active treatment extension phase over an additional 24 weeks. Using the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog, range 0-70 points max), modest but statistically significant benefits were noted in both studies at 24 weeks in the ChEI group (2.8 points

improvement in active *vs.* placebo groups in EXPRESS and 3.4 points improvement in active *vs.* placebo groups in EDON). Significant improvements were also noted in the EXPRESS study in several secondary outcome measures, including activities of daily living and burden of neuropsychiatric symptoms. 73% of those assigned to rivastigmine completed treatment, compared to 82% of those allocated to placebo; the main reason for premature withdrawal was adverse event occurrence. 93% of patients receiving rivastigmine provided follow-up data on at least one occasion, contributing to the efficacy analysis, compared with 92% in the placebo group. The study could be criticised, however, for the use of 'last observation carried forward' as the means of imputation of missing data for those lost to follow-up prior to 24 weeks. There were fewer deaths in the active treatment group (4/362 versus 7/179, OR 0.27, 95% CI 0.08 to 0.95, p = 0.04). Patients receiving rivastigmine in the active treatment extension study continued to derive a small improvement from the drug at 48 weeks [17]. A problem with both the EXPRESS and EDON RCTs is that they used the generic Diagnostic Statistical Manual IV (DSM-IV) criteria to define dementia in PD, and graded severity according to Mini-Mental Status Examination (MMSE) score. Neither the DSM-IV criteria nor the MMSE score capture the cognitive profile of PDD, potentially biasing the sample to patients with a more "Alzheimer-type" presentation, and excluding those with greater executive dysfunction who arguably may have benefited more from the ChEI intervention. It is possible for a PD patient to have dementia but a "normal" MMSE score, yet such patients would have been excluded from the EXPRESS and EDON studies. Furthermore, the ADAS-cog as a primary outcome measure is arguably better suited to the cognitive dysfunction observed in AD patients and is not ideally tailored to measure treatment effects in PDD. In particular, it is relatively insensitive to the prominent and early dysexecutive problems that characterise PDD (difficulties in the realization of complex cognitive tasks requiring the selection of information to be processed, finding a rule, shifting mental set, solving multiple step problems, resisting cognitive interference, sharing attentional resources, and actively retrieving information). Crucially, no quality of life, carer strain or health economic measures were reported in these studies.

A Cochrane review [18] identified only one RCT, the aforementioned EXPRESS study [12], that fulfilled pre-specified inclusion criteria and concluded that rivastigmine appeared to improve cognition and activities of daily living in PDD, resulting in clinically meaningful benefit in 15% of cases. Notably, this review suggested that future trials in PDD should involve other ChEIs, utilise analytic tools that limit any bias and also measure health economic factors. Patient and carer quality of life assessments were also recommended as outcome measures. To date, no trial has addressed these points. Also, no RCT has extended beyond one year, nor addressed drug effectiveness and impact in a PDD cohort limited to mild dementia at study entry. Two further protocols are entered on the Cochrane Website for the treatment of PDD [19, 20], although neither has yet reported. A search of major clinical trials databases (www.clinicaltrials.gov and www.controlled-trials.com/isrctn) performed on 6 August 2008 yielded only one additional open study of a cholinesterase inhibitor in dementia associated with Parkinson's disease. This is a 76 week safety study of rivastigmine capsule and patch in people with mild or moderately severe dementia. Neither quality of life nor health economic measures are included in the outcomes listed for this trial.

In 2006 the American Academy of Neurology Practice Parameter document suggested that donepezil or rivastigmine should be considered for the treatment of dementia in PD [21]. The justification for donepezil was primarily based on a single Class I randomised placebo-controlled cross-over study in only 22 patients. Each treatment period was 10 weeks, separated by a 6 week washout period [16]. In the same year, the NICE Parkinson's Disease Guidelines Development Group recognised that while cholinesterase inhibitors have been used successfully in individual people with PD dementia (Grade D evidence), further research is recommended to identify those patients

who will benefit from this treatment [8]. The NICE Guidelines also make further cholinesterase inhibitor trials in PDD a research priority, with particular emphasis upon cost-effectiveness.

Summary of Existing Research

Available evidence from randomised controlled trials provides limited support for the use of cholinesterase inhibitors in the management of PDD. These trials are limited in most cases by their small size, and in all cases by a relatively short duration and lack of clinically meaningful end-points. None of the trials have examined cost-effectiveness for these agents. Although the NICE PD Guidelines accept that people with PDD could benefit from the use of a cholinesterase inhibitor, they note that the evidence base for this recommendation is relatively weak and explicitly state that further research is necessary. The present trial has been designed to address the shortfalls in previous studies and to provide a much needed addition to the limited existing research base in this area.

Instruments to Assess Cognition in Parkinson's disease

Work has been conducted to assess the ability of rating cognitive impairment and determining changes resulting from clinical interventions. This work established the DRS-2, MoCA, PD-CRS and SCOPA-cog as suitable assessment tools in PD. Although the ability of these instruments to discriminate demented from non-demented subjects is well established, the performance of these scales in measuring change longitudinally (with the possible exception of the DRS-2), response to treatment, what is a minimally clinically important change and how this interfaces with quality of life is far less clear.

The usual means of assessing the performance of these global instruments has been to compare sensitivity and specificity for a diagnosis of PDD against a gold standard such as the Diagnostic Statistical Manual IV-R for dementia. Such an approach is entirely appropriate, but fails to evaluate the performance of one scale against another. It would be of huge benefit to clinicians and researchers to determine which of these scales performed best in terms of sensitivity to change and therapeutic intervention. In the face of a robust recommendation, the use of the chosen instrument in future studies would permit ease of comparison between studies globally, and inform the determination of "clinically meaningful" change.

Review of patient falls

Cognition (particularly attention) is an independent predictor of falls in PD [22, 23] representing a modifiable characteristic to reduce falls risk. In support of this, improved cognition through the use of ChEI reduced falls in PD without dementia [24]. ChEI usage in older adults with cognitive impairment from Alzheimer's disease or and vascular dementia, however, is associated with a greater risk of syncope and falls[25]. It is therefore unclear whether ChEI are beneficial or detrimental for falls in PDD. To address this question we will measure falls as an adverse event using a falls diary. Participants will complete a falls diary each month and return it in a stamped addressed envelope. If falls diaries are not received the participant or their carer will receive a telephone call to remind them to post the diary. Diaries should be returned even if there have been no falls. We will also record the participant's falls status at initial assessment by asking the following question:

Do you fall?
1 = never
2 = yes, but infrequently (defined as < 1/month)
3 = yes, frequently (defined as > 1/month)

In addition, we will measure balance confidence using the Activities Balance Confidence Scale (ABCS)[26]. This questionnaire, which takes approximately 3 minutes to administer, will be completed at each assessment point.

8. Objectives

This is an NIHR-funded patient randomised placebo controlled study to evaluate the clinical and cost-effectiveness of the cholinesterase inhibitor donepezil hydrochloride in the long term management of people with relatively mild dementia associated with Parkinson's disease.

In addition to the above the cognitive scales assessment component of the study is funded through the Michael J Fox Foundation.

Primary objective:
To demonstrate the superiority of donepezil hydrochloride over placebo in improving cognitive function, neuropsychiatric burden and functional ability (using the Mattis Dementia Rating, 10 item Neuropsychiatric Inventory and Bristol Activities of Daily Living Scale, respectively) in people with Parkinson's disease and mild dementia after 24 months of treatment.

Secondary objectives:

1. To establish the superiority of donepezil hydrochloride over placebo in improving patient quality of life using:
    a. the EQ5D as a generic preference-based measure of health related quality of life *and*
    b. the DEMQOL and DEMQOL-proxy as validated health-related quality of life measures for people with dementia.
2. To establish the superiority of donepezil hydrochloride over placebo in improving carer quality of life using the Scale of Quality of Life of Caregivers.
3. To demonstrate the cost-effectiveness of donepezil hydrochloride at 26, 52, 76 and 104 weeks.
4. To determine the instrument most suitable for evaluating change in cognition in people with Parkinson's disease and mild dementia.

9. Study Design

MUSTARDD-PD is a double-blind, randomised controlled trial of the (acetyl) cholinesterase inhibitor donepezil hydrochloride versus placebo in the management of mild dementia associated with PD. Randomisation will be by via a centralised web-based system. Analysis will be on the basis of intention-to-treat.

Setting: Community-living people with PD recruited via 22 elderly care and neurology units throughout the UK to reflect population diversity.

Target population: People with mild dementia (defined according to the Mattis Dementia Rating Scale) associated with PD, where the patient and/or their family has become aware of cognitive problems, with or without behavioural symptoms causing functional impairment.

