National Institute for Health Research

CHIEF PD

CHOLINESTERASE INHIBITORS TO PREVENT FALLS IN PARKINSON'S DISEASE

CHIEF-PD (CHolinesterase Inhibitor to prEvent Falls in Parkinson's Disease): A phase 3 randomised, double-blind placebo-controlled trial of rivastigmine to prevent falls in Parkinson's disease.

Approvals and IDs	***Reference***
Protocol version	Version 2.0
IRAS project ID	235625
REC Reference	TBC
EudraCT Reference	2018-003219-23
Sponsor	University of Bristol, 2844
ISRCTN	TBC
Funder (NIHR HTA)	16/31/13
NIHR CRN Portfolio	TBC

This protocol has regard for the HRA guidance

University of BRISTOL

Bristol Randomised Trials Collaboration

KEY TRIAL CONTACTS

Chief Investigator	Dr Emily Henderson Older People's Unit Royal United Hospitals NHS Foundation Trust Combe Park Bath, BA1 3NG Telephone: 0117 331 3903 Email: Emily.henderson@bristol.ac.uk
Co-investigators (applicants for funding)	Professor Yoav Ben-Shlomo, Professor of Clinical Epidemiology, University of Bristol Email: y.ben-shlomo@bristol.ac.uk Professor William Hollingworth, Professor of Health Economics, University of Bristol Email: william.hollingworth@bristol.ac.uk Professor Chris Metcalfe, Professor of Medical Statistics, University of Bristol Email: chris.metcalfe@bristol.ac.uk Dr Alan Whone, Consultant Senior Lecturer in Movement Disorder, University of Bristol Email: alan.whone@bristol.ac.uk Diana Steeds, PPI Representative
Lead Statistician	Professor Chris Metcalfe, Professor of Medical Statistics Bristol Randomised Trials Collaboration Population Health Sciences Bristol Medical School University of Bristol Canynge Hall 39 Whatley Road Bristol, BS8 2PS Telephone: 0117 928 7326 Email: chris.metcalfe@bristol.ac.uk
Trial Manager	Dr Sandra Neumann Email: chief-pd@bristol.ac.uk Telephone: 0117 428 3111
Web address	bristol.ac.uk/chief-pd

FUNDING AND SUPPORT IN KIND

Funder(s)	**Financial and non-financial support given**
NIHR Health Technology Assessment Programme National Institute for Health Research Evaluation, Trials and Studies Coordinating Centre University of Southampton Alpha House Enterprise Road Southampton, SO16 7NS Telephone: 023 8059 5586 Fax: 023 8059 5639 Email: netsmonitoring@nihr.ac.uk	Grant funding
Bristol Randomised Trials Collaboration (BRTC) Bristol Medical School, Department of Population Health Sciences University of Bristol Canynge Hall 39 Whatley Road Bristol, BS8 2PS Telephone: 0117 928 7393 Email: enquiry-brtc@bristol.ac.uk	Methodological expertise
Research and Enterprise Development One Cathedral Square Bristol, BS1 5DD Tel: 0117 42 83065 Email: research-governance@bristol.ac.uk	Sponsorship
Luye Pharma AG Am Windfeld 35 83714 Miesbach Germany	Commercial supplier
Sharp Clinical Services (UK) Ltd Waller House Elvicta Business Park Crickhowell Powys, NP8 1DF	Packaging and distribution of IMP
Royal United Hospitals Bath NHS Foundation Trust Combe Park Bath BA1 3NG	Host

Signed (Chief Investigator): _____ Date: _____

Signed (Sponsor): _____ Date: _____

Contents

GLOSSARY OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
BRTC	Bristol Randomised Trials Collaboration
ChEi	Cholinesterase inhibitor
CI	Chief Investigator
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
DSA	Data Sharing Agreement
DSUR	Development Safety Update Report
EC	European Commission
EU	European Union
FOG	Freezing of Gait
HES	Hospital Episode Statistics
HRA	Health Research Authority
HTA	Health Technology Assessment
ICH-GCP	International Conference on Harmonisation for Good Clinical Practice
IMP	Investigational Medicinal Product
ISRCTN	International Standard Randomised Controlled Trials Number
ITT	Intention to Treat
MDS	Movement Disorders Society
MHRA	Medicines and Healthcare Products Regulatory Agency
NHS R&D/R&I	National Health Service Research & Development/Research & Innovation
NIHR CRN	National Institute of Health Research Clinical Research Networks
NICE	National Institute for Health and Care Excellence

