Statistical Analysis Plan

Maintaining Independence in People with Dementia who had a fall: a pilot cluster randomised controlled trial (the Maintain Study)

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V0.1 DRAFT	Initial Draft	During Follow-Up	
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1. Introduction

1.1. Background and rationale

People living with Dementia are ten times more likely to fall than people who do not have dementia [1]. After a fall they may have a poorer recovery than people without dementia and have an increase in dependency and poorer quality of life. In a previous NIHR Health Technology Assessment (HTA) project we developed an intervention for helping people living with dementia (PWD) to recover after a fall and preventing further falls [2]. In the present study we aim to carry out a pilot cluster randomised controlled trial (RCT) of a modified version of this intervention. This will enable us to determine whether it is feasible to proceed to a full definitive cluster randomised controlled trial of the intervention.

1.2. Objectives

Primary Research Question

- Is it feasible to conduct a research study of an intervention, in people with dementia aged over 50 years old, whilst demonstrating benefits in other patient-reported, professional-reported and cost-effectiveness outcomes.

Aim

- The aim of the study is to test the feasibility of conducting a research study of the intervention.

Primary Objectives

- Deliver a pilot cluster RCT of an intervention to maintain independence in PWD, living in their own homes, who have already fallen.

Secondary objectives

- To examine the implementation and acceptability of the intervention for participants and professionals, and mechanisms of impact, including the roles of geriatricians and carer support via a process evaluation.
- To assess acceptability, completeness, and descriptive comparison of data collection for an economic evaluation for the full trial.
- To perform iterative refinement of the intervention for the full trial.
- To assess potential threats to allocation concealment based on: whether the participants were unblinded prior to consent; whether more or fewer participants are recruited in the intervention arm than the control arm; whether the characteristics of the participants differ markedly between the trial arms; whether loss to follow-up differs markedly between the trial arms.

2. Study Methods

2.1. Trial Design

The Maintain trial is a feasibility cluster randomised two-arm controlled trial of a complex intervention with a process evaluation. Participants within the two arms will be allocated on a 1:1 ratio.

2.2. Randomisation

Participating services (clusters) will be randomised in a 1:1 ratio to receive either the intervention plus usual care (intervention arm) or continue with usual care services (control arm). Randomisation will be undertaken based on computer-generated random numbers with no stratification factors.

After the baseline assessment, the clinical researcher will inform the central research team. If the participant is in a service (cluster) that is randomised to the intervention arm, the research team will send a referral to the intervention team using a structured referral form with details of the baseline assessments of the PWD and unpaid carer. The intervention team will then arrange an initial intervention assessment within 2 weeks.

2.3. Sample Size

We will randomise six rehabilitation services (clusters), one in each of 6 sites, and aim to recruit 60 PWD altogether (3 services and 30 PWD to each of the intervention and the control arms). Each service will recruit 10 PWD during the 6-month recruitment period, based on a recruitment rate of 1.7 PWD per service per month as achieved during our feasibility study. If recruitment is slower than expected, we will consider adding 2 additional sites.

The sample size calculation was based on the precision for estimating the proportion of eligible people that consent to participate in the study. We anticipate that we will have to approach 150 eligible people and 40% (60 participants) of these will agree to take part. The 150 who are screened is a large enough number to estimate the percentage that consent with a 95% confidence interval 29% to 51%. If the percentage that is followed up is 80%, 60 recruited participants is large enough to estimate this with a 95% confidence interval 66% to 91%, and the 30 participants in the intervention arm is large enough to estimate the percentage that attends at least 60% of the allocated sessions with a 95% confidence interval 60% to 93%. These confidence intervals take clustering into account [3] and are based on an assumed intra-cluster (intra-service) correlation coefficient of 0.05 to quantify variability across clusters in the feasibility parameters (i.e., percentage consented, followed-up, attending at least 60% of sessions).

2.4. Framework

A superiority hypothesis framework is being used for all outcomes within this trial.