Health technologies being assessed: the trial will evaluate the long term clinical and cost-effectiveness of the cholinesterase inhibitor donepezil hydrochloride in the management of mild dementia associated with PD versus placebo.

Measurement of costs and outcomes: Assessments of clinical effectiveness will be made via subject visits at baseline, and weeks 26, 52, 76 and 104.

Measurement of cognitive change: assessments of sensitivity to change and therapeutic intervention using the DRS-2, MoCA, PD-CRS and SCOPA-cog compared to the modified ADCS-CGIC at baseline, weeks 26, 52, 76 and 104.

Measurement of safety: review of balance and number and nature of falls assessed at baseline, weeks 26, 52, 76 and 104.

Primary outcome measures will be scores on the Mattis Dementia Rating Scale (DRS-2), the 10-item Neuropsychiatric Inventory (NPI-10) and the Bristol Activities of Daily Living Scale (BADLS). The Mattis DRS-2 is well suited to quantifying the cognitive impairments associated with PD-related dementia. The NPI-10 is administered to the caregiver and covers the broad spectrum of behavioural and psychiatric problems associated with PD-related dementia. It also yields a caregiver distress score. The BADLS is a caregiver rated tool, designed to assess activities of daily living in people with dementia.
Secondary outcomes measured at the same time points will comprise: patient quality of life (assessed using EQ5D as a generic preference-based health related quality of life instrument with previously determined feasibility and validity for PD, and the DEMQOL and DEMQOL-proxy as a validated health-related quality of life measure for people with dementia) and carer quality of life (assessed using the Scale of Quality of Life of Caregivers, which is sensitive to carer strain in PD). Data will also be collected using the Client Service Receipt Inventory for the economic evaluation of treatments, service use and carer inputs which will be turned into cost measures by applying local and national unit cost values. Quality-adjusted life years will be measured, based on the EQ5D and the DEMQOL, and these, along with other outcomes, will be employed in the cost-effectiveness analyses.

9.1 End of Study

The end of the study will be the date of last subject's last visit.

10. Subject Population

The study population will comprise people with PD and mild dementia residing in the UK. The inclusion criteria have deliberately been kept as broad as possible to maximise recruitment and give the trial findings greater external validity.

Inclusion Criteria

1. A diagnosis of Parkinson's Disease according to the UK Parkinson's Disease Society Brain Bank Criteria [27]. These criteria are in standard use throughout the NHS in the UK and are supported by the NICE guidelines.
2. People with mild dementia associated with PD, where the patient and/or their family have become aware of cognitive problems with or without behavioural symptoms causing functional impairment. "Dementia" will be defined according to recently published Movement Disorder Society Task Force criteria for dementia associated with Parkinson's Disease [28] and "operationalised" using the Addenbrooke's Cognitive Examination (ACE-R). The ACE-R permits some description of the dementia profile and also quantifies global impairment [29]. It is increasingly used by clinicians in the UK to identify demented subjects, is relatively quick to perform (15 minutes or so), requires no specific training and produces a total score (0-100), from which the MMSE (0-30) can also be extracted. Participants will have an ACE-R of 88 or less [29]. If this criterion is met, subjects will be further assessed using the Mattis Dementia Rating Scale (DRS-2). An age- and education-corrected total DRS-2 score of less than or equal to 8 but greater than or equal to 4 will be used to define "mild" dementia [30].
3. Community living and a spouse, close relative or well established carer to accompany the subject to act as an informant.
4. Where relevant, women of child bearing potential must be using adequate contraception for duration of study.

Exclusion Criteria

1. Dementia that develops within one year of the onset of motor symptoms. The reason for this "one year rule" is specifically to exclude participants with Dementia with Lewy Bodies (DLB). This exclusion criterion is consistent with recommendations made in the Movement Disorder Society Dementia Task Force Diagnostic Criteria [28] and the Third Report of the DLB Consortium [31].
2. People with such severe motor disability, or who are so impaired in their activities of daily living from other aspects of their PD, that it would interfere with cognitive and global assessments.
3. Severe current depressive episode. Low mood may impact upon accurate cognitive assessment, and major depression is therefore listed as a feature which, when present, makes it impossible to reliably diagnose PDD in the Movement Disorder Society Task Force PDD Criteria [28]. This will be operationalised using the self-completed Beck Depression Inventory and a cut-off score of 13, as recommended by a recent Movement Disorder Society Task Force report [32]. The BDI score is considered robust in the face of mild to moderate cognitive impairment.
   Patients who have clinically significant depression as highlighted by the BDI may be treated for their depression and potentially screened at a later date..
4. Unstable significant medical co-morbidity.
5. Patient currently receiving a non-selective centrally acting anticholinergic drug for control of parkinsonian motor symptoms or other indication (eg urinary urgency) are EXCLUDED and use of these medication is forbidden throughout the duration of the study.
   An 8-week washout is required should these agents be discontinued prior to study entry.
6. Previous exposure to any cholinesterase inhibitor excludes a patient.
7. Presence of a condition that is contraindicative to use of donepezil hydrochloride (including a clinically significant cardiac conduction defect found in patient history or from screening ECG); see Summary of Product Characteristics (SmPC) (Appendix A1 and 2) for details.
8. Allergy/hypersensitivity to excipients of donepezil hydrochloride or placebo.
9. Patient receiving the N-methyl-d-aspartate antagonist memantine; no exposure, previous or current, is permitted
10. Deep brain stimulation, or other neurosurgical procedure for Parkinson's disease, within 12 months of the screening visit.

Stable doses of atypical anti-psychotic medication (i.e. dose unchanged for 6 weeks prior to study entry) *will* be permitted. Many patients with PDD experience psychotic features (especially visual hallucinations) prior to the onset of cognitive decline which may require atypical anti-psychotic medication. It is felt that it would be both impractical and unethical to exclude the use, or require the withdrawal, of these agents in a placebo-controlled study.

11. Screening, Recruitment and Consent

11.1 Screening

Potential participants will be identified through routine outpatient appointments at trial sites and agreed participant identification centres. Where relevant, DeNDRoN staff will assist in the identification of potential participants in these clinics or screening of databases. All staff involved in identifying patients, with no direct bearing on the patients' care, will as a minimum have letters of access.

An eligibility screening form will be completed by the investigator to document fulfilment of the entry criteria for all patients considered for the study and subsequently included or excluded. Anonymised demographic details of those excluded will be recorded, to facilitate ascertainment of extent of participation bias, and reasons for exclusion will be recorded, insofar as is possible, to facilitate construction of the CONSORT diagram.

The screening assessments (as per routine clinical practice) will occur 2 weeks (+/- 2 days) prior to baseline visit, randomisation and start of study drug.

11.2 Recruitment

Eligible participants will be invited to participate by the site PI, or another member of site research staff with documented delegated responsibility, and the study explained to them. A study Patient Information Sheet will be provided at this time and the patient will be allowed to take this away for further consideration and discussion with significant others.

A screening log will be kept to document details of subjects invited to participate in the study. For subjects who decline participation, this will document any reasons available for non-participation. The log will also ensure that potential participants are only approached once.

11.3 Consent

Informed consent discussions will be undertaken by appropriately trained site staff (as per delegation log) involved in the study, including medical staff and research nurses, with opportunity for participants to ask any questions. Following receipt of information about the study, participants will be given reasonable time (a minimum of 24 hours) to decide whether or not they would like to participate. Those wishing to take part will provide written informed consent by signing and dating the study consent form. The principal investigator or another member of site research staff with documented delegated authority will counter-sign and date the consent form. Where the patient is unable to sign his/her name because of problems with literacy, or visual or motor impairments, verbal consent will be taken in the presence of an independent witness who will sign and date the consent form on behalf of the patient. Written informed consent should always be obtained prior to randomisation and prior to study specific procedures/investigations.

The original signed consent form will be retained in the Investigator Site File/Patient study folder, with a copy in the clinical notes and a copy provided to the participant. The participant will specifically consent to their GP being informed of their participation in the study.

The right to refuse to participate without giving reasons will be respected.

At the time of consent, all participants will have mental capacity. Capacity will be formally assessed using the MUSTARDD-PD Assessing Capacity Instrument prior to consent and at visit 5. Consent will also be obtained, however, from an informant (carer or close relative) at study entry. The informant will receive information about the study. This information will include a description of what is expected of them and will also explain their role, should the participant lose mental capacity during the course of the study. A back-up spokesperson and/or a Personal Consultee can be nominated by the participant at the time of entry into the study. A spokesperson/Personal Consultee is free to withdraw from the study at any time. The assistance of a back-up spokesperson should be sought if the original spokesperson withdraws or is no longer able to assist the participant.