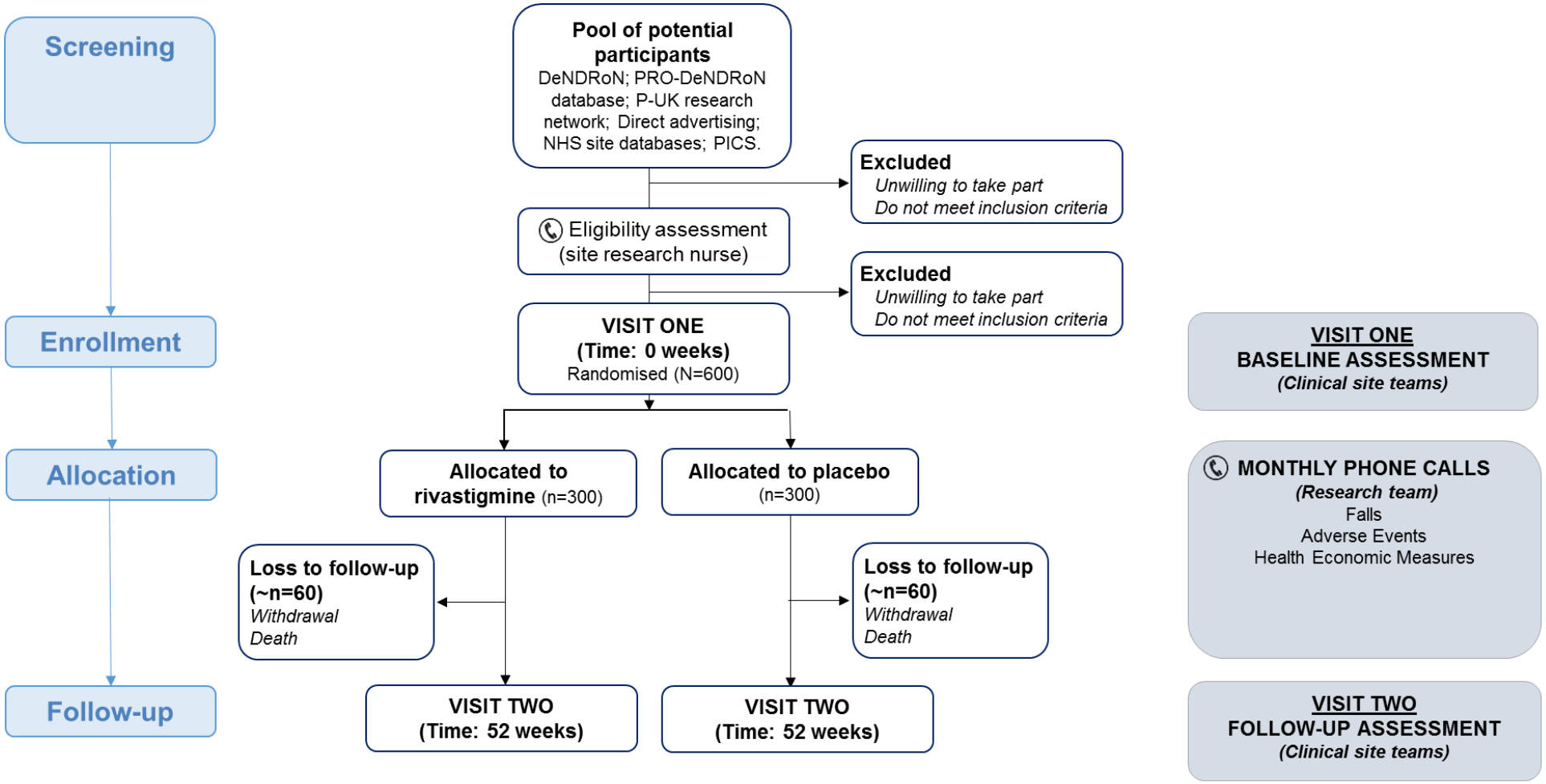
PI	Principal Investigator
PDG	Portfolio Development Group
PIB	Participant Information Booklet
PPI	Patient and Public Involvement
PQ	Participant Questionnaires
QALY	Quality Adjusted Life Years
RCT	Randomised Control Trial
RDSF	Research Data Facility Storage
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SLA	Service Level Agreement
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

TRIAL SUMMARY

Trial Title	A multicentre, phase III, double blind, randomised control trial of the cholinesterase inhibitor, rivastigmine versus placebo to prevent falls in Parkinson's disease
Short title	(Cholinesterase inhibitors to prevent falls in Parkinson's Disease) CHIEF-PD
Chief Investigator	Dr Emily Henderson
Sponsor	University of Bristol
Funder	NIHR Health Technology Assessment Programme
Trial Design	Randomised, participant and assessor blinded, placebo-controlled study
Trial Participants	Adults with a diagnosis of Parkinson's disease
Trial population and size	600 participants randomised with Parkinson's disease who have fallen in the past year
Number of study sites	>26
Intervention	Transdermal rivastigmine 4.6mg / 9.5mg / 13.3mg versus placebo (1:1 ratio)
Treatment duration	12 months
Inclusion criteria	a. Diagnosis of idiopathic Parkinson's disease. b. Modified Hoehn and Yahr stage 1-4 disease. c. Have experienced a fall in the previous year. d. Able to walk ≥10m without aids or assistance.
Exclusion criteria	a. Previous ChEi use in 12 months prior to enrolment. b. Hypersensitivity to rivastigmine c. Dementia diagnosed according to Movement Disorder Society (MDS) criteria. d. Inability to attend or comply with treatment or follow-up scheduling. e. Non-English-speaking patients (cognitive tests performed in English). f. Falling ≥4x per day. g. Unwillingness to use an acceptable method of contraception for the duration of the trial if they are of childbearing potential.
Primary objective	To determine the difference in fall rate between people with Parkinson's disease treated for 12 months with a cholinesterase inhibitor and those treated with placebo.
Primary outcome	Fall rate over 12 months

Secondary objective	a) To determine the effect of 12 months of treatment with ChEi versus placebo on: i. PD severity ii. Freezing of gait iii. Frailty and physical performance iv. Cognition v. Depression vi. Fear of falling vii. Dysphagia viii. Participant health related quality of life and capability ix. Carer quality of life x. Mortality xi. NHS, social service, and informal care costs and hospital admissions. b) To determine the overall cost-effectiveness of the treatment measured with EQ-5D-5L.
Study duration	51 months

TRIAL FLOWCHART



DeNDRoN: Dementia and Neurodegenerative Diseases Research Network; PRO-DeNDRoN: Parkinson's Register of the Dementias and Neurodegenerative Diseases Research Network; P-UK: Parkinson's UK; NHS: National Health Service; PICS: Patient Identification Centers; HES: Hospital Episode Statistics; Telephone calls

TRIAL PROTOCOL TITLE

CHIEF-PD (CHolinesterase Inhibitor to prEvent Falls in Parkinson's Disease): A phase 3, randomised double-blind, placebo-controlled trial of rivastigmine to prevent falls in Parkinson's disease.

1. BACKGROUND AND RATIONALE

Cognitive impairment and gait dysfunction commonly coexist and are potent antecedents of falls in other neurodegenerative conditions including dementia, stroke, frailty and ageing. Parkinson's disease (PD) is second only to Alzheimer's disease, as the most common neurodegenerative disease.

