Full Title:

Improving the diagnosis and management of neurodegenerative dementia of Lewy body type in the NHS.

Work Package 5A and 5B: A pilot cluster randomised study of the management toolkit in the NHS secondary care services.

Short Title/Acronym:

DIAMOND LEWY: A pilot study of care provided by NHS services.

Protocol Version & Date

5.0, 07/06/2018

Statement:

This protocol has regard for the HRA guidance.

RESEARCH REFERENCE NUMBERS

IRAS Number: 197104

RESEARCH SPONSOR

Sponsor Name: Northumberland Tyne and Wear NHS Foundation Trust

RESEARCH FUNDER

Funder Name: National Institute for Health Research (NIHR) Programme Grant

Funder Reference: DTC-RP-PG-0311-12001

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted. The Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the Research Governance Framework, Good Clinical Practice (GCP) guidelines, the relevant Standard Operating Procedures and other regulatory requirements as applicable.

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

Representative of the Research Sponsor

Name: **Mr Simon Douglas**

(print)

Position: Senior Manager for Research Innovation and Clinical Effectiveness

Signature: **Date:** **05.07.2018**

Chief Investigator

Name: **Professor John O'Brien**

(print)

Signature: **Date:** **07.06.2018**

Statistician

Name: **Dr Richard McNally**

(print)

Position: **Trial Statistician**

Signature: **Date:** **06.07.2018**

Economist

Name: **Professor Luke Vale**

(print) Luke Vale

Position: **Lead Economist**

Signature: [signature] **Date:** 1st July 2018

KEY TRIAL CONTACTS

Chief Investigator	Professor John O'Brien Foundation Professor of Old Age Psychiatry University of Cambridge, Addenbrooke's Hospital John.obrien@medschl.cam.ac.uk
Project Manager	Mrs Sarah Greenhalgh Research Project Manager Newcastle Clinical Trials Unit, Newcastle University sarah.greenhalgh@newcastle.ac.uk
Trial Manager	Miss Sarah Dunn Trial Manager Newcastle Clinical Trials Unit, Newcastle University Sarah.dunn2@newcastle.ac.uk
Sponsor	Northumberland Tyne and Wear NHS Foundation Trust Mr Simon Douglas Research Innovation and Clinical Effectiveness Department

Simon.douglas@ntw.nhs.uk

Funder(s)	National Institute for Health Research Programme Grant
Collaborators/Co-Investigators	Professor David Burn Professor of Movement Disorder Neurology, Newcastle University David.burn@newcastle.ac.uk Professor Alan Thomas Professor of Old Age Psychiatry, Newcastle University and Honorary Consultant at Gateshead Health NHS Foundation Trust A.j.thomas@newcastle.ac.uk Dr John-Paul Taylor Senior Clinical Lecturer, Newcastle University John-paul.taylor@newcastle.ac.uk Professor Ian McKeith Professor of Old Age Psychiatry, Newcastle University Ian.mckeith@newcastle.ac.uk Mr Tim Docking Group Director for Planned Care, Northumberland Tyne and Wear NHS Foundation Trust Tim.docking@ntw.nhs.uk Dr Richard McNally

Trial Statistician, Newcastle University

Richard.mcnally@newcastle.ac.uk

Mr Derek Forster

Lay Member and Consumer Representative

Derekf2@gmail.com

Dr Louise Allan

Clinical Senior Lecturer and Consultant in Geriatric Medicine, Newcastle University

Louise.allan@newcastle.ac.uk

Ms Claire Bamford

Senior Research Associate, Newcastle University

Claire.bamford@newcastle.ac.uk

Dr Tracy Finch

Senior Lecturer, Newcastle University

Tracy.finch@newcastle.ac.uk

Professor James Mason

Professor of Health Economics, University of Warwick

J.mason@warwick.ac.uk

Professor Luke Vale

Health Foundation Chair in Health Economics, Newcastle University

Luke.vale@newcastle.ac.uk

TRIAL SUMMARY

Trial Title	**Work Package 5A and 5B** A pilot cluster randomised study of the management toolkit in NHS secondary care services.
Acronym	DIAMOND-Lewy Work Package 5
Summary of Trial Design	Pilot, cluster randomised controlled trial (cRCT)
Summary of Participant Population	A: Patients referred for assessment and diagnosis of memory problems to dementia/memory assessment services, aged 60 and over and their carers B: Patients aged 60 and over, diagnosed with Parkinson's disease and their carers.
Planned Sample Size	A: 60 patients entered into the cRCT & their carers B: 60 patients entered into the cRCT & their carers Total Sample size: 240 participants (patients + carers)
Planned Number of Sites	8 services A: Memory assessment services (Dementia with Lewy Bodies) B: Neurology and geriatric services (Parkinson's Disease Dementia)
Intervention	Management Toolkit for neurodegenerative dementia of Lewy body type
Follow Up Duration	6 months
Planned Trial Period	3 years
Main Objectives	• Determine feasibility of use of the intervention • Assess the impact of the assessment and management toolkit on patient management, health outcomes, and its impact on informants/carers • Provide an exploratory comparison of the cost-effectiveness of the new assessment and management toolkit for LBD with usual care

Contents

GLOSSARY OF ABREVIATIONS

ABBREVIATION	DEFINITION
AD	Alzheimer's Disease

CI	Chief Investigator
cRCT	Cluster Randomised Clinical Trial
CRF	Case Report Form
CSRI	Client Service Receipt Inventory
DLB	Dementia with Lewy Bodies
GCP	Good Clinical Practice
HRA	Health Research Authority
HTA	Human Tissue Authority
HTAct	Human Tissue Act
ICF	Informed Consent Form
ICER	Incremental Cost-Effectiveness Ratio
IRMER	Ionising Radiation (Medical Exposure) Regulations
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
LBD	Lewy Body Dementia
NCTU	Newcastle Clinical Trials Unit
NHS	National Health Service
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
QA	Quality Assurance
QALYs	Quality Adjusted Life Years
QC	Quality Control
QoL	Quality of Life
PDD	Parkinson's Disease Dementia
R&D	Research & Development
RCT	Randomised Control Trial

REC	Research Ethics Committee
RUD	Resource Utilisation in Dementia instrument
WP	Work Package

1. BACKGROUND

The accurate recognition of dementia, the diagnosis of subtypes of dementia and ensuring appropriate management are central to improving the care of patients with dementia. There is evidence that accurate diagnosis reduces levels of depression and anxiety, and improves quality of life (QoL), both of people receiving a diagnosis and their carers/informants.