Due to the small subject population, the information sheet and consent form for the study will be available only in English. Interpreters will be arranged for all visits of patients who require them either for verbal translation or for deaf subjects wishing to take part in the study, via local NHS arrangements. Qualified interpreters will be used to explain the consent form and information sheet, and great priority will be placed on finding the most direct communication.

12. Study Medication / Intervention Details

12.1 General Information

Donepezil hydrochloride is a centrally acting cholinesterase inhibitor; it is indicated for the symptomatic treatment of mild to moderate Alzheimer's dementia and is therefore being used outwith its Marketing Authorisation in this trial. It increases synaptic levels of the neurotransmitter acetylcholine by inhibiting the enzyme acetylcholinesterase. Given the strong convergent evidence that cognitive and neuropsychiatric symptoms are at least in part mediated by cortical and subcortical cholinergic deficits in PDD, there is therefore a clear rationale for the use of this agent in the context of this trial.

In MUSTARDD-PD 500 people with Parkinson's disease and mild dementia will be randomised to receive either donepezil hydrochloride or matching placebo in a 1:1 ratio. The use of a third arm (*i.e.* a second cholinesterase inhibitor such as rivastigmine, in addition to donepezil hydrochloride and placebo) was discounted since the sample size required to indicate any difference between active treatments would be unfeasibly large, while the clinical impact of any such difference would be likely to be negligible.

Donepezil hydrochloride was chosen, rather than rivastigamine or galantamine, because it is the most commonly prescribed cholinesterase inhibitor in the UK for all dementia syndromes, with 75-80% of the market share. The reasons for this may include ease of titration, once daily dosing and better tolerability, all of which are relevant to this study by potentially improving drug adherence and reducing attrition rate.

Donepezil hydrochloride is widely used in the UK for the treatment of Alzheimer's disease. Even though it is also used throughout the UK to treat PDD, this is an unlicensed indication. For the purposes of this study, donepezil hydrochloride will therefore be treated as an investigational medicinal product (IMP).

For reported side effects of donepezil hydrochloride please refer to section 19 Pharmacovigilance.

Donepezil hydrochloride, purchased by the Sponsor, has a shelf life of 3 years and should be stored below 30°C.

Please refer to the summary of product characteristics (Appendix A1 and 2) for more detail.

Blinding will be achieved by over-encapsulation.

The placebo will be gelatine capsules with microcrystalline cellulose.

12.2 Administration of Study Drug

Study medication will be labelled according to the requirements of Annex 13. All study medication for a particular site will be provided by Piramal to the site pharmacist following site initiation. Study medication will be for use by trial participants only. There will be study-specific prescriptions, and medication will be dispensed by the site pharmacist when the participant attends for their study assessments. Treatment will be taken on an out-patient basis.

Active and placebo study medication will be provided either as 5mg or 10mg capsules. Each participant pack will be presented as bottles in an outer carton.

Weeks 1-26:	5 bottles (5mg) for 5mg or 10 mg dose as directed by team caring for patient. If patient tolerates 5mg dose after 8 weeks then dose to be increased to 2 x 5mg. If between week 9 and week 26 patient does not tolerate increased dose, it can be reduced back to 5mg.
Weeks 26-52:	2 bottles (10mg od)
Weeks 52-78:	2 bottles (10mg od)
Weeks 78-104:	2 bottles (10mg od)

The starting dose will be 5mg/day. All participants will be titrated up to 10mg/day after eight weeks. Side effects will be documented by the participant throughout the course of the trial and will be assessed by the clinical team by telephone contact prior to dose escalation from 5mg to 10mg. Any participant reporting significant side effects on 10mg donepezil hydrochloride/day may have their dose decreased back to 5mg/day, for a further two week period prior to attempting to re-escalate to 10mg/day.

A seven-day visit window is allowed for each 26 weekly dispensing visit. Each visit date should be planned from the date of T0, and not the previous visit.

Study medication will be prescribed by a study clinician according to the protocol, and dispensed to the patient or clinical staff according to local pharmacy policy. Patients in possession of their study medication shall return all trial supplies in their original packaging (even if empty) to the Pharmacist every 26 weeks. All returned, or unused, study medication will be stored in Pharmacy until the end of the study, or until the Trial Manager has completed appropriate reconciliation.

Documentation of prescribing, dispensing and return of study medication shall be maintained for study records.

At the end of the study, MUSTARDD-PD participants will be given the option to start donepezil hydrochloride through normal prescription starting at a dose of 5mg/day, titrated to 10mg/day after eight weeks. Those withdrawing prematurely from the MUSTARDD-PD trial will not be given this option. Donepezil hydrochloride prescribed at the end of the study must be supplied from normal local pharmacy stock. Alternatively, subjects may be given the option of being prescribed rivastigmine, a cholinesterase inhibitor licensed for use in dementia associated with PD.

12.3 Concomitant Medication

For interaction with other therapeutic agents and management of concomitant therapies, please refer to the Donepezil hydrochloride Summary of Product Characteristics (Appendix A1 and 2).

The use of other cholinesterase inhibitor medications will be prohibited throughout the study. The use of the N-methyl-d-aspartate antagonist memantine will also be prohibited at study entry and throughout the study.

Stable doses of atypical anti-psychotic medication (i.e. dose unchanged for 6 weeks prior to study entry) *will* be permitted. The use of these agents during the study *will* also be permitted if, in the opinion of the investigator, they are required to manage psychotic symptoms associated with PDD.

No restrictions will be placed upon the use of anti-parkinsonian drugs (other than non-selective centrally acting anticholinergic drugs (as per exclusion criteria), which are contraindicated in people with PD and cognitive impairment, and which may antagonise the action of cholinesterase inhibitors. These are prohibited at study entry and throughout the study.

A complete listing of all concomitant medication (including over the counter medications) received during the treatment phase must be recorded in the relevant CRF.

Patient will be provided with the study specific drug interaction safety card and a medication card to confirm their daily dose at each stage of the study.

13. Randomisation

A blocked allocation system will be used to allocate patients (on a 1:1 ratio) to the two groups (block size will not be disclosed to the investigators). Randomisation will be stratified by site only.

Randomisation will be administered centrally via Newcastle Clinical Trials Unit using a secure password-protected web-based system.

PRIOR TO RANDOMISATION PLEASE ENSURE YOU HAVE COMPLETED THE INCLUSION/EXCLUSION CRF AND THE RANDOMISATION CRF, thus ensuring that the patient is eligible and has the following scores:

ACE-R ≤ 88
Mattis DRS-2 ≤8 but ≥4
Beck Depression Inventory <13

Contact details for Randomisation: http://apps.ncl.ac.uk/random/

(available 24 hours a day)

Randomisation will generate a 4-digit kit number for each participant that links to the corresponding allocated study drug (blinded), in accordance with block size and strata. The kit number must be clearly documented by the investigator on the trial prescription to ensure that the study pharmacist dispenses the correct study medication.

PATIENTS MUST START THEIR STUDY MEDICATION ON THE SAME DAY AS RANDOMISATION.

14. Blinding

Assignment to either active or placebo arm will be blinded to both the participant and investigator/assessor (double-blind) through the use of matched placebo. The assessor at each visit for the Mattis DRS-2, NPI-10 and BADLS will be independent, and thus blinded not only to the treatment arm, but also to reports of general symptoms, progress and adverse events. The latter, in particular, could potentially influence the assessor as to which treatment the participant may be taking.

Code breaking can be achieved by accessing the secure website, http://apps.ncl.ac.uk/random/ via password access. In addition sealed code-break envelopes will be kept in the Central Pharmacy (The Newcastle upon Tyne Hospitals NHS Foundation Trust) and in the pharmacy at participating hospitals; unblinding should only occur in an emergency and the Chief Investigator immediately informed. If the code is broken, details including the participant number, who broke the code, why and when shall be recorded and maintained in the site file. Code breaks will not be routinely made for participants who complete study treatment. Following a code break, should a clinician wish to supply donepezil hydrochloride on an open label prescription basis, this must then be supplied from normal routine pharmacy stock and not from clinical trial supplies.

At the final visit, the integrity of the blind will be assessed by asking both the participants and their treatment assessor: "Do you think you were taking donepezil hydrochloride or the dummy pill? Why do you think this?" The treatment assessor will be asked to record their answers on a separate CRF, prior to asking the participant to avoid bias.