There is a high incidence of falls in patients with PD. A quarter of people with PD fall at least once a month and they are twice as likely to fall on recurrent occasions compared to older people. Falls lead to hospital admissions, hip fracture, fear of further falling, increased dependency and nursing home placement. Reduced mobility is associated with constipation, pressure sores, poor sleep and osteoporosis.

To compensate for gait slowing and instability people with PD need to pay more attention to their walking in order to not fall. However, even in early disease, executive dysfunction attenuates the cognitive attentional resource that is available. Stability is particularly compromised during the execution of complex motor activities (e.g. turning) or whilst walking and performing concurrent tasks where demands on attention outweigh available resource. Gait therefore becomes unstable and falls occur.

The propensity to fall results from underlying loss of cholinergic function in cognitive (frontocortical) and gait (mesencephalic locomotor area) critical brain areas. Animal studies have established that the dual loss of dopaminergic and cholinergic networks precipitates gait instability, freezing of gait and falls in PD (1). Amelioration of this underlying cholinergic deficient with cholinesterase inhibitors (ChEis) represents a promising strategy, targeting the aetiology of falls in PD. Efficacy has been suggested in 3 small, phase 2 trials (2–4) .

A phase 3 trial is required with a larger sample to definitively estimate the clinical and cost effectiveness of ChEis in this population. This will determine whether the reduction in falls achieved in small single centre studies can be matched in a larger multi–centre trial delivered in standard NHS clinics. Unlike phase 2 trials, the treatment will be delivered as in clinical practice (transdermally, over a longer time, at higher doses). The trial will specifically determine a) clinical and cost - effectiveness b) the impact of treatment on health and Quality of Life measures and c) whether the intervention operates through cognitive improvement. Emergent evidence suggests that there may a relationship between gait, falls and dysphagia with exploratory data showing a correlation between dysphagia severity and falls efficacy (15). Quantification therefore of the degree of dysphagia will be undertaken as these axial symptoms that are refractory to dopaminergic therapy may share non-dopaminergic pathophysiology in the brain that can be targeted with ChEi therapy.

This multi-centre double-blind Randomised Control Trial (RCT) will establish whether ChEi compared to placebo prevents falls. CHIEF-PD will provide definitive evidence that can be immediately translated into clinical practice. Powered to detect a treatment effect that is meaningful to clinicians and patients it will also establish the cost-effectiveness of the treatment in preventing falls which are potentially devastating for patients and expensive for the NHS. Positive findings will provide robust evidence to change clinical practice.

2. AIMS AND OBJECTIVES

2.1. Aim

To determine whether ChEi treatment reduced the rate of falls in Parkinson's and is cost-effective.

2.2. Primary objective

To determine the difference in fall rate over 12 months between people with PD treated for 12 months with a ChEi and those treated with a placebo.

2.3. Secondary objectives

a) To determine the effect of 12 months of treatment with ChEi versus placebo on
   i. PD severity
   ii. Freezing of gait
   iii. Frailty and physical performance
   iv. Cognition
   v. Depression
   vi. Fear of falling
   vii. Dysphagia
   viii. Participant health related quality of life and capability
   ix. Carer quality of life
   x. Mortality
   xi. NHS, social service, and informal care costs and hospital admissions.

b) To determine the overall cost-effectiveness of the treatment measured with EQ-5D-5L.

2.4. Primary outcome measure

The primary outcome is fall rate measured using monthly diaries and telephone calls prospectively over 12 months from the day the IMP is commenced. A fall is defined as "unintentionally coming to rest on the ground or other lower surface without overwhelming external force or a major internal event" (5).

2.5. Secondary outcomes: (measured at baseline and 12 months unless stated)

Outcome	Tool / method
Parkinson's Disease (PD)	MDS-UPDRS total score in the practically defined 'ON' state and each individual subscale (1-4),
Freezing of gait	New Freezing of Gait Questionnaire (NFOGQ)
Frailty and physical performance	Short physical performance battery (SPPB), gait speed and frailty status
Cognition	Montreal Cognitive Assessment (MoCA) and
Depression	Geriatric Depression Scale (GDS)
Fear of falling	Iconographical Fall Efficacy Scale (ICON-FES)
Dysphagia	Swallowing Disturbance Questionnaire (SDQ)
Participant health related quality of life	EuroQoL 5D-5L health status questionnaire (EQ-5D-5L) (at baseline,1,3,6 9 months and 12 months)
Care-related quality of life	Carer Experience Scale (CES)
Capability of older people	ICEpop CAPability measure for Older people (ICECAP-O)
Mortality (all cause and PD-related)	Office of National Statistics (ONS) data (at 12 months)
Cost effectiveness and NHS resource use	EQ-5D-5L and NHS Hospital Episode Statistics (HES) data

3. TRIAL DESIGN

A multicentre, phase 3, RCT of the ChEi rivastigmine versus placebo to prevent falls in PD.

4. TRIAL SETTING

This trial will be delivered in a secondary care setting across >26 sites in the United Kingdom.

Sites will be selected based on their research capacity and capability.

5. ELIGIBILITY CRITERIA

5.1. Subject population

People with PD residing in the community and care homes recruited across the UK.

5.2. Inclusion criteria

a. Diagnosis of idiopathic Parkinson's disease.
b. Modified Hoehn and Yahr stage 1-4 disease as determined at baseline visit.
c. Have experienced a fall in the previous year.
d. Able to walk ≥10m without aids or assistance.

5.3. Exclusion criteria

a. Previous ChEi use in 12 months prior to enrolment.
b. Hypersensitivity to rivastigmine
c. Dementia diagnosed according to MDS criteria (6).
d. Inability to attend or comply with treatment or follow-up scheduling.
e. Non-English-speaking patients (cognitive tests performed in English).
f. Falling ≥4x per day.
g. Unwillingness to use an acceptable method of contraception for the duration of the trial if they are of childbearing potential.