Dementia with Lewy Bodies (DLB) is a type of dementia that shares symptoms with both Alzheimer's disease (AD) and Parkinson's disease (PD). DLB is the second most common cause of dementia in older people after AD. **Parkinson's Disease Dementia (PDD)** occurs when a patient with Parkinson's disease develops progressive dementia. Longitudinal studies show that PDD develops in up to 80% of people with Parkinson's.

PDD and DLB together are known as **Lewy Body Dementia (LBD)** as they share common clinical features, have closely overlapping neurobiology and respond to similar approaches to management. Lewy bodies are small deposits of protein found in nerve cells. Their presence is linked to a loss of connection between nerve cells, and over time there is a progressive death of nerve cells and loss of brain tissue. The loss of these cells causes dementia, but it is not yet understood why or how Lewy bodies occur in the brain. LBD accounts for 15-20% of all dementia cases, affecting between 160,000 and 200,000 people in the UK. It is expected that this prevalence will approximately double over the next 30 years, and therefore, LBD represents an important disease affecting a growing proportion of the population.

Currently, even in specialist hospital services, there is evidence of under recognition and inappropriate management of people affected by LBD. This is because the signs and symptoms of LBD, such as visual hallucinations, variability in memory and changes in sleep are very hard to detect. Improved diagnosis of LBD may be facilitated by the introduction of an assessment tool into routine practice which systematically explores these symptoms. Inappropriate management, when LBD is not recognised, could include use of antipsychotic agents which can have serious adverse reactions in LDB subjects, and the failure to recognise and manage distressing symptoms such as sleep disorder and autonomic features.

2. RATIONALE

2.1 The need to improve the recognition and management of DLB

Current evidence indicates that only around 1 in 3 cases of DLB are currently detected, with the other 2 either not detected or misdiagnosed (usually with Alzheimer's disease). The Galvin study (J.E Galvin et al 2010) showed almost 80% of DLB cases were initially given a non DLB diagnosis, with half receiving more than 10 clinic visits before the correct diagnosis was made. For those patients recognised as having DLB, the management care pathways are poorly developed in comparison with AD.

Some of the key reasons for the difficulties in recognising, diagnosing and appropriately managing patients with DLB include:

1) A lack of assessment of key clinical symptoms such as visual hallucinations, slowness of movement and sleep disorder in dementia assessment services.
2) A lack of knowledge among clinicians regarding the management of DLB in comparison to the other two main and better established causes of dementia; AD and vascular dementia.
3) Delays in translating recent advances in DLB management into NHS care.

There is a particular danger that patients who have not been diagnosed with DLB could be prescribed antipsychotics due to their high prevalence of psychotic symptoms. Prescriptions of these are contra-indicated in DLB because of potential catastrophic sensitivity to these drugs and increased mortality. This highlights the importance of disease specific information and management.

2.2 The need to improve the recognition and management of PDD

Patients with PD are often reviewed regularly in neurology or geriatric medicine services, but there are still problems in recognising and diagnosing PDD. Only around 1 in 3 of those with PDD are currently recognised and diagnosed, and this often occurs late in the disease.

Some of the key reasons for the difficulties in recognising, diagnosing and appropriately managing patients with PDD include:

1) Cognitive impairment develops insidiously and at a variable time after PD diagnosis.
2) Initial symptoms such as fluctuation, attentional problems and visual hallucinations may be thought to be related to medication side effects.

2.3 The need to improve the recognition and management of LBD (DLB and PDD)

When dementia is recognised there are effective pharmacological and non-pharmacological strategies for cognitive symptoms, psychosis, sleep disturbance and other psychiatric problems. The recognition of dementia allows the provision of support, education and advice, access to services, financial and other benefits and opportunities for future planning and attending to medico-legal issues. This improves long term outcome in terms of reducing carer stress and delaying the need for care.

There is a clear need to improve the assessment, diagnosis and management of LBD both in memory/dementia services and movement disorder services. There is currently no single, simple tool which incorporates the range of clinical symptoms for LBD, and there is no unified evidence based management care pathway. This study is looking to develop a management toolkit for routine use in patients with DLB and PDD in NHS services.

2.1. Work Packages

This overall work programme is aiming to improve the NHS care of people with dementia by increasing detection and optimising management of LBD in routine secondary care services. In order to achieve this there are a total of 5 related work packages. Although this protocol refers to Work Package 5, the other four work packages are also briefly outlined below.

Work Package 1 (WP1): This was a baseline study of current Lewy Body Dementia (LBD) diagnosis and management in memory, neurological and medical services. The proportion of cases diagnosed with DLB and PDD and their management pathways were compared to non-DLB dementia cases and PD cases without dementia, respectively.

Work Package 2 (WP2): This was a series of qualitative studies to explore and understand perceived barriers and facilitators to introducing an assessment tool and management toolkit into routine NHS practice. It examined current practice through observing clinic consultations, and conducting interviews with professionals, patients and carers.

Work Package 3 (WP3): This study involved developing an evidence based management toolkit to guide clinicians in the management of LBD. A systematic review of existing evidence was conducted and guided using a Delphi panel approach of a group of expert clinicians and PPI members.

Work Package 4 (WP4): This study brought together previously validated assessment methods into a simple LBD assessment tool suitable to use in the NHS. The assessment tool and previously developed

management toolkit were piloted in Gateshead NHS Trust. Modifications to the tools were made following feedback from staff, patients and carers.

Work Package 5 (WP5): This study involves introducing the management toolkit into routine NHS care in a minimum of 8 different services. A pilot cluster randomised controlled trial (cRCT) will be conducted to test the management toolkit. WP5A will focus on DLB and will run in memory assessment services. WP5B will focus on PDD and will run in movement disorder (neurology and geriatric) services. **This is the focus of this protocol.**

2.2. Risk Assessment

Low risk to patients: Participating services will be randomised to use either the management toolkit or usual management care. The management toolkit provides recommended guidelines to be used by clinicians as part of their clinical patient management. The toolkit does not recommend any treatments or assessments that are not already used in the NHS.