2.5. Statistical Interim analyses and stopping guidance

There are no planned interim analyses or stopping guidance for this trial.

2.6. Timing of final analysis

Analysis will be conducted following the final participant’s 28 Week follow-up visit.

2.7. Timing of outcome assessments

Outcomes are being assessed at baseline and at a follow-up date which is at 26 weeks for the control group and 28 weeks for the intervention group. For the Goal Attainment Scale (GAS), there is an additional follow-up at 12 weeks. Data for follow-up will be considered within window if it collected within two weeks of the expected date of collection. However, for this feasibility study, all data will be used regardless of whether it is within window and a proportion of data being collected within and outside of the window will be reported.

3. Statistical Principles

3.1. Confidence intervals

Ancillary analysis is being performed on potential definitive trial outcomes and both mean differences and 95% confidence intervals will be reported for these outcomes for information on potential effectiveness. As this is all exploratory analysis, no p-values will be reported.

3.2. Intervention adherence and protocol deviations

For the purpose of this feasibility study, there is no deemed intervention adherence, but the number of visits that participants receive will be reported as part of the feasibility outcomes. Visits occurring out of window will also be reported as a proportion. Other protocol deviations will be reported by line-listing.

3.3. Analysis populations

For all analysis of outcome measures within this trial, an intention-to-treat approach will be implemented, except for analysis of safety and harms data, where an as-treated approach will be used. For a participant to be included within the safety population data, they must have received at least one intervention session to be considered within the intervention group for analysis.

Data for these analyses will use observed data only, with no use of imputation planned as part of the analysis.

4. Trial population

4.1. Screening data

All screening data will be reported in the form of a table (see appendix) containing the numbers and proportions within each category.

4.2. Eligibility

Eligible participants are people with dementia, over the age of 50 and currently residing within their own home, on the Primary Care Quality Outcomes Framework (QOF) Dementia register who have sustained at least one fall within six months prior to identification as a study participant.

Eligible carers are either a close family member or friend who receive no financial compensation for the care they provide to the patient participant.

4.3. Participant Flow

Participant flow including recruitment, consent and withdrawal in the Maintain trial will be described through use of a CONSORT diagram.

Numbers of participants declined to consent and withdrawn/lost to follow-up will be included within this CONSORT alongside accompanying reasons.

Withdrawals may either be a partial withdrawal (where a participant withdraws from the intervention but continues to provide data) or a full withdrawal. In both cases, the numbers of partial withdrawals and full withdrawals will be reported.

4.4. Baseline patient characteristics

The following characteristics will be reported in a table containing both number and proportion reported by group allocation.

For Patients and Carers:

- Age
- Ethnicity
- Sex

For Patients Only:

- Residence Type
- Living Arrangement
- English Language Status
- Education Level
- Smoking Status
- Number of Falls

For Carers Only:

- Frequency of Visits to Patient
- Relationship to Patient

5. Statistical Analysis

5.1. Outcome definitions

Feasibility Outcomes that will determine whether to proceed to full trial are as follows:

- Proportion of eligible patients consenting to pilot trial
- Proportion of participants that attend $\geq$ 60% of sessions as planned
- Proportion of consented participants that provide key outcome data at week 28

Pilot Randomised Controlled Outcomes are as follows:

- Activities of daily living (ADL) assessed with the Disability Assessment for Dementia (DAD) at Baseline and 28 Weeks
- European Quality of Life Instrument (EQ-5D-5L) at Baseline and 28 Weeks
- Quality of Life - Alzheimer's Disease (QOL-AD) at Baseline and 28 Weeks
- International short form Falls Efficiency Scale (Short-FES-I) at Baseline and 28 Weeks
- Timed Up and Go test at Baseline and 28 Weeks
- Goal Attainment Scaling (GAS) (intervention only) at Baseline, 12 Weeks and 28 Weeks
- Cognition assessed with Mini-ACE at Baseline
- Falls Diary assessed during the 6 months of follow up
- Carer burden assessed with the Zarit burden interview 12 (ZBI-12) at Baseline and 28 Weeks
- Carer participant quality of life assessed with the European Quality of Life Instrument (EQ-5D-5L) at Baseline and 28 Weeks
- Carer rated Patient participant quality of life assessed with the EQ-5D-5L proxy at Baseline and 28 Weeks
- Carer rated patient participant quality of life QoL-AD Proxy at Baseline and 28 Weeks
- Health and social care Utilisation Questionnaire (HUQ) at Baseline, 12 Weeks and 28 Weeks

Methods of calculation for all outcomes are defined within the protocol in Table 2.

5.2. Analysis Methods

Participant flow through the trial will be summarised using a CONSORT flow diagram for cluster randomised controlled trials.

Baseline characteristics of the services and participants will be described using means and standard deviations for continuous and count variables and numbers and percentages for categorical variables. We will report the following parameters with 95% confidence intervals that are widened to allow for clustering: % of screened people that are eligible; % of eligible people that consent to participate; % of participants that provide data at the 6-month follow-up; and % of intervention arm participants that attend at least 60% of scheduled sessions. To estimate these parameters, mixed logistic regression models with Satterthwaite's degrees of freedom correction will be fitted to binary outcomes that represent eligibility status, consent status, follow-up status and whether attended at least 60% of the scheduled sessions. The constant from these models is the log odds of the parameters which will (along with the 95% CIs) be converted to the percentage scale.

We will also report estimates of the standard deviations for continuous outcomes measured at baseline and week 28.

In order to assess the extent to which randomisation of clusters before recruiting participants may have resulted in recruitment bias due to the research nurses being unblinded, we will report the percentage of eligible people that participate in each of the intervention and control arms and examine the characteristics of the participants between the trial arms.

Finally, in ancillary analyses, we will report intention-to-treat estimates of the effect of the intervention at week 28, using 95% confidence intervals to quantify potential effectiveness. The comparison between trial arms will be undertaken by fitting mixed ("multilevel") linear regression models for continuous outcomes and mixed Poisson regression models for count outcomes; in both instances, using Satterthwaite's degrees of freedom correction to recognise the small number of clusters in the study. Comparisons will be adjusted for the baseline score of the outcome. No p-values will be reported as it is not an objective of this study to conduct a definitive test of the intervention effect.

5.3. Economic data

In order to inform data collection for an economic evaluation in the full trial, the analysis will provide descriptive statistics on the number (percentage) of completed, partially completed and non-completed health and social care resource use questionnaires including completion of individual items within the questionnaire. The analysis will also report the number (percentage) of missing scores due to incomplete individual question items for both participant and caregiver EQ-5D-5L.

5.4. Missing data

For all patient-reported outcome measures that have been collected, at least 90% of all questions/items must have been completed for this to be considered within the analysis. In these cases, the missing individual items will be imputed. If less than 90% of questions has been answered, the total outcome will be considered missing. For all measures, the number of participants that had data acceptable for use within the analysis will be reported.

5.5. Additional analyses and sensitivity analyses

As this is a feasibility trial, no sensitivity analyses will be undertaken.

5.6. Harms

All harms that have been collected shall be reported as a total number that have occurred in the duration of the trial, and then reported by group on an as-treated basis.

5.7. Statistical software

The latest available version of STATA at the time of analysis will be used for all trial analyses. At time of writing, this is STATA 18.5.

6. Related Documents

Relevant Documents held in the Trial Master File:

- Protocol Version 5.0, Implemented on 22nd May 2024
- Data Management Plan Version 1.0
- Randomisation Requirements Version 1.0

7. References

1. Allan, L.M., et al., Incidence and prediction of falls in dementia: a prospective study in older people. PLoS ONE [Electronic Resource], 2009. 4(5): p. e5521.