5.4. Operationalisation of criteria

Clinically probable PD is defined as bradykinesia in combination with at least 1 of rest tremor or rigidity, the absence of absolute exclusion criteria and the balance of red flags counterbalanced by supportive criteria as detailed in the trial manual.

Hoehn and Yahr staging range is 1 (Unilateral involvement only) through to 4 (Severe disability; still able to walk or stand unassisted)

A fall is defined as "unintentionally coming to rest on the ground or other lower surface without overwhelming external force or a major internal event" (5)**.**

Hypersensitivity to rivastigmine is usually related to the development of allergic contact dermatitis.

Dementia diagnosed according to the MDS criteria requires Parkinson's disease diagnosed before the onset of dementia and decreased cognition, sufficient to impact daily living that cannot be attributed to motor or autonomic symptoms.

5.5. Potential participants who are at higher risk of adverse effects

Certain conditions (sick sinus syndrome or conduction defects (sino-atrial block, atrio-ventricular block; active or predisposition to gastric or duodenal ulcers; urinary obstruction, seizures; asthma or obstructive pulmonary disease and clinically significant hepatic impairment). These conditions are NOT exclusion criteria and no additional monitoring is required but the PI should consider this risk during the eligibility assessment process. The PIB explains this additional risk to potential participants

5.6. Co-enrolment in other research studies

If potential participants are enrolled in other clinical trials, due care will be paid as to the burdens of co-enrolment in this trial. Enrolment will be considered on a case-by-case basis taking into consideration other factors such as comorbidities, social support and distances necessary to travel. Participants taking part in another CTIMP cannot be enrolled in this trial.

5.7. Prior and concomitant therapies

Treatment with other cholinesterase inhibitors or memantine are not permitted during the trial.

In the event of a participant requiring a general anaesthetic, participant will carry a card with them that will inform any medical professionals they encounter that the participant is part of the trial and potentially taking a ChEi.

Participants will be advised that there is a theoretical risk of interference with anticholinergic medications but that concomitant use is not contraindicated. The use of dietary and herbal supplements (including e.g. vitamin D and calcium supplements, cod liver oil) during the trial is NOT prohibited.

5.8. Emergency contact procedure for participants

Details of what a participant should do if they experience any problems or side effects whilst taking part in the trial is detailed in a “how to take your medications” booklet. If the participant experiences mild symptoms, they are advised to leave the patch in situ and inform the trial team. Participants are provided with contact details for the central research team and details of their local research site team.

If a symptom is troublesome or serious (explained in the PIB) they are advised to seek medical help in the normal way e.g. via 111, their GP, or in an emergency phoning 999 or via an Emergency Department. The central trial team will ONLY advise a participant action to take with respect to the IMP and will not provide any other medical advice.

Each participant will be given a card to carry indicating that they are participating in the CHIEF_PD which they can show to any health professionals involved in their care.

6. RECRUITMENT

6.1. Identification

Six hundred participants will be recruited and randomised over a 2-year period. The following routes of recruitment will be used;

6.2. Clinical lists and local advertising

Potential participants will be identified locally at sites by PD specialists, PD specialist nurses, local and regional network staff reviewing clinical lists and /or local databases. Recruitment posters will be displayed locally.

6.3. Research registers

We will interrogate the ProDeNDRoN (Parkinson's Register of the Dementias and Neurodegenerative Diseases Research Network) database which is an inclusive register of research interested participants in South West England, who have agreed to be approached about new studies. We will utilise other organisations such as Parkinson's UK who host the Parkinson's UK Research Network and the Cure Parkinson's Trust.

6.4. National organisations and committees

We will utilise the established Parkinson's Portfolio Development Group (PDG) and the NIHR neurodegeneration network to further enhance recruitment. Leads for the UK Parkinson's Excellence Network and other local organisations such as National Institute for Health Research Clinical Research Networks (NIHR CRN) will disseminate the opportunity to participate to members in their regions.

6.5. Publicity

We will utilise various media outlets to publicise the opportunity to participate in the research. Details of the trial will be posted on the area of the relevant websites (such as Parkinson's UK, Fox Trial Finder, etc.) that advertise taking part in clinical trials. Potential participants may approach the central or site teams directly having read about the trial e.g. from online trial registries or through word-of-mouth. Posters will also be placed around participating sites especially within PD clinic areas. Participants that contact the central trial team will be directed towards their closest active site and the research team will ensure that the site has received the green light from the Sponsor before enrolling participant into the trial.

6.6. Screening and consent

Potential participants will be given a Participant Information Booklet (PIB) to read (via various routes including by post (including a covering letter) or website) and a pre-paid reply slip to return to the local site trials team indicating if they wish to take part or not. They will be given at least 24 hours (although in practice this is likely to be longer) to consider the information. If no reply slip is received the local site research staff may contact the participant by phone to see if they would like to take part in the trial.

Paper screening logs will be kept that include where possible, reason for non-participation. The details of the screening will be added to the database by site staff. This will ensure that participants are not approached more than once and will highlight participants that are willing to be contacted in future (e.g. due to an acute intercurrent illness at that time).

Willing and potentially eligible participants will be invited for a screening/baseline visit at their local site. Formal eligibility screening will be conducted by the local research team, this will be documented in the participant CRF. Eligibility of participants will be confirmed by a medically qualified doctor. Consent will be sought by the local research team by someone with the appropriate training and experience. A copy of the consent will be filed in the participant's hospital notes with a record of the discussion and copy of the PIB. A copy of the consent form will be sent to the central research team.

Participants will be reimbursed for travel and parking related expenses. There will be no other financial incentive to participate.

6.7. Randomisation

The randomisation sequence will be generated by the Bristol Randomised Trials Collaboration (BRTC) Clinical Trials Unit (CTU) using their online randomisation system. Participants will only be randomised after eligibility and consent have been confirmed. Randomisation will be stratified by site and by the following three minimisation criteria (number of falls in previous year (1-4 falls low, 5+ high); age (18-64 low, 65 + high) and cognitive impairment measured using MoCA (1-25 low, 26-30 high)). Participants will be allocated to each treatment group using the minimisation method with a probability of 0.8.