3. AIMS, OBJECTIVES AND OUTCOME MEASURES

3.1. Aims and Objectives

The overall aim of the programme is firstly to improve the recognition and prompt diagnosis of LBD in routine NHS secondary services using a simple clinical tool for assessment of key symptoms. Secondly, for clinicians to improve patient management after diagnosis using an evidence based management toolkit.

Work package 5 will conduct a pilot cluster randomised controlled trial (cRCT) to test the management toolkit. It will look to:

- Determine feasibility of use of the intervention
- Assess the impact of the management toolkit on patient management, health outcomes and impact on carers/informants
- Provide an exploratory comparison of the cost-effectiveness of the new assessment and management toolkit for LBD with usual care

The cRCT will provide data on impact on patient symptoms, outcomes, quality of life and informant/carer stress (quality of life). It will provide data on rates of consent and drop out, as well as suitability of the outcome measures. It will also provide data on the use of the management toolkit by clinicians.

An exploratory health economic analysis will be conducted using data collected from WP1 and WP5 to estimate the overall cost effectiveness of implementing the new management toolkit in the NHS compared to usual care, as well as economic impact on the NHS, personal social services, informal carers and relatives.

Hypothesis:

We hypothesise that DLB and for PDD subjects treated in services randomised to implementing the management toolkit will result in symptom improvement, increased quality of life and decreased carer stress at 6 months compared to baseline.

3.2. Outcome Measures

Outcome measures:

- Symptom measurement (reduced Neuropsychiatric Inventory (NPI) score; lower unified Parkinson's disease rating scale score; lower Cornell depression score, Geriatric Depression Scale)
- Patient quality of life (patient EQ-5D-5L and carer proxy EQ-5D-5L for incapacitated patients; patient DEMQOL and carer DEMQOL-proxy scales)
- Carer stress and quality of life (carer EQ-5D-5L; HADS; and Zarit burden scale)
- Time spent caring for the person with dementia
- Changes in management (including changes in prescribed medication)
- Rates of cognitive decline (MMSE; and MoCA)
- Global outcomes (observer and carer rated)
- Heath economic measures:
    - Primary and secondary health care resource use, use of personal social services
    - Cost to primary and secondary health care and personal social services
    - Patient costs (time and travel costs of accessing health care services)
    - Unpaid costs to carers based on the time spent caring for the person with dementia
    - Patient quality adjusted life years (QALYs) estimated from patient responses to the EQ-5D-5L and DEMQOL, and carer responses to proxy EQ-5D-5L and the DEMQOL-proxy measures, respectively
    - Carer QALYs estimated from carer responses to a carer's EQ-5D-5L

- Incremental cost per QALY gained calculated from the total costs and QALYs of the patient and the carer in order to compare the new assessment and management toolkit with usual care

4. TRIAL DESIGN

A pilot cluster randomised controlled trial (cRCT) design will be used to test the management toolkit. Participating services will be cluster randomised with half implementing the management toolkit (intervention arm) and half implementing usual clinical care (control arm). The study team will disseminate the management toolkit to the clinical teams in the intervention arm and provide appropriate training. Clinicians will use the toolkit as part of their clinical management of LBD patients according to their clinical judgement.

The study will be discussed and consent taken from the patient (or consultee) and the carer/informant for the additional study visits and for data to be collected for the study. For both arms of the study an additional visit will be arranged to conduct a baseline visit, 3 month and 6 month follow up visits.

5. STUDY DURATION AND SETTING

This is a multi-centre study with at least 8 participating services. This study will be divided into two smaller parts: a) WP5A which will involve patients from memory assessment services, (Dementia with Lewy Bodies), and b) WP5B which will involve patients from neurology and geriatric services (Parkinson's Disease Dementia).

The total study duration will be 3 years. This will include a recruitment period of 24 months, a follow up period of 6 months and a final 6 months for data analyses, interpretation and dissemination of results. Submission of abstracts will continue beyond this period to target specific conferences and publications.

The management toolkit is a recommended guideline and will be used according to clinician judgement in the intervention arm. It could be used at a single visit only, or over multiple visits/patient contacts across several months. The management toolkit will be used as part of routine practice and will remain with sites after the end of the study. Additional study visits will be conducted at baseline, 3 months and

6 months, and clinicians in the intervention arm will be asked to complete a clinician toolkit use questionnaire.

Recruitment will be reviewed at the end of month 1 and regularly thereafter at study Trial Management Meetings. The end of month 30 will be the end of the study for all participants.

6. ELIGIBILITY CRITERIA

6.1. Inclusion Criteria

Cluster randomised controlled trial to test the management toolkit:

- A clinician diagnosis of LBD has been documented as the result of specialist service assessment (possible or probable diagnosis).
- Consent can be obtained from the patient or, for those subjects lacking capacity, from a consultee.

In addition to the above criteria:

- WP5A: Patients aged 60 and over with at least 1 active clinical issue as determined by the treating clinical team;
- WP5B: Patients aged 60 and over with a diagnosis of Parkinson's disease where a memory problem has developed.

6.2. Exclusion Criteria

- Patients who have explicitly expressed a wish not to be approached to take part in research
- Patients who have been approached to take part in this study previously (as part of another participating service)
- Patients who have a severe or terminal illness and reduced life expectancy which compromises their ability to comply with the protocol
- Insufficient English to allow completion of the study measures
- Patients who are assessed as not able to complete the outcome measures for the study

Clinicians may choose not to use the management tool at some assessments if they feel it is not appropriate.

NB: Enrolling a patient onto the trial who does not meet the inclusion/exclusion criteria is considered a protocol waiver. PROTOCOL WAIVERS REQUIRE THE AUTHORISATION OF THE RESEARCH SPONSOR PRIOR TO IMPLEMENTATION.

7. TRIAL PROCEDURES

7.1. Recruitment

7.1.1. Patient Identification and Screening

Potential participants will be identified by the clinical teams, network staff or the study team through the review of medical records and patient clinic lists at the participating services. If appropriate the clinician may hand out the letter of invitation and participant information sheet at the end of the clinical appointment (e.g. if this is a diagnosis appointment). Otherwise, after the clinical appointment potentially eligible patients will discussed with the clinician regarding mental capacity to consent for the study and the need for a consultee. Contact details will be obtained and used to send out a letter of invitation and relevant participant information sheet(s).