2. Allan, L.M., et al., An intervention to improve outcomes of falls in dementia: the DIFRID mixed methods feasibility study. Health Technology Assessment (Winchester, England). 23(59): p.1-208.

3. Gélinas, I., et al., *Development of a Functional Measure for Persons With Alzheimer's Disease: The Disability Assessment for Dementia.* American Journal of Occupational Therapy, 1999. 53: p. 471-81.

8. Appendices

Table 1- Patient Demographics 1

	Control Group		Maintain Group	
Patient Demographics	**N**	**n (%)**	**N**	**n (%)**
Dementia Subtype				
Alzheimer’s Disease				
Vascular Dementia				
Mixed Dementia				
Dementia with Lewy Bodies				
Parkinson’s Disease Dementia				
Frontotemporal Dementia				
Unspecified Dementia				
Other				
Ethnicity				
White				
Mixed/Multiple Ethnic Groups				
Asian/Asian British				
Black/African/Caribbean/Black British				
Other				
Sex				
Male				
Female				
Residence Type				
Private Home				
Sheltered Accommodation				
Other				
Living Arrangement				
Lives Alone				
Lives with Spouse/Partner				
Lives with Other Family Member				
Lives with Someone Other than Family				
Other				
Does the Participant Speak/Read and Understand English?				
Yes				
No				
Highest Education Level				
Secondary School or Equivalent				
Sixth Form/College/Apprenticeship				
University Undergraduate				
University Postgraduate				
Smoking Status				
Never Smoked				
Ex-Smoker				
Current Smoker				

Table 2- Patient Demographics 2

	Control Group			Maintain Group		
Patient Demographics	**N**	**Mean**	**SD**	**N**	**Mean**	**S.D**
Age						
Number of Falls in the last 6 Months						

Table 3- Carer Demographics 1

	Control Group			Maintain Group		
Carer Demographics	**N**	**Mean**	**SD**	**N**	**Mean**	**S.D**
Age						

Table 4- Carer Demographics 2

	Control Group		Maintain Group	
Carer Demographics	**N**	**n (%)**	**N**	**n (%)**
How Often does Carer Typically See Patient				
Every Day				
Most Days				
Once a Week				
Less than Once a Week				
Relationship to Patient				
Spouse/Partner				
Son/Daughter				
Grandchild				
Sibling				
Other Family Member				
Friend				
Other				
Ethnicity				
White				
Mixed/Multiple Ethnic Groups				
Asian/Asian British				
Black/African/Caribbean/Black British				
Other				
Sex				
Male				
Female				

Table 5- Stop/Go Criteria Outcomes

Screening/Eligibility Feasibility Outcomes	**N**	**n (%)**
Proportion of Eligible Patients Consenting to Pilot Trial		

Proportion of Participants who Attend ≥60% of Sessions as Planned.		
Proportion of consented participants retained for key outcome data at week 28		

Table 6- Screening Demographics 1

Screening Demographics	**N**	**n (%)**
Ethnicity		
White		
Mixed/Multiple Ethnic Groups		
Asian/Asian British		
Black/African/Caribbean/Black British		
Other		
Sex		
Male		
Female		

Table 7- Screening Demographics 2

Screening Demographics	**N**	**Mean**	**SD**	**Min**	**Max**
Age					

Table 8- Cognition Assessed with Mini ACE

	Control Group			**Maintain Group**		
Mini-Ace Outcomes	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
Cognition assessed with Mini-Ace at Baseline						

Table 9- Clinical Baseline Characteristics

Clinical Baseline Characteristics	**N**	**Mean**	**SD**	**Min**	**Max**
Clinical Frailty Score at Baseline					

Table 10- Charleston Co-Morbidity Index

Charleson Co-Morbidity Index	**N**	**n (%)**

Myocardial infarction		
Congestive heart failure		
Peripheral vascular disease		
Cerebrovascular accident or transient ischemic attack		
COPD		
Connective tissue disease		
Peptic ulcer disease		
Liver disease		
Diabetes mellitus		
Hemiplegia		
Moderate to severe chronic kidney disease		
Solid tumour		
Leukaemia		
Lymphoma		
AIDS		