The PI (or authorised delegate) will log onto the online randomisation system, enter the minimisation variables and then receive the code that allocates the participant to a treatment pack. They and the participant will remain blinded as to which treatment group this code refers to. The unblinded randomisation code will be held by the site pharmacy and BRTC. Trial participants will be allocated to one of two treatment groups (active rivastigmine patch or matched placebo patch).

6.8. Internal pilot

Participants will be recruited over a 2-year period. Participant and site recruitment will be reviewed at 9 months and assessed on an ongoing basis. If >90% of expected participants and >50% sites have been recruited, the trial will continue. If 50%-89% of expected participants and / or <49% of expected sites have been recruited, then the TMG will identify remediable factors and discuss with the TSC and submit recovery plan to HTA with new targets for the following 6 months. If <50% of expected participants are recruited and/ or <25% of expected sites are actively recruiting, we will stop the trial unless there is a strong case that unanticipated remediable factors have been identified and can be addressed after further discussion with the funder (Table 1).

Table 1 Internal pilot 'Stop / Amend / Go' criteria

	Participants		Sites	Anticipated action
GO (green)	>=90% of expected patients recruited (104 patients)	AND	>=50% of expected sites actively recruiting (13 sites)	Continue
AMEND (amber)	50%-90% of expected patients recruited (58 – 104 patients)	AND/ OR	and/or <49% of expected sites actively recruiting (<13 sites)	Identify remediable factors, discuss with TSC and submit recovery plan to HTA with new targets for the following 6 months
STOP (red)	<50% of expected patients recruited (<58 patients)	AND/ OR	<25% of expected sites actively recruiting (<7 sites)	Stop the trial unless there is a strong case that unanticipated remediable factors have been identified and can be addressed

6.9. Planned recruitment rate

The aim is to recruit a conservative 1.18 participants per site / per month or 14 participants per site per year until we have reached our target recruitment of 600 participants. This considers staggered recruitment of sites.

7. TRIAL PROCEDURES

7.1. Schedule of assessments

Participants in the trial will undergo a face-to-face assessment at baseline (0 months) and follow-up (12 months).

Research staff at the sites will complete assessments at baseline (time 0), and final visit (12 months). Monthly phone calls to participants will be coordinated centrally (from Bristol) by research assistants, blinded to treatment status. These phone calls remind participants to return their fall diaries and screen for adverse events and collect data on health care use and quality of life. Table 2 summarises the assessment schedule and outcomes measured at each time point.

Table 2 Schedule of assessment visits and outcomes measurement

Month	0	1	2	3	4	5	6	7	8	9	10	11	$12^{+/-10}$
Activity													
Procedures													
Eligibility criteria review	●												
Informed consent	●												
Sociodemographics	●												
Medical history	●												
Drug history	●												●
Examination (HR, BP, height, weight, MDS-UPDRS III, frailty, gait, SPPB)	●												●
Falls	●	●	●	●	●	●	●	●	●	●	●	●	●
MoCA	●												●
GDS	●												●
MDS-UPDRS I, II, IV	●												●
NFOGQ	●												●
ICON-FES	●												●
SDQ	●												●
ICECAP-O	●												●
EQ5D-5L	●	●		●			●			●			●
CES**	○												○
Medication													
IMP dispensing	●		●					●					
IMP return			●					●					●
Safety													
Adverse events		●	●	●	●	●	●	●	●	●	●	●	●
ECG*	○												
Formal & informal care use		●		●			●			●			●
Hospital care and mortality	**(HES via NHS Digital and ONS data linkage)**												

*IMP: Investigational Medicinal Product, SPPB: Short Performance Physical Battery MDS-UPDRS: Movement Disorder Society-Unified Parkinson's Disease Rating Scale NFOGQ: New Freezing of Gait Questionnaire ICON-FES: Iconographical Falls Efficacy Scale GDS: Geriatric Depression Scale MoCA: Montreal Cognitive Assessment CES: Carer Experience Scale. SDQ: Swallowing Disturbance Questionnaire*ECG as per arrythmia safety protocol **Completed by carer*

7.1. Pre-baseline visit (month -1)

Potentially eligible participants identified from clinic lists and other recruitment strategies (see section 6.1) will be given a Participant information booklet (PIB) and invited to attend clinic for baseline visit.

With their appointment letter they will be sent the following self-completed questionnaires to complete (ideally but not essentially) **prior** to the visit to minimise fatigue and burden. If they are unable to self-complete these can be facilitated by the researcher during the visit. In respect to consent, the cover of this questionnaire booklet clearly articulates that if the questionnaires are completed pre-visit but the participant declines to participant or is ineligible these data will not be retained. This arrangement is explained in the PIB.

- Appointment Letter
- MDS-UPDRS Parts I and II performed in the practically defined ON state (defined as patients taking their normal daily medications in the optimally medicated state)
- NFOGQ
- ICON-FES
- ICECAP-O
- GDS
- SDQ
- EQ5D-5L

7.2. Baseline visit (month 0)

At the baseline visit, the eligibility criteria will be reviewed by a medically qualified doctor, the trial explained, and informed consent obtained. The following assessments and procedures will be completed:

- Review eligibility criteria
- Obtain written informed consent
- Collection of sociodemographic data, medical and drug history including previous falls
- Brief examination: heart rate (+/-ECG as per the trial specific instructions), lying and standing blood pressure, height and weight, MDS-UPDRS III, IV, frailty and dual task gait assessment (consisting of 2, 10m walks, one of which will be performed with a dual (naming) task), SPPB.
- Neuropsychometry: MoCA
- Quality of life and cost effectiveness: EQ-5D-5L

7.3. Diaries and telephone calls (monthly)

Falls and concordance with the IMP will be recorded using a diary. Participants will receive a diary on entry to the trial that includes detailed instructions. The fall calendars will be returned monthly to the central trial team in pre-paid envelopes provided. Participants will be telephoned monthly and asked to corroborate information returned in the diary. In the event of a diary not being returned the team will prompt the participant at the next phone call or record the information during the call.