In all cases patients will be given a minimum of 24 hours to read the information sheet, and longer if they need time to discuss with family with whom they don't live. They will have the option to contact the team immediately if they do not wish to take part. If no objection is received, a follow up phone call will be made by the study team to arrange a study visit (either in the patient's home or in a clinical setting) to obtain consent and conduct the baseline measurements. It may not be possible for this baseline visit to be conducted before the management toolkit is used in clinical practice, but will be as soon as is reasonably and practicably possible.

A screening log will be completed to document fulfilment of the entry criteria for all patients considered for the study, including those who are subsequently included or excluded. Eligibility to the study will be confirmed by the delegated member of the study team at the baseline visit, prior to seeking consent.

7.2. Consent

Participating services will be randomised to either the intervention arm or the control arm. The cRCT design removes the need for individual participant randomisation. Consenting to the study will not affect the management method that the clinician uses as part of patient care. If the patient does not consent for any reason, the data will not be collected and used for the study and the study visit measurements will not be done.

Consent will only be taken by members of the clinical research network or study team with documented and delegated responsibility. The study team will have communicated with clinical staff ahead of the baseline study visit to assess mental capacity of the patient. Consent will be sought from the patient in the first instance whenever possible. If the patient is found to lack mental capacity, but they still appear to be willing, an opinion will be sought from a consultee. This will be the patient's carer, next of kin or nominated person as defined in the Mental Capacity Act 2015. If a patient had capacity and consented to the baseline assessment, but loses capacity during the study, then an opinion will be sought from a consultee and the patient would only continue to be included in the study if they appeared willing and the consultee agreed. If either at recruitment or at any point throughout the study, the patient appears unwilling to be included or take part in the study in the study, then they will not be included.

Consent will be also sought from the informant/carer who is present at the visit, as they will also be acting as a participant in their own right.

The patient (or consultee) will provide written informed consent by completing and dating the consent form, which will be witnessed by the person who has documented and delegated responsibility to do so. The original signed consent forms will be retained in the ISF, with a copy filed in the clinical notes and a copy provided to the participant/consultee.

The right to refuse to participate without giving reasons will be respected. All participants will have the right to withdraw at any time.

The information sheets and consent form will be available only in English.

7.3. Randomisation

Participating services will be randomised to administer either the management toolkit (intervention arm) or continue with usual care services (control arm). Randomisation will be done using computer generated randomisation at a service level, stratified by site (North East and East Anglia).

7.4. Blinding

As far as is possible, all measurements for the CRCT will be undertaken by staff who are blinded to the randomisation schedule. This will be achieved by using a member of the Clinical Research Network DeNDRoN team who are not involved with the study in any way, and who are located geographically in a different location from both the study team and the services. Where possible, the follow up visits will be

conducted in the same environment as the baseline visit (patient home or in a clinical environment). All visits for each participant will be done by the same person whenever possible/practicable.

7.5. Unblinding

There will be no need for unblinding for this study, as the clinical teams involved will already be unblinded.

7.6. Baseline Measurements & Data

The following assessments would be undertaken:

Patient:

- Mini-mental state examination (MMSE) [3]
- Montreal Cognitive Assessment (MoCA)[2]
- Geriatric Depression Scale (GDS-15)[5]
- Motor symptoms (Unified Parkinson's disease rating scale, Part III) [6]
- The dementia specific quality of life measure (DEMQOL) [8]
- Generic quality of life measure (EQ-5D-5L)
- Current management (e.g. medications prescribed, non-cognitive approaches used) would be recorded

Informant (regarding the patient):

- Neuropsychiatric symptoms (neuropsychiatric inventory (NPI)) [4]
- Cornell scale for depression in dementia[5]
- Activities of daily living (Bristol activities of daily living scale) [7]
- Dementia Cognitive Fluctuation Scale (DCFS-R)
- The dementia specific quality of life measure (DEMQOL proxy) [8]
- Generic quality of life measure (Proxy EQ-5D-5L)
- Baseline Global rating scale (regarding patient)
- Global rating scale(regarding patient)

- Use of health care and personal social services and patient and care incurred costs collected via questionnaires based on a bespoken questionnaire derived from the Client Service Receipt Inventory (CSRI) and the Resource Utilisation in Dementia (RUD) instrument.

Informant (regarding carer own health and wellbeing):

- Hospital Anxiety and Depression Scale (HADS) [9]
- Generic quality of life measure (EQ-5D-5L)
- Zarit burden scale[10]
- Use of Health and Personal social services (collected on same Questionnaires reported above)

Researcher to complete about the patient :

- Galvin Lewy Body Composite Score
- Global outcome scale

Clinician:

- Clinician Toolkit Use Score (administered either on paper or electronically)

7.7. Trial Assessments

Measurements will be conducted at 3 months (+-2 weeks) and 6 months (+-2 weeks) after the baseline visit as listed in table 1. The primary outcome for the study will be the 6 month assessment. If it is determined at the follow up visits that the patient is no longer able to complete the additional measurements, the visit may continue with the informant/carer providing information as a participant.
The informant/carer does not need to be present at all follow up visits as some questions can be completed on the telephone.