Following the completion of the study treatment, and data analysis, a patient's treatment can be unblinded and information confirming the treatment made available to patients upon request.

15. Study Data

15.1 Assessments / Data Collection

Each study visit should last approximately 3 to 3.5 hours for assessment of both the participant and carer/informant. The exception to this is Visit 1 where the number of assessments including the recording of background information will make this the longest visit.

Visit 1: Screening (-14 days +/- 2 days, e.g. days 12-16)
The following procedures and assessments will be carried out at the screening visit:

1. Capacity Assessment
2. Informed consent for participant and carer informant
3. Nomination of back-up spokesperson and/or Personal Consultee
4. Checking that the participant fulfils the UK Queen Square Brain Bank Criteria for PD
5. Establishing the nature and temporal sequence of onset of cognitive symptoms in relation to parkinsonism (dementia that develops ≤ 1 year of onset of motor symptoms represents an exclusion criterion as the person would be classified as having Dementia with Lewy Bodies under such circumstances)
6. ACE-R (must score ≤ 88)
7. If screen positive (≤ 88) on ACE-R, Mattis DRS-2 (must have an age- and education-corrected total score of ≤ 8 but ≥ 4, to define "mild" dementia)
8. Beck Depression Inventory: completed by participant. If score ≥ 13 then exclude on the basis of significant depression, which may be a confounder for cognitive assessments.
9. Medical history
    a. such severe motor disability, or participants so impaired in their activities of daily living from other aspects of their PD, as to render it impossible to accurately assess cognitive and neuropsychiatric function and ability to rate BADLS would represent an exclusion criterion
    b. unstable ongoing medical co-morbidity (would represent an exclusion criterion)
    c. neurosurgery for PD (e.g. DBS) within 12 months of the screening visit
10. Drug history
    a. concomitant medications (stable dose of antipsychotic agents *are* permitted providing dose has remained unchanged for previous 6 weeks)
    b. previous exposure to a cholinesterase inhibitor is an exclusion criterion
    c. known sensitivity to donepezil hydrochloride or the excipients of donepezil hydrochloride or placebo are exclusion criteria
    d. current or previous exposure to memantine is an exclusion criterion
    e. current use of a non-selective centrally acting anticholinergic drug for control of motor symptoms is an exclusion criterion
11. Motor sub-section of the new Movement Disorder Society sponsored version of the Unified Parkinson's Disease Rating Scale (UPDRS)
12. ECG (conduction defect or bradycardia deemed to be clinically significant by the investigator would represent an exclusion criterion)
13. Routine haematology (full blood count, vitamin B12) and biochemical (urea and electrolytes, random blood glucose, thyroid function tests and liver function tests). These tests should be analysed in the site's laboratories.

Visit 2: Baseline (t=0)
The following procedures and assessments will be carried out at the baseline visit:

1. Mattis DRS-2
2. NPI-10 (administered to caregiver/informant)
3. BADLS (administered to the caregiver/informant)
4. Modified ADCS-CGIC interview **only**
5. Montreal Cognitive Assessment (MoCA)
6. Parkinson's Disease Cognitive Rating Scale (PD-CRS)
7. Scales for Outcomes of Parkinson's disease-cognition (SCOPA-cog) (administered to the patient)
8. EQ-5D
9. DEMQOL and DEMQOL-proxy (latter administered to the caregiver/informant)
10. Scale of Quality of Life of Caregivers (administered to the caregiver/informant)
11. UPDRS
12. Client Service Receipt Inventory (assessing service use over preceding 6 months) (administered to the caregiver/informant)
13. Activities-specific Balance Confidence Scale (ABC)
14. Provision of falls diaries
15. Check concomitant medications
16. Randomisation via web-based service
17. Dispense study medication along with study drug interaction safety card and medication card
18. Patient commences medication (same day as randomisation)

Note: Assessments 1 – 7 must be carried out by an independent rater (that is, an investigator who is unaware of the outcome of the other assessments to be performed at this visit, such as recording of adverse events, which could potentially un-blind the assessor). The participant should be requested not to discuss possible adverse events or interim problems with this rater prior to their assessments being performed.

Note: Ensure an adequate rest break is provided during the visit along with refreshments for the patient and the spokesperson.

Visit 3: Telephone Call (week 8 ± 5 days)
The purpose of this call is to record any adverse events that may have occurred on the study medication (placebo or donepezil hydrochloride 5mg per day) and check concomitant medications. This call will be made by the Study Nurse. If there are no adverse events that are deemed by the study team to be dose-limiting, then the subject will be requested to increase the dose as prescribed to 10mg per day of donepezil hydrochloride or matching placebo. ***Ensure the patient records an increase in the dose on the study medication card.***

Visit 4: 26 weeks (± 7 days)

The following procedures and assessments will be carried out at this visit:

1. Mattis DRS-2
2. NPI-10 (administered to caregiver/informant)
3. BADLS (administered to caregiver/informant)
4. Modified ADCS-CGIC interview and scoring
5. Montreal Cognitive Assessment (MoCA)
6. Parkinson's Disease Cognitive Rating Scale (PD-CRS)
7. SCales for Outcomes of PArkinson's disease-cognition (SCOPA-cog) (administered to patient)
8. EQ-5D
9. DEMQOL and DEMQOL-proxy (latter administered to caregiver/informant)
10. Scale of Quality of Life of Caregivers (administered to caregiver/informant)
11. UPDRS
12. Client Service Receipt Inventory (assessing service use over preceding 6 months) (administered to caregiver/informant)
13. Activities-Specific Balance Confidence Scale (ABC)
14. Provision falls diaries
15. Review any adverse events
16. Check concomitant medications
17. Check study medication returned
18. Dispense study medication and medication card.

Note: Assessments 1-7 must be carried out by an independent rater (that is, an investigator who is unaware of the outcome of the other assessments to be performed at this visit, such as recording of adverse events, which could potentially un-blind the assessor). The participant should be requested not to discuss possible adverse events or interim problems with this rater prior to their assessments being performed.

Note: Ensure an adequate rest break is provided during the visit along with refreshments for the patient and the spokesperson.

Visit 5: 52 weeks (± 7 days)

The following procedures and assessments will be carried out at this visit:

1. Capacity Assessment
2. Mattis DRS-2
3. NPI-10 (administered to caregiver/informant)
4. Modified ADCS-CGIC interview and scoring
5. Montreal Cognitive Assessment (MoCA)
6. Parkinson's Disease Cognitive Rating Scale (PD-CRS)
7. SCales for Outcomes of PArkinson's disease-cognition (SCOPA-cog) (administered to patient)
8. BADLS (administered to caregiver/informant)
9. EQ-5D
10. DEMQOL and DEMQOL-proxy (latter administered to caregiver/informant)
11. Scale of Quality of Life of Caregivers (administered to caregiver/informant)
12. UPDRS
13. Client Service Receipt Inventory (assessing service use over preceding 6 months) (administered to caregiver/informant)
14. Activities-Specific Balance Confidence Scale (ABC)
15. Provision falls diaries
16. Review any adverse events
17. Haematological and biochemical tests (full blood count, urea and electrolytes, random blood glucose, and liver function tests)
18. Check concomitant medications
19. Check study medication returned
20. Dispense study medication and medication card.

Note: Assessments 2-8 must be carried out by an independent rater (that is, an investigator who is unaware of the outcome of the other assessments to be performed at this visit, such as recording of adverse events, which could potentially un-blind the assessor). The participant should be requested not to discuss possible adverse events or interim problems with this rater prior to their assessments being performed.

Note: Ensure an adequate rest break is provided during the visit along with refreshments for the patient and the spokesperson.

Visit 6: 76 weeks (± 7 days)

The following procedures and assessments will be carried out at this visit:

1. Mattis DRS-2
2. NPI-10 (administered to caregiver/informant)
3. BADLS (administered to caregiver/informant)
4. Modified ADCS-CGIC interview and scoring
5. Montreal Cognitive Assessment (MoCA)
6. Parkinson's Disease Cognitive Rating Scale (PD-CRS)
7. SCales for Outcomes of PArkinson's disease-cognition (SCOPA-cog) (administered to patient)
8. EQ-5D
9. DEMQOL and DEMQOL-proxy (latter administered to caregiver/informant)
10. Scale of Quality of Life of Caregivers (administered to caregiver/informant)
11. UPDRS
12. Client Service Receipt Inventory (assessing service use over preceding 6 months) (administered to caregiver/informant)
13. Activities-Specific Balance Confidence Scale (ABC)
14. Provision falls diaries
15. Review any adverse events
16. Check concomitant medications
17. Check study medication returned
18. Dispense study medication and medication card.