Participants will be asked about the occurrence of any adverse events and where necessary, advised according to clinical judgement of the central research nurse and local research team (blind to treatment allocation), in conjunction with the relevant trial specific instructions about adjustment of dose (see section 8.2 Titration side effects). This information will be communicated securely to the site team. Participants will be given telephone numbers of their local study team and the central research team to seek advice at any point during the trial.

7.4. Dispensing visits

Participants will be provided with the active or placebo patches at baseline, at the end of 2 and 7 months. Participants will be required to attend their local site pharmacy to collect the boxes of patches. This is covered in detail in Section 8.6.

7.5. End of treatment visit (week 52)

In the same manner as the baseline visit, participants will be sent questionnaires in the post to complete prior to the end of treatment visit. The following assessments will be performed as per Table 2. The participants bring the completed questionnaires to their visit. If they are unable to complete them then the research nurse can assist at the visit.

Completed pre-appointment

- MDS-UPDRS Parts I and II performed in the practically defined ON state (defined as patients taking their normal daily medications in the optimally medicated state)
- NFOGQ
- ICON-FES
- ICECAP-O
- GDS
- SDQ
- EQ5D-5L

Completed at visit

- Review of medical and drug history and falls sustained (if required)
- Brief examination: heart rate, lying and standing blood pressure, height and weight, MDS-UPDRS III, IV, frailty and dual task gait assessment ((consisting of 2, 10m walks, one of which will be performed with a dual (naming) task), SPPB.
- Neuropsychometry: MoCA
- Quality of life and cost effectiveness: EQ-5D-5L

7.6. Blinding

The central research team, investigator site staff and participants will be blinded to the allocation of treatment group, except for the Junior Trial Statistician and Data Manager, and local hospital Pharmacist.

7.7. Unblinding

Treatment codes will only be released to the investigative team once written confirmation has been received that the trial database has been locked. Each investigator site pharmacy will then send the central research team a list of all participants and their treatment allocation. Participants will be informed of their allocation by the central trial team after the trial has concluded. Following each randomisation, coding information will be sent to the central research team to ensure protocol deviations and stock control are managed.

7.8. Emergency Unblinding

The safety profile of the IMP within the trial is well established, therefore unblinding should not be expected unless clear clinical need dictates this. In the event of a medical emergency the participant's treating physician will contact the local site pharmacy who will hold the unblinding codes. Sites will follow the trial specific instructions for unblinding.

7.9. Withdrawal from the trial

Participants can choose to withdraw for any reason at any time during their involvement in the trial. The PI can also decide to withdraw participants based on clinical opinion at any time during the trial. This section does **not** include treatment discontinuation (see 8.2)

Examples *of a complete withdrawal from all trial related activity would be:*

- Participants who become ineligible due to some of the exclusion criteria listed in section 5.3 of the protocol, namely criterion (c), Dementia diagnosed according to MDS criteria, (d) Inability to attend or comply with treatment or follow-up scheduling and (g) Unwillingness to use an acceptable method of contraception for the duration of the trial if they are of childbearing potential.
- any change in the participant's condition (i.e. the participant progresses to develop dementia) which warrants the use of cholinesterase inhibitor treatment which means equipoise no longer exists about the use of rivastigmine or other ChEi,
- inability to attend or complete assessments that in the opinion of the investigator warrants withdrawal from the trial
- intercurrent illness as determined by the PI.

In the event of any form of withdrawal, participants will be requested to return the treatment packs to their local recruiting hospital pharmacy department. Data obtained up to this point will be retained for analysis.

7.10. End of Trial

The end of trial for CHIEF-PD will be when the last patient has completed their 12 month visit which includes completion of the 12 month questionnaire and diary, and subsequent data analysis.

7.11. Carer Involvement

Primary carers will be recruited concurrently to assess the impact of treatment on the participant's care needs on carers. Their involvement is detailed in Appendix 1). A carer is defined as an individual who undertakes informal or formal care responsibility for the participant. The carer will be approached only with the agreement of the participant and be consented separately. If carers do not wish to consent to take part, or if there is no carer, the participant is still eligible to participate in the trial.

8. INTERVENTION / IMP

8.1. General information

Rivastigmine is a reversible non-competitive inhibitor of acetylcholinesterase. It is currently licensed for use in mild to moderate dementia in PD and in mild to moderate dementia in Alzheimer's disease.

8.2. Assessment and management of risk

This trial is categorised as 'Type B' according to the MHRA (testing authorised medicinal products according to treatment regimens outside the marketing authorisation). Rivastigmine is marketed and used in participants with Parkinson's Disease dementia. Its safety profile is well characterised.

Using Rivastigmine for falls represents a new indication in an essentially established patient group albeit without dementia. Up-titration to (now licensed) 13.3mg is routine in clinical practice.

It is not anticipated that application of placebo represents any risk above that of standard care.

8.3. Supply of the IMPs

The active and placebo transdermal patches will be supplied by:

Luye Pharma AG, Am Windfeld 35, 83714 Miesbach, Germany.

They will perform QP release before shipping to Sharps for packaging and labelling.

8.4. Packaging and labelling of IMP

The IMP and placebo will be packaged and labelled by:

Sharp Clinical Services (UK) Ltd, Waller House, Elvicta Business Park, Crickhowell, Powys, NP8 1DF.

The core label texts for all packaging will comply with the requirements of Annex 13 of the Rules Governing Medicinal Products in the European Union and the national laws in force in the UK. Sharps will perform QP release prior to release to greenlighted sites for onward dispensing by site pharmacy to patients.

8.5. Return and destruction of IMP

Any IMP that is returned by participants will be destroyed in line with the local site's pharmacy trial specific instructions on the disposal of IMP.