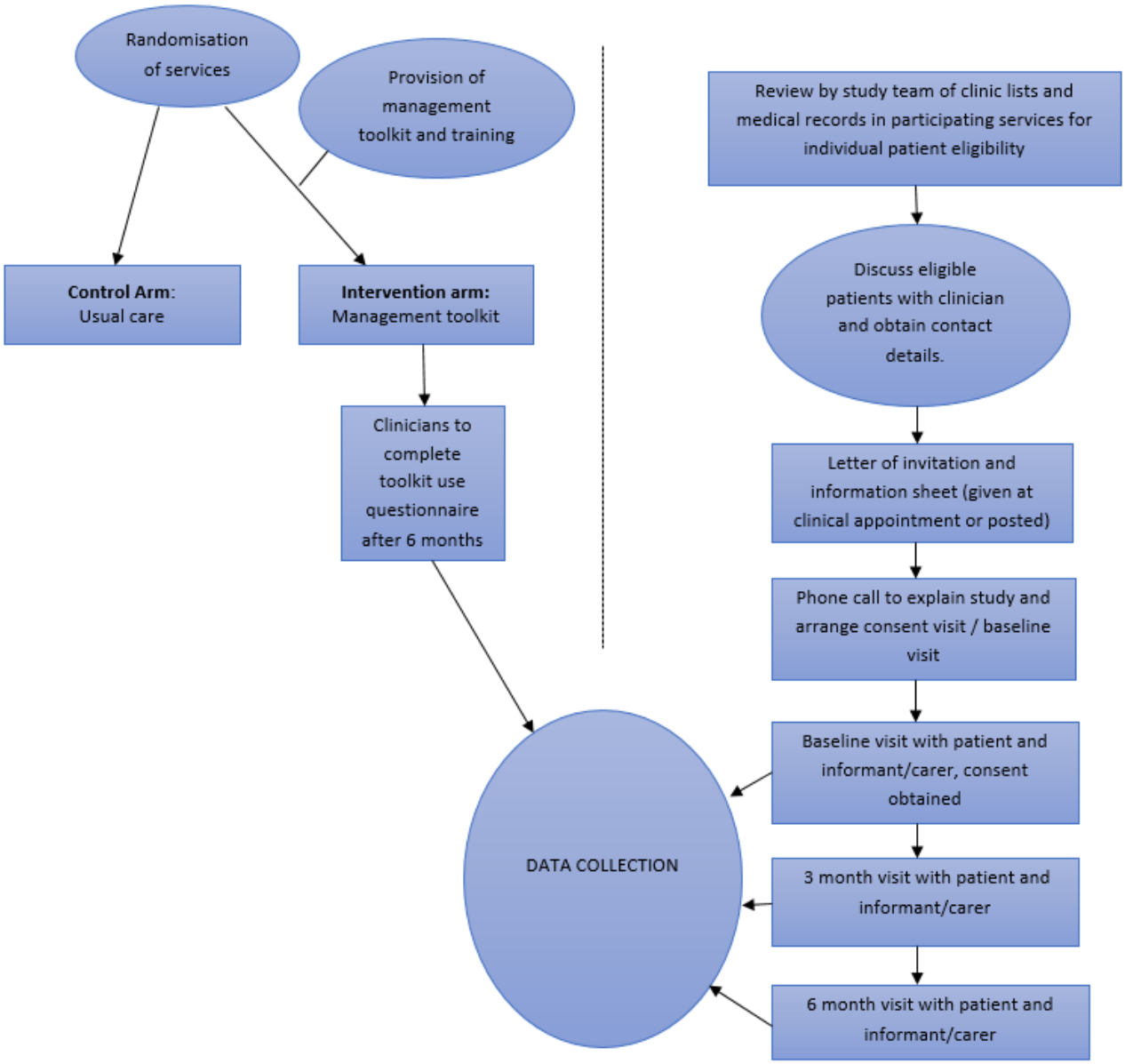
Table 1.

	Baseline	3 Months	6 Months
Patient			
Consent	X		
MMSE	X	X	X
MoCA	X	X	X
GDS-15	X	X	X
UPDRS-III	X	X	X
DEMQOL	X	X	X

EQ-5D-5L	X	X	X
Carer/informant relating to patient			
Consent	X		
NPI	X	X	X
Cornell	X	X	X
BADL	X	X	X
DCFS-R	X	X	X
DEMQoL-Proxy	X	X	X
Proxy EQ-5D-5L	X	X	X
Baseline Global outcome scale (regarding patient)	X		
Global outcome (regarding patient)		X	X
Use of services and costs*	X	X	X
Time and travel questionnaire*			X
Carer/informant relating to themselves			
Zarit	X	X	X
EQ-5D-5L	X	X	X
HADS	X	X	X
Use of services and costs*	X	X	X
Time and travel questionnaire*			X
Researcher relating to patient			
Galvin Lewy Body Composite Score	X		X
Global Outcome Scale		X	X

*The same questionnaires will give the information of the services used, and time and travel needed for both the patient and the carer

7.7.1. Flow Chart



Explanatory notes for flow chart:

Management Toolkit:

- Participating services will be cluster randomised to either the intervention arm (management toolkit) or the control arm (usual management care).
- Services that are randomised to the intervention arm will receive the management toolkit for use in their contacts with patients who require management, as well as appropriate training to use the toolkit.

- The management toolkit will be used according to clinican judgement and is a recommended guideline. It may be used at a single clinic visit, or over multiple visits/patient contacts. The clinicans may use the sections of the toolkit that they feel are appropriate for the patient.
- Clinicians in the intervention arm will be asked to complete a questionnaire regarding their use of the toolkit at 6 months after randomisation.

Screening and Recruitment:

- Potential participants will be identified by network staff, the clinical team or the study team through the review of medical records and patient lists at participating services.
- If appropriate, a study invite letter and participant information sheet may be given at the clinical appointment where there is a need for management identified e.g. an appointment for diagnosis.
- Otherwise, eligible patients will be discussed with a clinician after the clinical apointment regarding the need for a consultee to be present at the study visit. Contact details will be obtained if agreed it is appropriate to continue and the invite letter and relevant participant information sheet(s) will be posted.
- In all cases, a minimum of 24 hours will be given to consider the information, and longer if they need time to discuss with family/friends.
- All potential participants will have the option to contact the team straight away if they definitely do not want to take part in the study.
- If no 'opt out' is received, a follow up telephone call will be made by a member of the study team to answer questions and arrange the baseline study visit in the presence of an informant/carer.
- The baseline visit will be additional to routine care and will be made as soon as is reasonably and practically possible after the patient has been identified for the study. The visit may take place in a clinical environment or at the patients home.
- An eligibility screening log will be completed.

Baseline Visit:

- The delegated staff member will discuss the study with the patient (or consultee) and answer any questions. Staff will be blinded to the randomisation schedule wherever possible.
- Infomed consent will be sought from the patient in the first instance. The study team member will perform an assessment of mental capacity to ensure the patient is able to consent to the study. If not, and the patient appears willing, an opinion will be sought from the consultee.
- Informed consent will also be sought from the informant/carer as a participant in the study.
- Baseline measurements will be performed (patient and informant/carer).

- Health economic data will be collected using patient and carer responses to the EQ-5D and DEMQOL questionnaires as well as the use of health and social services questionnaire and the time and travel questionnaire.