Table 11- Activities of Daily Living (ADL) Measured with the Disability Assessment for Dementia (DAD)

	Maintain Group			Control Group			Model Statistics	
Disability Assessment for Dementia Outcomes	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**Mean Difference**	**95% CI**
ADL assessed with the DAD at Baseline							▨	▨
ADL assessed with the DAD at 28 Weeks								

Table 12- Mobility Assessed using the Timed Up and Go (TUG)

	Maintain Group			Control Group			Model Statistics	
Timed Up and Go Outcomes	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**Mean Difference**	**95% CI**
Mobility assessed with the TUG at Baseline							▨	▨
Mobility assessed with the TUG at 28 Weeks								

Table 13- Patient Health Related Quality of Life (HRQL) assessed with the EQ-5D-5L and EQ-5D-5L Proxy

	Maintain Group			Control Group			Model Statistics	
Patient Health Related Quality of Life Outcomes	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**Mean Difference**	**95% CI**
HRQL assessed with EQ-5D-5L at Baseline							▨	▨
HRQL assessed with EQ-5D-5L at 28 Weeks								
HRQL assessed with EQ-5D-5L Proxy at Baseline								
HRQL assessed with EQ-5D-5L Proxy at 28 Weeks								

Table 14- Patient Health Related Quality of Life assessed with the QoL-AD and QoL-AD Proxy

	Maintain Group			Control Group			Model Statistics	
Patient Health Related Quality of Life Outcomes	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**Mean Difference**	**95% CI**
HRQL assessed with QoL-AD at Baseline							▨	▨
HRQL assessed with QoL-AD at 28 Weeks								
HRQL assessed with QoL-AD Proxy at Baseline								
HRQL assessed with QoL-AD Proxy at 28 Weeks								

Table 15- Psychological Consequences of Falling Using the Short-FES-I

	Maintain Group			Control Group			Model Statistics	
Patient Health Related Quality of Life Outcomes	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**Mean Difference**	**95% CI**
Short-FES-I at Baseline								
Short-FES-I at 28 Weeks								

Table 16- Frequency of Falls Assessed Using the Falls Diary

	Maintain Group			Control Group			Model Statistics	
Patient Health Related Quality of Life Outcomes	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**IRR**	**95% CI**
Falls Diary at 28 Weeks								

Table 17- Carer burden assessed with the Zarit burden interview 12 (ZBI-12)

	Maintain Group			Control Group			Model Statistics	
Carer Burden Outcomes	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**Mean Difference**	**95% CI**
Carer Burden assessed with ZBI-12 at Baseline								
Carer Burden assessed with ZBI-12 at 28 Weeks								

Table 18- Carer quality of life assessed with the EQ-5D-5L

	Maintain Group			Control Group			Model Statistics	
Carer Health Related Quality of Life Outcomes	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**Mean Difference**	**95% CI**
HRQL assessed with EQ-5D-5L at Baseline								
HRQL assessed with EQ-5D-5L at 28 Weeks								

Table 19- Goal Attainment Scale (Maintain Group Only)

	N	Mean	SD
Goal Attainment Scale at Baseline			
Goal Attainment Scale at 12 Weeks			
Goal Attainment Scale at 28 Weeks			

Table 20- Proportion of Follow-Ups Occurring Within Window

	Maintain Group		Control Group	
Deviations- Timing of Visits	**N**	**n (%)**	**N**	**n (%)**
Proportion of Follow-Ups Occurring Within Allowed Window at Final Follow-Up				

For all tables:

N = Total Number of Responses (Denominator)
n = Number whom the given option applied to (Numerator)
SD = Standard Deviation
IRR = Incident-Rate Ratio