8.6. Administration and routine titration

There are 3 strengths of patch. All patients will commence LOW dose (4.6mg / 24 hours) patches with the aim to escalate up through MEDIUM dose to HIGH dose (Figure 1).

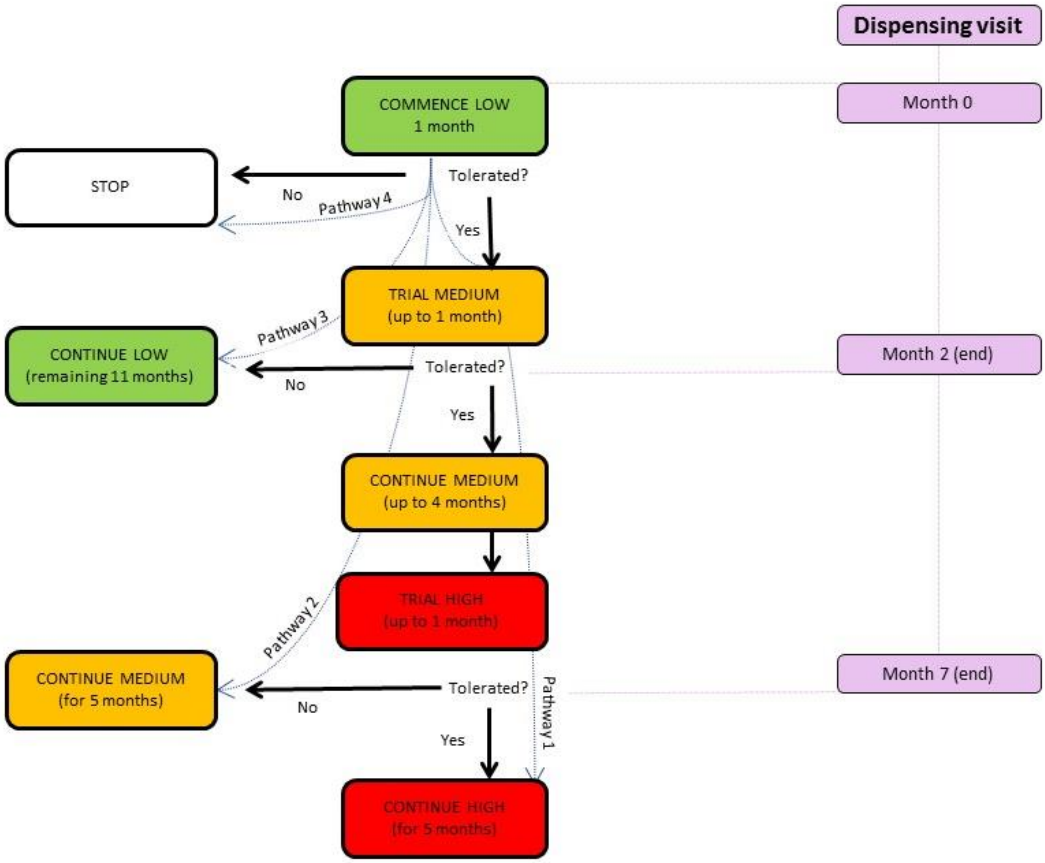
After one month of LOW dose, participants will escalate to the MEDIUM (9.5mg/ 24 hours) patch. They will remain on this for 5 months. After 6 months (1 month LOW, 5 months MEDIUM) they will escalate to the HIGH (13.3mg dose), having followed pathway 1.

If they do not tolerate the LOW dose the IMP will be discontinued, having followed pathway 4.

If they do not tolerate the MEDIUM dose they will remain on LOW dose for the remaining 11 months of the trial having followed pathway 3.

If they do not tolerate the HIGH dose, they will remain on MEDIUM dose for the remaining 11 months of the trial having followed pathway 2.

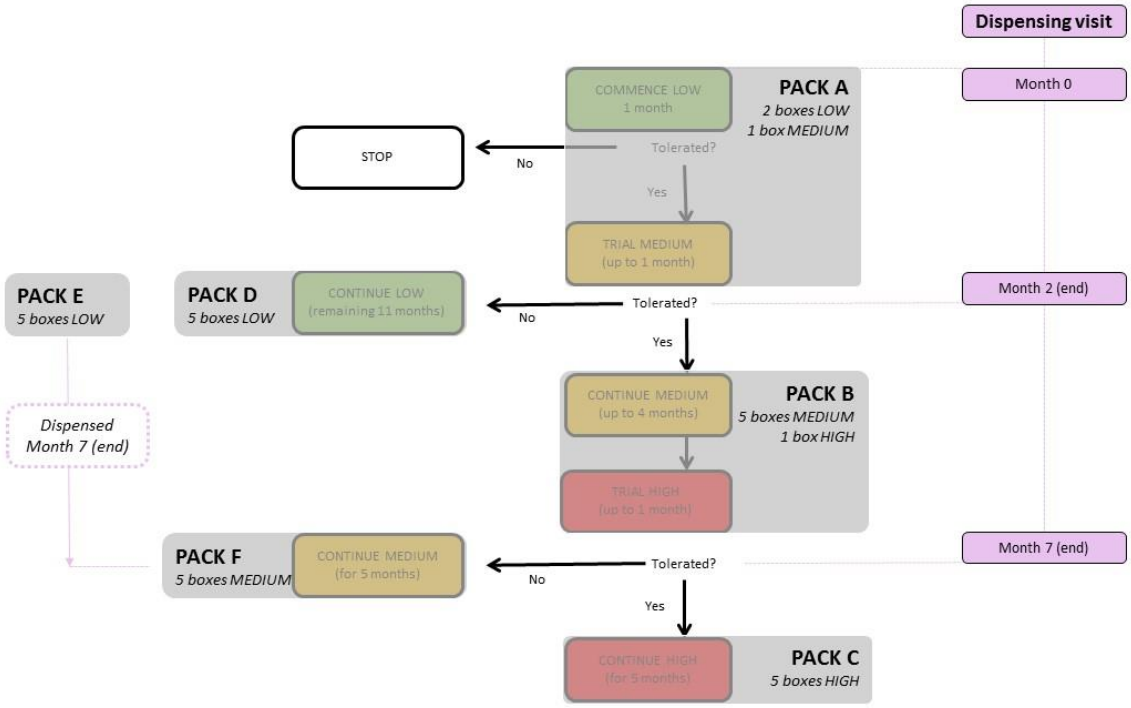
Figure 1 Titration of IMP according to tolerability