Follow up visits – approximately 3 months (+/ - 2 weeks) and 6 months (+/ - 2 weeks) after baseline

- Wherever possible the follow up visits will be performed in the same environment as the baseline visit, and by the same delegated study team member.
- Measurements will be performed at 2 further study visits, approximately 3 months and 6 months after baseline.
- If the patient is no longer able to complete the measures, the visit will continue with the informant providing carer information as a participant.
- If the informant/carer is not able to attend all follow up visits, some information may be collected by telephone.
- Health economic data collection will be repeated. In addition a time and travel questionnaire will be administered at 6 months to estimate the time and travel costs of accessing health and personal social services.
- If it is felt not appropriate to do the time and travel questionniare at the last visit, it can be left with participant for completion and returned by post.

Data Collection

Data will be collected and used for the study from:

- Study visits: data collected from the measurements used at the baseline, 3 month and 6 month visits, as well as health economic data.
- Clinician questionnaire: data collected from the clinician toolkit use questionnaire completed approximately 6 months following service randomisation and at the end of the study.

7.8. Withdrawal Criteria

Due to the cRCT design, participants will receive the management toolkit or usual care whether they consent to the study or not. Participants can withdraw the use of the information collected at any time throughout the study. Consultees may also withdraw the patient if they feel they are experiencing anxiety or distress by continuing in the study.

All participants have the right to withdraw their information at any time, without having to give a reason. Investigator sites should try to ascertain the reason for withdrawal and document this reason on the withdrawal form and participant's medical notes.

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

- Participant withdrawal of consent
- Significant protocol deviation or non-compliance
- Investigator's discretion that it is in the best interest of the participant to withdraw
- Termination of the study by the sponsor

Participants who withdraw from the trial will not be replaced.

7.9. End of Trial

The last contact for all participants in Work Package 5 will be at month 30. The end of the trial for regulatory purposes will be the locking of the database.

8. TRIAL INTERVENTION

8.1. Name and Description of Interventions

Management Toolkit:

The management toolkit is a guideline document that has been produced as part of the overall DIAMOND-Lewy programme grant. It is a document that offers practical advice to clinicians who are providing treatment and care to people with LBD (DLB and PDD).

8.2. Assessment of Compliance

Clinicians from participating services in the intervention arm will be asked to complete a questionnaire regarding use of the management toolkit. This will indicate:

- The level of completion and reasons
- Rates of compliance
- User experience

Consent will be implied through completion of the questionnaire. All clinicians in the intervention arm will be given the opportunity to complete the questionnaire at approximately 6 months following service randomisation and at the end of the study. This data will be used to answer key questions about the feasibility of use of the management toolkit in standard clinical care.

9. STATISTICAL CONSIDERATIONS

9.1. Analysis Population

Within the identified services all DLB cases (existing or new diagnosis) will be identified and will be eligible for inclusion, as long as they meet the inclusion criteria. Based on a previous work package where 70 DLB subjects were identified and recruited from a similar number of services over 18 months, it is anticipated work package 5 will recruit at least 60 subjects to enter the pilot study of the management toolkit (i.e. 30 in each arm).

In an earlier work package prevalence rates of PDD to be 10% were found of all PD subjects, therefore 8 services should be sufficient to allow a similar number of PDD subjects to be recruited (60 subjects, 30 in each arm) to enter the pilot study of the management toolkit.

9.2. Statistical Analyses

Hypothesis

For the definitive trial we hypothesise that DLB and for PDD subjects treated in services randomised to implementing the management toolkit will result in symptom improvement (reduced neuropsychiatric inventory score, lower unified Parkinson's disease rating scale score, greater improvement in CGIC global and symptom ratings), increased quality of life (DEMQOL and DEMQOL-proxy scales) and decreased carer stress (HADS, Zarit burden scale) at 6 months compared to baseline. In this pilot study, we will conduct an exploratory analysis where we will rehearse the analysis proposal for the full trial.

9.2.1. Analysis of the Outcome Measures

For the exploratory analysis, T-tests will used to compare the means of two samples when data is normally distributed and a Wilcoxon Signed test will be used to compare the medians of two samples when data is

skewed. The association of a binary outcome with a categorical predictor with 2 or more levels will be tested using the Chi-square test. As there is a single management tool covering both dementia with Lewy bodies and Parkinson's disease dementia, then it will be appropriate to undertake exploratory analysis on the combined PDD and DLB subject group.

Information on the variability of continuous variables measuring the symptoms such as neuropsychiatric inventory score will be useful in power calculations for a larger study.

9.2.2. Statistical Analyses

As the management tool covers both DLB and PDD it will be appropriate to undertake exploratory analysis on the combined PDD and DLB subject group. As the hypothesis concerns changes in symptom scores between baseline and 6 months we will use T-tests in an exploratory analysis to compare the means of two samples when data is normally distributed and a Wilcoxon Signed test will be used to compare the medians of two samples when data is skewed. The association of a binary outcome with a categorical predictor with 2 or more levels will be tested using the Chi-square test. Further analysis involving the data measured at baseline, 3 months and 6 months will be done by using a linear mixed regression model to test for between group and between time differences.

9.3. Statistical Size Calculations

This is a pilot study and the sample sizes may be insufficient to test the hypothesis. However information on the variability of continuous variables measuring the symptoms such as neuropsychiatric inventory score will be used in power calculations for a larger study. The choice of 30 cases in each arm of the pilot study is a rule of thumb advocated by clinical trial researchers (ref Lancaster G.A 2002).

10. ECONOMIC EVALUATION

The main objective of the economic evaluation of this pilot cluster randomised trial is to rehearse the methods for a definitive evaluation and perform an exploratory cost-effectiveness analysis of the new assessment and management toolkit compared with the usual care provided for dementia. Within this exploratory economic evaluation we will report costs to the NHS, PSS, and patients and carers as well as cost per quality adjusted life year (QALY) with QALYs based on generic (EQ-5D, proxy EQ-5D) and condition specific health state utilities (DEMQOL, DEMQOL- proxy).

In terms of health service use, we will use refined tools from those used in WP1 to estimate resource use. The key refinement will be to tailor the data collection tools to ensure the capture of health service, personal social services and costs falling on patients and carers in the most parsimonious way. Using the same methods used in WP1 we will estimate relevant unit costs. The resource data will be collected within the trial at baseline, 3 and 6 months based on the Case Report Forms (CRF) of the trial.

In addition to the use of health services, at the end of the trial (6 months) we will seek to elicit the costs of administering the tool. This will involve the completion of a structured questionnaire by a small sample of practitioners asking about the time, travel and material involved in the process of using the toolkit.