Note: Assessments 1-7 must be carried out by an independent rater (that is, an investigator who is unaware of the outcome of the other assessments to be performed at this visit, such as recording of adverse events, which could potentially un-blind the assessor). The participant should be requested not to discuss possible adverse events or interim problems with this rater prior to their assessments being performed.

Note: Ensure an adequate rest break is provided during the visit along with refreshments for the patient and the spokesperson.

Visit 7: End of study - 104 weeks (± 7 days)

The following procedures and assessments will be carried out at this visit:

1. Mattis DRS-2
2. NPI-10 (administered to caregiver/informant)
3. BADLS (administered to caregiver/informant)
4. Modified ADCS-CGIC interview and scoring
5. Montreal Cognitive Assessment (MoCA)
6. Parkinson's Disease Cognitive Rating Scale (PD-CRS)
7. SCales for Outcomes of PArkinson's disease-cognition (SCOPA-cog) (administered to patient)
8. EQ-5D
9. DEMQOL and DEMQOL-proxy (latter administered to caregiver/informant)
10. Scale of Quality of Life of Caregivers (administered to caregiver/informant)
11. UPDRS
12. Client Service Receipt Inventory (assessing service use over preceding 6 months) (administered to caregiver/informant)
13. Activities-Specific Balance Confidence Scale (ABC)
14. Review any adverse events
15. Haematological and biochemical tests, as outlined above for visit 5
16. Check concomitant medications
17. Check study medication returned.

Note: Assessments 1-7 must be carried out by an independent rater (that is, an investigator who is unaware of the outcome of the other assessments to be performed at this visit, such as recording of adverse events, which could potentially un-blind the assessor). The participant should be requested not to discuss possible adverse events or interim problems with this rater prior to their assessments being performed.

Note: Ensure an adequate rest break is provided during the visit along with refreshments for the patient and the spokesperson.

Note: If a participant withdraws prematurely from the study, the end of study visit procedures and assessments should be attempted at the point of withdrawal.

Visit 8: Telephone Call (week 106 ± 2 days)

The purpose of this call is primarily to record any adverse effects that may have occurred in the two weeks after discontinuation of study medication.

Note: please see section 17.1 with regards to patient compliance and reminder telephone calls.

15.2 Study Schedule

	Visit 1 Screening	Visit 2 Baseline visit			Visit 3 Telephone	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8 Telephone
Time	**-14 days +/- 2 days**	**0**	**0a**	**0b**	**Week 8 +/- 5 days**	**Week 26 +/- 7 days**	**Week 52 +/- 7 days**	**Week 76 +/- 7 days**	**Week 104 +/- 7 days**	**Week 106 +/- 2 days**
Confirm UK Queen Square Brain Bank Criteria met	X									
Review onset of cognitive symptoms (≤1 year onset from motor symptom is an exclusion)	X									
Capacity Assessment	X						X			
Informed consent	X									
Beck Depression Inventory	X									
ACE-R[1]	X									
ECG	X									
Medical History	X									
Haematology & biochemistry[2]	X						X		X	
Mattis DRS-2[3]	X		X			X	X	X	X	
10-item NPI[4]			X			X	X	X	X	
BADLS[5]			X			X	X	X	X	
Quality of life questionnaires[6]			X			X	X	X	X	
CSRI[7]			X			X	X	X	X	
UPDRS[8]	X		X			X	X	X	X	

Modified ADCS-CGIC[9]			X			X	X	X	X	
MoCA			X			X	X	X	X	
PD-CRS			X			X	X	X	X	
SCOPA-cog			X			X	X	X	X	
ABC			X			X	X	X	X	
Provision of falls diary			X			X	X	X		
Randomisation (after all eligibility checked)				X						
Study medication dispensed[10]				X		X	X	X		
Study medication checked						X	X	X	X	
Adverse events					X	X	X	X	X	X
Concomitant medications	X		X		X	X	X	X	X	

1: Addenbrooke's Cognitive Examination; 2: full blood count, vitamin B12 and biochemical (urea and electrolytes, random blood glucose, thyroid function tests and liver function tests); 3 Mattis Dementia Rating Scale; 4: 10-item Neuropsychiatric Inventory; 5: Bristol Activities of Daily Living Scale; 6: comprise EQ5D, DEMQOL, DEMQOL-proxy, and Scale of Quality of Life of Caregivers; 7: Client Service Receipt Inventory; 8: Motor Subsection of the 2008 Movement Disorder Society-sponsored Unified Parkinson's Disease Rating Scale, 9: Baseline CGIC interview only, visits 4, 5, 6 & 8 interview & scoring 10: Patient commences medication

15.3 Data Handling and Record Keeping

Data collection and transfer in this study will comply with NRES and Caldicott guidelines and the Data Protection Act (1998). The quality and retention of study data will be the responsibility of Professor Burn, as Chief Investigator. All study data will be retained in accordance with the latest Directive on GCP (2005/28/EC) and local policy.

All patients will be allocated a unique study identifier, which will be used on all data collection forms and questionnaires to preserve confidentiality; names and addresses will not appear on completed questionnaires or case report forms. Only a limited number of members of the research team will be able to link this identifier to patient-identifiable details (name, date of birth (DOB) and address).

All study documentation will be held in secure offices, which will not be open to the public. All members of the research team with access to identifiable or anonymised data will operate to a signed code of confidentiality. Transmission of hard-copy records (e.g. CRFs, questionnaires) between sites and the NCTU will be by secure fax, post or hand delivery by the research nurses / Trial Manager. Participants will be informed in the patient information sheet about the transfer of information to the NCTU and about levels of access to patient identifiable data, and will be asked to consent to this. Any data used in publications from MUSTARDD-PD will be fully anonymised; it will not be possible to identify individual patients from such publications.

Study data will be entered from source, paper CRFs and questionnaires into a 21 CFR part 11 compatible clinical data management software package for processing and management, allowing a full audit trail of any alterations made to the data post entry. Access to the NCTU study databases will be password protected. All personal information obtained for the study will be held securely at the trial sites and will be treated as strictly confidential. Site numbers, screening and randomisation codes will permit the removal of much personal detail (eg name and address) prior to transfer of data to the trial office in Newcastle.

Long term data storage

At the end of the study, original questionnaires, case report forms and consent forms will be securely archived for 15 years following publication of the last paper or report from the study, in line with Sponsor policy and NCTU standard operating procedures. This will also allow any queries or concerns about the data, conduct or conclusions of the study to be resolved.

Data sharing

Permission for data sharing with third parties at the end of the study will be sought from all participants, the appropriate Research Ethics Committees and Caldicott Guardians. All data to be shared will be anonymised, with a unique study identifier (for patient or carer as appropriate) allowing linkages between multiple records and files. The quantitative data sets will be fully documented both in terms of internal labelling (eg in 'system' files for commonly used statistical packages such as SPSS and STATA) and external description (data dictionary). These data sets will be prepared during the last 4 months of the study. For the first 24 months after the end of the study, the data will only be available to members of the study team (while papers are being prepared for publication). Thereafter, the quantitative data sets will be made available for independent, external usage. Formal application and registration to use the data will be required.

All efforts should be made to collect all study date for each visit. If a patient is unable to attend a study visits, even with the + 7 days window, due to ill health the following two items should be conducted over the telephone with the care-giver/informant:

BADL
NPI-10

16. Statistical Considerations

The primary outcomes, the DRS, NPI-10 and the BADLS, will be assessed at baseline and then at weeks 26, 52, 76 and 104.

16.1 Statistical Analysis

Analysis will be on the basis of intention to treat. The main statistical challenge in analysing such data is to take into account incomplete data which will be due to a number of factors including the occurrence of side effects or the death of individual participants. Although approximately 50% of patients are expected to discontinue medication prematurely during the study, the actual loss to follow up at 104 weeks is expected to be around 20%, yielding 80% of the original group providing data on the primary outcome measures at 104 weeks. It is likely that those participants who are lost to follow up during the trial may also be people with a tendency to experience poorer outcomes (in terms of the DRS scores) than those who remain in the study.

It is necessary to take into account any difference in dropout rates and the non-randomness of the drop out when comparing functional status between the two treatment groups. This will be done by jointly modelling "survival in the study" and the repeated measures of functional status simultaneously [33] using software that has been developed as part of an MRC funded programme of work (Grant G0400615; Statistical methodology for longitudinal studies in clinical research; Williamson PR, Diggle PJ and Henderson R). Time to drop-out will be analysed using a Cox proportion hazards model incorporating random effects. Functional outcomes will be modelled using mixed models appropriate for repeated measures. A key feature of each of these models is that within each it is possible to fit a latent variable that can be conceptualised as the patient's propensity to experience poor outcomes (both their likelihood to drop out of the study and their likelihood to have poor DRS scores). It is the inclusion of this latent variable that allows us to adjust our estimates of the treatment effect to allow for the different rates of drop out in each group. Both models are estimated simultaneously; parameter estimates are based on maximising the joint likelihood over both the survival and repeated measures data.