As far as the patients' quality of life (QoL) is concerned, this will be derived from the responses of the participants to the EQ-5D (or the responses of the carer to a proxy version the EQ-5D for those patients that are incapacitated) and the 28-item DEMQOL in combination with the carer responses to the 31-item DEMQOL-proxy questionnaires, which will be administered at baseline, 3 months and 6 months to the patients and carers, respectively. The data collected will then be converted using the appropriate algorithms in order to generate the generic (EQ-5D) and dementia specific (DEMQOL) utilities of the different health states of LDB. On the other hand, the health related quality of life of the carer will be measured using the carer responses to the EQ-5D administered at the three time points. QALYs will be estimated by using the 'area under the curve' approach for each trial participant and carer (Morris et al, 2007 [1]). The derived QALYs from each questionnaire (i.e. EQ-5D and proxy EQ-5D; patient and carer EQ-5D; DEMQOL (with missing data replaced by DEMQOL-proxy; and DEMQOL-proxy) will then be compared and used for the cost-effectiveness analysis of the study.

Mean costs and mean QALYs will be calculated for each trial intervention and based on them, the incremental cost-effectiveness ratio (ICER) will be calculated. One- and/or multiple-way sensitivity analyses will be conducted to explore uncertainties (alternative utility measures, alternative unit costs, changes in study perspective etc.). In addition to this, stochastic analysis will be conducted to explore the statistical imprecision surrounding estimates of costs, QALYs and ICERs. This analysis will be presented as cost-QALY plots and cost effectiveness acceptability curves (CEACs).

If the intervention is more effective but more costly we will explore the impact of extrapolating from trial findings using data from the literature on effectiveness of treatments.

11. DATA HANDLING

11.1. Data Collection Tools and Source Document Identification

Data will be collected on paper Case Report Forms by the study team at each participating service. It will then be entered on to a secure validated system with an auditable data trail.

11.2. Data Handling and Record Keeping

Each participant will be allocated a unique identification number when they are enrolled into the study and all subsequent records will be identified using this number.

Data will be handled, computerised and stored in accordance with the Data Protection Act 1998. No participant identifiable information will leave the hospital site. All original consent forms will be held in the ISF, with a copy in the clinical notes and a copy given to the participant. Caldicott approval will be obtained as part of local NHS permission from each site to enable the collection of personal identifiable information as part of this trial. The quality and retention of study data will be the responsibility of the CI. All study data will be retained in accordance with the latest Directive on GCP (2005/28/EC) and local policy.

11.3. Access to Data

The trial economist and/or statistician will only need access to anonymised data. Members of the study team will have access to patient identifiable data and access to study data. Anonymised data will be shared with other researchers and research groups, including the Dementia Platform UK, but within and outside of the EU. This will be included in the participant consent forms.

12. ETHICAL AND REGULATORY CONSIDERATIONS

12.1. Research Ethics Committee Review and Reports

The NCTU will obtain a favourable ethical opinion from an NHS Research Ethics Committee (REC) prior to the start of the trial. All parties will conduct the trial in accordance with this ethical opinion. Local approvals will be sought before any recruitment may commence.

Information sheets will be provided to all eligible participants and written informed consent obtained prior to any data collection for the study. All participants will be given a copy of their signed consent form.

The CI and Project Manager will notify the REC of all required substantial amendments to the trial and those non-substantial amendments that result in a change to trial documentation (e.g. protocol or participant information sheet). Substantial amendments that require a REC favourable opinion will not be implemented until such opinion is obtained. The CI and Project Manager will notify the REC of any serious breaches of GCP or the protocol, urgent safety measures or USARs that occur during the trial.

An annual progress report will be submitted each year to the REC by CI and Project Manager until the end of the trial. This report will be submitted within 30 days of the anniversary date on which the original favourable ethical opinion was granted.

The CI and Project Manager will notify the REC of the early termination or end of trial in accordance with the required timelines.

12.2. Peer Review

Peer review was undertaken by the study funder as part of the overall work package. The sponsor has confirmed that no further peer review will be required. Peer review will also be undertaken as part of the NIHR portfolio adoption process.

12.3. Public and Patient Involvement

The management toolkit was first developed in work package 3, using a Delphi panel of more than twenty national and international multi-disciplinary experts in LBD management. The proposed content of the management toolkit was reviewed in two PPI workshops attended by patients and carers affected by LBD which resulted in the addition of information on general principles.

Mr Derek Forster is a lay co-applicant on this proposal. He has and will continue to provide PPI input to the programme at all stages and is a member of the overall study steering group. The programme is additionally supported by a PPI group comprising three people with experience of PD and/or LBD in

addition to Mr Forster. This PPI group meets as required to provide advice and support to the programme team.

12.4. Regulatory Compliance

The trial will be conducted in accordance with the Research Governance Framework or current (equivalent) regulation. Before any site can enrol patients into the trial, that study must have received all appropriate regulatory approvals and have been assessed for local capacity.

12.5. Protocol Compliance

Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used.

12.6. Notification of Serious Breaches to GCP and/or the Protocol

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

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

The sponsor must be notified immediately of any incident that may be classified as a serious breach. The CI will notify the NHS REC within the required timelines in accordance with the Sponsor SOP.

12.7. Data Protection and Patient Confidentiality

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

Patient initials, hospital number and date of birth will be collected and recorded at site in order to prevent entry of duplicate participants to the study. Consent will be obtained for this information to be collected at sites. Identifiable information will also be obtained for the study team to contact participants during the study. All information will be used only for the stated purpose(s) and then securely destroyed at site at the end of the study.

12.8. Indemnity

Conduct

The Sponsor has liability for clinical negligence that harms individuals toward whom they have a duty of care. NHS Indemnity covers NHS staff and medical academic staff with honorary contracts conducting the trial for potential liability in respect of negligent harm arising from the conduct of the study at site.

Management

NTW is Sponsor and through the Sponsor, NHS indemnity is provided in respect of potential liability and negligent harm arising from study management.

Design

Indemnity in respect of potential liability arising from negligent harm related to study design is provided by NHS schemes for those protocol authors who have their substantive contracts of employment with the NHS and by Newcastle University Insurance schemes for those protocol authors who have their substantive contract of employment with the University. This is a non-commercial study and there are no arrangements for non-negligent compensation.

Payment

No payment will be given to participants for taking part in the trial. All participants who have their study visits at clinic will be reimbursed for reasonable travel and out of pocket expenses. They will be fully supported throughout study and thanked for their time.

12.9. Amendments

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

Substantial amendments will be submitted to the REC and will not be implemented until this approval is in place. It is the responsibility of the CI and Project Manager to submit substantial amendments.

Non-substantial amendments may be made at any time with a record of the amendment held in the Trial Master File. Any non-substantial amendment that requires an update to the trial documentation will be submitted to the NHS REC for acknowledgement of the revised version of the document.

Substantial amendments and those minor amendments which may impact sites will be submitted to the relevant NHS R&D Departments for notification to determine if the amendment affects the NHS permission for that site. Amendment documentation will provide to sites by the CI and Project Manager.

13. REFERENCES

1. Morris S, Devlin N and Parkin D (2007). Economic Analysis in Health Care. Wiley, 2007
2. Hoops S, Nazem S, Siderowf AD, Duda JE, Xie SX, Stern MB, et al. Validity of the MoCA and MMSE in the detection of MCI and dementia in Parkinson disease. Neurology. 2009 Nov 24;73(21):1738-45.
3. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. Journal of Psychiatric Research. 1975;12(3):189-98.
4. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology. 1994;44(12):2308-14.
5. Alexopoulos GS, Abrams RC, Young RC, Shamoian CA. Cornell Scale for Depression in Dementia. Biological Psychiatry. 1988;23(3):271-84.
6. Fahn S. Unified Parkinson's disease rating scale. *Recent developments in Parkinson's disease*. New York: Mcmillan 1987:153-63.
   53 Bucks RS, Ashworth DL, Wilcock GK, Siegfried K. Assessment of activities of daily living in dementia: development of the Bristol Activities of Daily Living Scale. Age Ageing. 996;25(2):113-20.
7. 54 Smith SC, Lamping DL, Banerjee S, Harwood RH, Foley B, Smith P, et al. Development of a new measure of health-related quality of life for people with dementia: DEMQOL. Psychological Medicine. 2007 May;37(5):737-46.
8. Golderberg D, Williams P. A user's guide to the General Health questionnaire. Windson, UK: NFER-Nelson 1988.
9. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatrica Scandinavica. 1983 Jun;67(6):361-70.

10. Zarit SH, Reever KE, Bach-Peterson J. Relatives of the impaired elderly: correlates of feelings of burden. Gerontologist. 1980 Dec;20(6):649-55.

14. APPENDICES

14.1. Appendix 2 – Amendment History

Amendment Number	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
1 (Substantial Amendment)	3.0	01.06.16	Sarah Dunn	Amendments to the protocol: Dr Emma Burton has replaced Andrew West as Project Manager and Miss Sarah Dunn has been added as the Trial Manager. Professor Luke Vale has been added as the lead economist to the signature page. The patient population has been amended to include reference to the patients' carers as this was not clear previously. The total sample size has also been added as this refers to the 60 DLB patients and their carers and the 60 PDD patients & their carers. The combined total of patients and carers is 240. Reference to the Falls diary document and adverse events have been removed from the protocol as these will not be recorded for this study. Reference to the Kings Hallucination Scale has been removed from the protocol as this scale will not be used. The version of the validated questionnaire EQ5D has been specifically stated as EQ-5D-5L in the protocol on pages 17, 22, 23 & 24. This is the version that will be used in the study.

				The questionnaires relating to the researcher have been added to the schedule of events. The global outcome scale (carer version) has been renamed 'Baseline Global outcome scale (regarding patient)'. The global outcome scale (patient version) has been removed from the list of patient questionnaires, renamed 'global outcome scale (regarding patient)' and added to the informant/carer list of questionnaires. The procedure for those patients who lose capacity during the study has been updated. The research team would seek a consultee rather than remove the patient from the study should they lose capacity during the study. This has also been amended on the IRAS Form (A35). The clinician toolkit use questionnaire may be sent in either paper or electronic format to the clinician and so this has been stated in the protocol. Amendments to Questionnaires: The 2 health economics questionnaires have been amended as per description below. Time and Travel Questionnaire - Further instruction as to how to calculate the distance travelled has been added to Questions A6, A7, C6 & C7 Use of Healthcare and Social Services- The wording has been altered in questions A1, A2, A3 & C1. A box has been added to table in Questions B1, B2, B3 & B4 to indicate whether the service stated was NOT used. Question C4 has been added to give the participant the option to opt out of answering questions relating to their income.

				Question D1 referring to the patients medication profile has been removed from the new version of the questionnaire. Questions I to K have been removed from this questionnaire. Other: An information document for practitioners has been produced by the trial team. Two Trusts have been added to the list of research sites in the IRAS form as listed below: City of Sunderland Hospitals NHS Foundation Trust Ipswich Hospitals NHS Foundation Trust.
2.0 (minor amendment)	3.0	30.06.16	Sarah Dunn	Minor amendment made to the coding in 'Time and Travel' and 'Use of Health and Personal Social Services' questionnaires. Instead of yes = 1 and no = 2 as written in the old version, the new version states now yes = 1 and no = 0. Don't know was changed to be recorded as 555 rather than the next sequential number.
3.0 (minor amendment)	4.0	19.10.2016	Sarah Dunn	Amendments to the protocol: Sarah Greenhalgh has replaced Emma Burton as Project Manager. Her details have been added to the Key Contacts on page 4. The frequency of the Clinician Toolkit Feedback Questionnaire has been amended on pages 26 & 28. The Clinicians randomised to receive the management toolkit will now be asked to complete the questionnaire at two time points (approximately 6 months post randomisation and at study end). Amendments to the Clinician Toolkit Questionnaire: The Questionnaire has been updated to reflect the changes in frequency that it will be completed and to make it more general about the clinicians' view of the toolkit, so incorporating all patients who have been managed rather than per patient.

10.0 (minor amendment)	5.0	07.06.2018	Sarah Dunn	Amendments to the protocol: Richard McNally has replaced Peter James as Trial Statistician. His details have been added to the Signature page on pg. 3 and the key trial contacts on pg. 6.

{Enter all amendments to the protocol here whether substantial or non-substantial. Substantial amendments will require approval by the NHS REC. Non-substantial amendments should be sent to the NHS REC for acknowledgement only}