Within this framework we will estimate the effect of donepezil hydrochloride on our primary outcomes allowing for key baseline covariates including disease severity and possible differences between centres. The NPI-10 and BADLS scores will be analysed using the same method because there may be differential drop-out in the two treatment groups and, in addition, we cannot assume that the propensity of the subject to drop out of the study will not be correlated with the propensity of the carer to experience poor outcomes. Secondary outcomes in the form of repeated measures will be analysed using the same procedures.

No interim analysis is planned unless specifically requested by the Trial Steering Committee.

16.2 Sample Size Calculation

Although not rigorously defined, a difference of 5-6 points in DRS-2 has previously been considered to be "clinically significant" [34] and 2 points on the NPI-10 as "significant" [12]. We believe the latter is likely to be of dubious *clinical* significance to the patient and carer, however, and have thus adopted a difference of 3-4 points for the sample size calculation. From previous longer term dementia trials in AD, we anticipate that 50% of the study participants may discontinue medication during the trial. We hope however to retain 80% (i.e. lose only 20%), by encouraging those subjects who withdraw prematurely from medication to adhere to the follow-up schedule for ongoing assessments.

Assuming a loss to follow-up rate at 24 months of 20% we will recruit a total of 500 patients (two groups of 250) to the trial in order to ensure complete data on 400 patients (two groups of 200). This final sample size will give us 90% power to detect a difference between groups of 4.4 in the mean DRS score and 3.9 in mean NPI-10 score. The calculation assumes a two tailed hypothesis test, a type 1 error rate of 5% and that the standard deviations of the DRS and NPI-10 scores are 13.5 and 12.0 respectively, yielding effect sizes of 0.325 in each case.

An effect size of 0.325 on the BADLS will correspond to a difference in mean scores of around 3.2. Although the range of scores possible is 0-60, the spread of values found is usually narrower than this. The BADLS has good sensitivity and specificity in differentiating change in dementia, with cut-off for improvement having previously been determined to be < -3 points, and for decline of > 1. The sample size will therefore provide us with adequate power to detect clinically significant differences in these primary outcome measures.

16.3 Health Economics Analysis

Data on health and social service utilisation patterns, medication, and (unpaid) carer inputs will be collected and calculated for each participant, based on data collected using a modified version of the CSRI. This instrument has been tailored recently for use in a number of studies of older people with dementia, and will be adjusted as needed for this study. Questions will ask about care and support over the period since previous interview. Unit costs will be attached using national figures taken from the Quality-Adjusted Life Year (PSSRU) annual compendium, where available, and from individual service providers as necessary (particularly for individual hospitals and care homes, given the inherent unit cost variation between settings).

Costs will be combined with each of the primary measures in turn and with Quality-Adjusted Life Year (QALY) gains, allowing for a parallel series of cost-effectiveness analyses. We will analyse changes in cognitive function in Parkinson's disease for patients administered donepezil hydrochloride and placebo over 104 weeks using the DRS-2, and then calculate the difference in effectiveness. We will measure costs over the same period, covering all health and social care services used, medication and unpaid carer time. An incremental cost-effectiveness ratio will be computed, and a cost-effectiveness acceptability curve will be plotted, generated from the net benefit approach and using bootstrap regression for a range of values of willingness to pay for incremental improvements in cognitive function on the DRS-2. The difference in, first, Behavioural and Psychological Symptoms of Dementia (BPSD) for patients allocated to both groups over the study period using the NPI will then be assessed,

and then the difference in activities of daily living using the BADLS will be assessed. Again, incremental cost-effectiveness ratios and acceptability curves will be used as needed.

A secondary economic evaluation will examine QALY gains for people with dementia. The QALY gains will be computed based on both the EQ5D and DEMQOL. Again, an incremental cost-effectiveness ratio and acceptability curve will be used as needed. The incremental values for QALY gains for these analyses can be guided by, for example, the implicit NICE threshold.

Each cost-effectiveness analysis will be conducted from the perspective of (a) the NHS and social services, and (b) society as a whole. The main difference will be the exclusion of the costs of unpaid care and any out-of-pocket payments by carers. Payments by patients/users or families for services will need to be measured; whether or not they are treated as health and social care system costs is dependent on a number of things, including future policy as to the funding of long-term care. The study will assess the sensitivity of findings to different assumptions regarding key assumptions made in the analyses.

16.4 Cognitive Scales Performance Analysis

Prior to study completion of the last enrolled patient, all analyses comparing cognitive assessment instruments will be based on blinded study data (*i.e.* donepezil- and placebo-treated patients combined). These interim analyses comparing the different neurocognitive instruments will use the CGIC score as the primary outcome measure for clinical improvement. Once the last enrolled participant has completed the study, additional analyses will examine ability of the various neurocognitive instruments to specifically detect cholinesterase inhibitor treatment effects (*i.e.* donepezil hydrochloride versus placebo assignment) on cognition.

Analysis of the outcome variables can best be understood as slopes of scale score change over the length of the study. These slopes may be affected by many covariates, including treatment assignment, initial score on the outcome variables, some demographic/disease features and perhaps site of enrolment. The basic analytic approach will utilize a mixed model in which changes in the outcome measures over time will include a fixed effect of treatment group assignment and random effects of intercepts (the scale scores at baseline) that will be included to have both random variation (person-specific) and specific variation associated with rate of change in outcome. Adjustments for possible confounding covariates (demographics; site, etc) will be included.

Data exploration, graphical representations and analysis of residuals will be used to assess the potential impact of problems such as correlations of the various scale scores within a given subject, and to potentially inform decisions of appropriate transformations, if required. To assess the "best" scale for assessing change in cognition, both linear modelling of each scale's effect size (determined from the mixed model analysis of change over time by treatment), and analysis of sensitivity/specificity of different cut-off scores by receiver-operator characteristic analyses (ROC) will be employed.

17. Compliance and Withdrawal

17.1 Subject Compliance

Participants will be telephoned to remind them of a forthcoming visit and to ask them to bring with them their used and unused study medication. Windows of +/- 7 days on follow-up visits should ensure visit attendance; non-attendance for study visits will prompt follow-up by telephone.

Compliance with study medication will be assessed by checking and recording the remaining number of capsules after each visit. Study drug accountability will be assessed and documented by the local pharmacy. The clinical team will also perform a quick review of any returned study medication at each study visit to identify any obvious compliance concerns and address these immediately with the participant.

17.2 Withdrawal of Participants

The study drug must be discontinued if:

- the participant decides they no longer wish to continue
- recommended by the investigator
- the participant loses mental capacity during the study and, in the opinion of the carer/informant would be distressed by the prospect of continuing in the study

Participants have the right to withdraw from the study at any time for any reason (and without stating a reason for withdrawal). The investigator also has the right to withdraw patients from the study drug in the event of inter-current illness, AEs, SAEs, SUSARs, protocol violations, cure, administrative reasons or other reasons.

It is understood by all concerned that an excessive withdrawal rate could render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided. Should a patient decide to withdraw from the study, all efforts will be made to report the reason for withdrawal as thoroughly as possible and to conduct an 'end of study' follow-up assessment. Should a patient wish to withdraw from study drug, or be withdrawn from treatment, efforts will be made to continue to obtain follow-up data in line with the study protocol, with the permission of the patient. This is essential for the statistical analysis (intention to treat) and will be made clear in the patient information sheet at the time of initial consent.

Participants who wish to withdraw from study medication will be asked to confirm whether they are still willing to provide the study specific data at the remaining scheduled visits.

If participants agree to any of the above, they will be asked to complete a confirmation of withdrawal form to document their decision.

18. Data Monitoring, Quality Control and Quality Assurance

18.1 Discontinuation Rules

The trial may be prematurely discontinued on the basis of new safety information, or for other reasons given by the Data Monitoring and Ethics Committee / Trial Steering Committee, sponsor, regulatory authority or ethics committee concerned.

Following 12 months of recruitment, initial rates of recruitment will be used to project total recruitment to ensure sufficient participants to power the trial. The Trial Steering Committee (TSC) will advise on whether to continue or discontinue the study and make a recommendation to the sponsor and funder. If the study is prematurely discontinued, active participants will be informed and no further participant data will be collected.

18.2 Monitoring, Quality Control and Assurance

The trial will be managed through the Chief Investigator, Professor Burn and the Newcastle Clinical Trials Unit (NCTU). The MUSTARDD-PD Trial Management Group (TMG) will include: Professor Burn, together with the Trial Manager (Senior Manager and Manager dedicated to study), the Trial Statistician, Data Manager, Project Secretary and a representative from the DeNDRoN UK coordinating centre. *Ad hoc* members will comprise representatives of the Sponsor Organisation's R&D Department, University Finance (Grants and Contracts) and the Institute of Ageing and Health, Newcastle University.

The Principal Investigators will be responsible for the day-to-day study conduct at each site.

NCTU, primarily through the MUSTARDD-PD Trials Manager, will provide day-to-day support for the sites and provide training via Investigator meetings, site initiation visits/teleconferences and routine monitoring visits.

Quality control will be maintained through adherence to NCTU-wide SOPs, MUSTARDD-PD study-specific SOPs, the study protocol, the principles of GCP, research governance regulations and clinical trial regulations.

An independent Data Monitoring and Ethics Committee (DMEC) will monitor efficacy and safety endpoints. Only the DMEC will have access to un-blinded study data. The committee will convene on a 6-monthly basis. Other than the initial meeting, these meetings may be held by teleconference. At the first meeting, the DMEC will discuss and advise on the inclusion of an interim analysis and possible adoption of a formal stopping rule for efficacy or safety. The membership of the MUSTARDD-PD DMEC is listed in Appendix K. The DMEC will agree its terms of reference and mode of operation at its first meeting, drawing on the DAMOCLES charter.

A Trial Steering Committee (TSC) will provide overall supervision of the trial. The membership of the TSC is listed in Appendix L. The committee will meet every 6 months for the duration of the trial. The TSC will agree its terms of reference and mode of operation at the first meeting.

Monitoring of study conduct and data collected will be performed by a combination of central review and site monitoring visits to ensure that the study is conducted in accordance with GCP. Study site monitoring will be undertaken by the trial manager. The main areas of focus will include consent, serious adverse events, recording of primary outcome measures, essential documents in study files, and drug accountability and management.

Site monitoring will be determined following a full risk assessment of the study and production of the study Monitoring Plan. It is anticipated that this will include:

- All original consent forms, reviewed as part of the study file.
- The presence of a copy of the consent form in the patient hospital notes. This will be confirmed for a selected number of patients as determined by the study risk assessment and Monitoring Plan.
- All original consent forms, compared against the study Participant Identification List and the Study Personnel Delegation Log.
- All reported serious adverse events, verified against treatment notes/medical records (source data verification).
- A check of the presence of all essential documents in the study file.
- Source data verification of primary endpoint data and eligibility data will be undertaken for a random sample of participants entered in the study. The numbers will be determined by the study risk assessment and Monitoring Plan.
- Drug accountability and management checked at site level.

Central monitoring will include:

- All applications for study authorisations or submissions of progress/safety reports will be reviewed for accuracy and completeness, prior to submission.
- All documentation essential for study initiation reviewed prior to site authorisation.
- Statistical monitoring of data, including outliers and inconsistencies.

All monitoring findings will be reported and followed up with the appropriate persons in a timely manner.

The study may be subject to inspection and audit by The Newcastle upon Tyne Hospitals NHS Foundation Trust under their remit as sponsor, and other regulatory bodies (eg MHRA) to ensure adherence to GCP. The investigator(s) / institutions will permit trial-related monitoring, audits, REC review and regulatory inspection(s), providing direct access to source data/documents.

19. Pharmacovigilance

19.1 Definitions

Adverse event (AE): Any untoward medical occurrence which does not necessarily have a causal relationship with the treatment. "Treatment" includes all investigational agents (including comparative agents) administered during the course of the study. Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment.

Adverse Reaction (AR): Any untoward or unintended responses to an Investigational Medicinal Product (IMP) related to any dose administered - All AEs judged by either the reporting investigator or the sponsor as having reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression "reasonable causal relationship" means to convey in general that there is evidence or argument to suggest a causal relationship.

Causality:
The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in the table below. All adverse events judged as having a reasonable suspected causal relationship to the IMP(s) (i.e. definitely, probably or possibly related) are considered to be adverse reactions. If any doubt about the causality exists, the local Principal Investigator should inform the Chief Investigator. In the case of discrepant views on causality between the Principal Investigator and others, all parties will discuss the case. In the event that no agreement is made, the MHRA, main REC and other bodies will be informed of both points of view.

Relationship	***Description***
Unrelated	*There is no evidence of any causal relationship*
Unlikely	*There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).*
Possible	*There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).*
Probable	*There is evidence to suggest a causal relationship and the influence of other factors is unlikely.*
Definitely	*There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.*
Not assessable	*There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.*

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR): any untoward medical occurrence or effect that, at any dose:

- Results in death
- Is life-threatening – refers to an event in which the subject was at risk of death at the time of the event; does not refer to an event which hypothetically might have caused death if it were more severe
- Requires hospitalisation, or prolongation of existing inpatients' hospitalisation
- Results in persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect.

Medical judgement should be exercised in deciding whether an AE/AR is serious in other situations. Important AE/ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

Suspected, Unexpected Serious Adverse Reaction (SUSAR): an adverse reaction that is both unexpected and serious. An adverse reaction is 'unexpected' if its nature or severity is not consistent with the applicable product information (see Appendix A1 and 2).

Severity (intensity) of Adverse Events and Adverse Reactions
Severity of all AEs and ARs will be graded on a three-point scale of intensity (mild, moderate, severe):

Mild: Discomfort is noticed, but there is no disruption of normal daily activities.
Moderate: Discomfort is sufficient to reduce or affect normal daily activities.
Severe: Discomfort is incapacitating, with inability to work or to perform normal daily activities.

An AE or AR may be severe but not serious.

19.2 Expected Adverse Reactions

Most adverse events and adverse drug reactions that occur in this study, whether they are serious or not, will be expected treatment-related toxicities due to the drugs used in this study. These include diarrhoea, muscle cramps, tiredness, sleeplessness and nausea. These problems can occur in up to 10% of people but are usually mild in nature. For a full list of expected undesirable effects of donepezil hydrochloride, please refer to the Summary of Product Characteristics (Appendix A1 and 2).

19.3 Protocol Specifications

For purposes of this protocol

- All non-serious adverse reactions will be recorded at visits 3-7.
- Any serious adverse events will be recorded throughout the duration of the trial until 2 weeks after the trial medication is stopped.
- Serious adverse events exclude any pre-planned hospitalisations not associated with clinical deterioration.
- Serious adverse events exclude routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
- Serious adverse events exclude elective or scheduled treatment for pre-existing conditions that did not worsen during the study.

19.4 Recording and Reporting Serious Adverse Events or Reactions:

All adverse events should be reported. Depending on the nature of the event, the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator or MUSTARDD-PD Trial Manager in the first instance. Figure 1 summarises the reporting procedures.

Adverse Event (including Adverse Reaction): All non-serious adverse events / reactions during drug treatment will be reported on the study CRF and sent to Newcastle Clinical Trials Unit within 2 weeks of the form being due. Severity of AEs will be graded on a three-point scale (mild, moderate, or severe – see above). Relation of the AE to the treatment should be assessed by the investigator at site. The individual investigator at each site will be responsible for managing all adverse events / reactions according to local protocols as the study drug is licensed for use in other indications.

Serious Adverse Event / Reaction (SAE/SAR, including SUSARs): All SAEs, SARs and SUSARs during drug treatment will be reported to the Chief Investigator within 24 hours of learning of their occurrence. The initial report can be made by telephone, fax or e-mail. In the case of incomplete information at the time of initial reporting, all appropriate information should be provided as follow-up as soon as this becomes available. Relationship of the SAE to the treatment should be assessed by the investigator at site, as should the expected or unexpected nature of any serious adverse reactions.

The MHRA and main REC will be notified of all SUSARs occurring during the study according to the following timelines; fatal and life-threatening within 7 days of notification and non-life threatening within 15 days. All investigators will be informed of all SUSARs occurring throughout the study on a case-by-case basis.

The Chief Investigator will ensure that the Newcastle upon Tyne Hospitals NHS Foundation Trust is notified of any SUSARs in accordance with local Trust policy.

Local investigators should report any SUSARs and / or SAEs as required by their Local Research Ethics Committee and/or Research & Development Office.

19.5 Pregnancy

19.5.1 Time period for collecting pregnancy information

All pregnancies in female subjects will be reported after the start of dosing and until last follow up visit.

19.5.2 Action to be taken if pregnancy occurs

The investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study. The investigator will record pregnancy information on the appropriate form and submit it to the Chief Investigator within 2 weeks of learning of a subject's pregnancy. The subject will also be followed-up to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Chief Investigator. Generally, follow-up will be no longer than 8-12 weeks after the estimated delivery date.

Any premature termination of the pregnancy will be reported. While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE (see AE/SAE section of the protocol and the SPM for definitions and a description of follow-up). A spontaneous abortion is always considered to be an SAE and will be reported as such.

Furthermore, any SAE occurring as a result of a post-study pregnancy, and considered reasonably related to the investigational product by the investigator, will be reported to the Chief Investigator. While the investigator is not obligated actively to seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating will be withdrawn from the study.

Any female who becomes pregnant during dosing will stop dosing immediately.

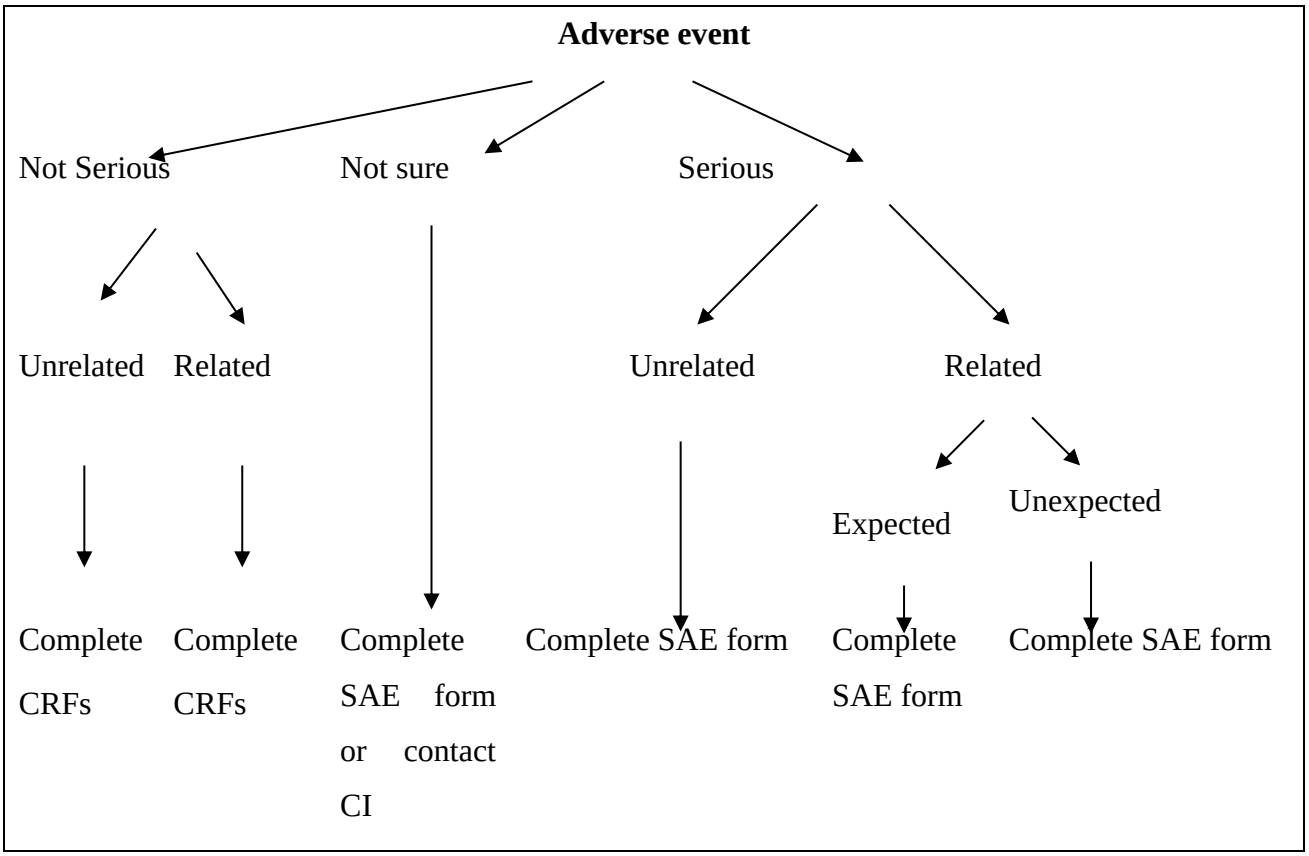

Figure 1

Contact details for reporting SAEs and SUSARs
Please send SAE form(s) via Fax: 0191 580 0450
or
Telephone: 0191 208 5364

20. Ethics and Regulatory Issues

The conduct of this study will be in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964, and later revisions including the 2008 revision (Appendix C).

Favourable ethical opinion from a Type 3 Research Ethics Committee and Clinical Trial Authorisation from the Medicines and Healthcare Products Regulatory Agency will be sought prior to commencement of the study via the IRAS system; R&D approval will be sought via the Coordinated System for gaining NHS Permissions, or in line with The Newcastle Clinical Trials Unit will require a written copy of local approval documentation before each centre and is initiated and participants are accepted into the study.

Information sheets will be provided to all eligible subjects and written informed consent obtained, prior to any study procedures, by study personnel recorded on the Delegation Log for that site.

21. Confidentiality

Personal data will be regarded as strictly confidential. To preserve anonymity, any data leaving the site will identify participants by their initials, DOB and a unique study identification code only. The study will comply with the Data Protection Act, 1998, and appropriate permissions will be sought and obtained from the Caldicott Guardian at each site. All study records and Investigator Site Files will be kept at site in a locked filing cabinet with restricted access.

22. Insurance and Finance

This is a non-commercial trial and as such is mandated to have indemnity in respect of non-negligent harm only; there is no provision for indemnity in respect of liabilities arising from non-negligent harm. Indemnity in respect of the management of the study will be provided through The Newcastle upon Tyne Hospitals NHS Foundation Trust, acting as sponsor of this study. The participating NHS Trusts have liability for clinical negligence that harms individuals toward whom they have a duty of care, and this will provide indemnity in respect of negligent harm arising in the conduct of the study. NHS Indemnity covers NHS staff and academic staff with honorary contracts conducting the trial. Indemnity in respect of liabilities arising from negligence in study design and protocol authorship will be provided by University insurance policies in respect of protocol authors whose substantive contract of employment is with a University and via NHS schemes for protocol authors whose substantive contract of employment is with the NHS.

The NIHR Health Technology Assessment Programme is funding the study. The Michael J Fox Foundation has funded the comparison of cognitive scales component of this study.

Neither investigators nor participants are receiving personal payments for involvement in this study. Study participants will receive reimbursement for travel costs incurred for participating and offered refreshments during each study visit.

23. Study Report / Publications

The data will be the property of the HTA Applicants. Publication will be the responsibility of the Chief Investigator and published under the authorship agreed with the Co-Applicants and Collaborators (i.e. non co-applicant site PIs) who have entered patients into the study. A written publication policy, to include details of assignment of authorship, will be developed and agreed at the beginning of the study.

In addition to the final report monograph to be submitted to HTA it is planned to publish this study in high impact peer reviewed articles and to present data at national and international meetings. Results of the study will also be reported to the Sponsor and Funder, and will be available on the HTA web site. All manuscripts, abstracts and other modes of presentation will be reviewed by the Trial Steering Committee and HTA, in accordance with their contractual stipulation, prior to submission. Individual participants will not be identified in any study report.

In line with NIHR policy, electronic copies of any research papers that have been accepted for publication in a peer-reviewed journal (or final reports and / or executive summaries) will be deposited at the earliest opportunity – and in any case within six months - in UK PubMed Central (http://ukpmc.ac.uk/).

Any output (e.g. paper, abstract, poster) resulting from the MUSTARDD-PD study that includes any or all of the Scales Assessment-specific data (*i.e.* any use of data involving the additional instruments incorporated purely to facilitate the Scales Assessment Study, SAS) will include all members of the relevant Advisory Group (AG) as authors. The authorship order will be decided by the SAS-AG for each output depending upon the intellectual input, drafting of the manuscript and other related factors.

Any output resulting from the MUSTARDD-PD study that includes any or all of the SAS-specific data (*i.e.* any use of data involving the additional instruments incorporated purely to facilitate the SAS) will acknowledge the Michael J Fox Foundation as a funding source.

Participants will be informed about their treatment and their contribution to the study at the end of the study, including a summary of the results.

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