Key *Low: 4.6mg/day Medium: 9.5mg /day High: 13.3mg / day*

Medication packs will be dispensed at month 0 and end of months 2 and 7. Each pack allows for a one-month trial of up titration to the next dose prior to the next pack being dispensed. This is shown diagrammatically overlaying the titration illustration in Figure 2.

Figure 2. Medication packs dispensed at months 0, 2 and 7 depending on tolerability.



Key *Low: 4.6mg/day Medium: 9.5mg /day High: 13.3mg / day*

8.7. Common side-effects

Application site skin reactions (usually mild to moderate application site erythema), are the most frequent adverse reactions observed with the use of rivastigmine transdermal patch. The next most common adverse reactions are gastrointestinal upset including nausea and vomiting.

8.8. Titration for side effects

In the event of a participant experiencing side effects the central and local research team will refer to the relevant trial specific instructions. This will determine whether down titration or ceasing the IMP is necessary. Whilst this decision is taken centrally it will be done according to pre-specified instructions and discussion with the site CI and /or treating clinician (e.g. Parkinson's specialist) will be undertaken if clinically necessitated. This will be communicated to the site team via (secure) email with the relevant prescription form attached to be signed by a medically qualified doctor at site.

The same dosing schedule will be applied to participants in both groups with dummy dose titration being applied to the placebo group. Compliance will be monitored using the diary.

If the participant discontinues the medication because of unacceptable side effects or by choice, then they remain enrolled in the trial (unless they explicitly withdraw see section 7.9) and will complete the further assessments as per protocol.

8.9. Dispensing of IMP

Each investigator site pharmacy will be responsible for dispensing the IMP and will maintain the IMP dispensing log. The pharmacy staff member who hands the pack to the participant or site nurse will be blinded. The trial pharmacist who fulfils the trial prescription will be unblinded.

Local hospital pharmacies will be required to nominate a research pharmacist and deputy who will be responsible for the IMP at site. Storage instructions, dispensing and alike will be detailed in a trial specific working instruction.

8.10. Post-trial

Continuation of the treatment following the end of the intervention phase is the responsibility of the participant's normal PD clinician, an arrangement which is explicitly described in the PIB and site agreements.

8.11. Drug accountability

Activity	Responsibility
Supply of IMP, placebo and overtapes	Luye Pharma AG
Provision and QP of IMP, placebo and overtapes to Sharps Clinical Services	Luye Pharma AG
Package and labelling of IMP and placebo	Sharps Clinical Services
QP release IMP and placebo to site pharmacies	Sharps Clinical Services
Receive IMP/placebo and overtapes and store appropriately	Site pharmacy
Dispense IMP/placebo and overtapes in line with randomisation schedule to participant	Site pharmacy
Maintain dispensing log	Site pharmacy
Report stock levels at site	Site pharmacy
Arrange additional deliveries of IMP/Placebo and overtapes at site	Sharps Clinical Services
Return of unused trial medicines	Participants will return unused medicine to recruiting site
Destruction of unused trial medicines	Site pharmacy

Activity	Responsibility
Unblinding	Site pharmacy

9. TRIAL DATA

Collection of sociodemographic information will facilitate defining the population studies including comorbidities, medication use and fall history. Neuropsychometric testing will be performed using MoCA which is one of the Movement Disorder Society recommenced scales for the Level 1 assessment of PD-MCI. The concurrence of depression can confound interpretation of cognitive function and will therefore be measured using the MDS recommended Geriatric Depression Scale (GDS). Fear of falling will be measured using the Iconographical Falls Efficacy Scale (ICON-FES) and dysphagia using the Swallowing Disturbance Questionnaire which is validated in PD (7, 16).

The new Freezing of Gait Questionnaire (NFOGQ) is a validated tool that detects FOG and assesses impact and severity of FOG episodes. PD severity is quantified using the MDS-UPDRS scale which captures non-motor and motor symptoms and signs and is the recognized gold standard in clinical PD trials. Functional physical performance will be assessed using the Short Physical Performance Battery (SPPB). Questions from the SHARE-FI index and assessment of grip strength be used as part of the frailty status assessment. Functional performance will be assessed using the short physical performance battery (SPPB) as well as timed gait assessment with and without dual task. This is designed to stress attentional resource between a physical and cognitive task to better elucidate underlying gait and cognitive dysfunction. Quality of life will be assessed using EQ-5D-5L to calculate QALYs. We will collect the EQ-5D-5L at the baseline and 12-month research clinic visits. We will also administer the EQ-5D-5L by telephone at 1, 3, 6- and 9-months post-randomisation to measure the quality of life trajectory during the trial

A well-being measure, ICECAP-O will be used at baseline and 12 months, to capture the broader impact of PD-falls on participants. ICECAP-O is a relatively new measure of capability in older people which has been previously used in patients with PD (8). In participants who have a primary carer who is also willing to take part in the trial and attend baseline and 12-month research clinics, we will use the Carer Experience Scale (CES) (9) to determine the impact of participant's care needs on carers. The CES focuses on 'care-related quality of life' rather than health-related quality of life, comprising attributes that are pertinent to family and friends who act as informal carers.

10. PHARMACOVIGILANCE

Please refer to the Safety Reporting section of the trial manual for additional information in this section.

10.1. Operational definitions

Pharmacovigilance will be carried out in accordance with the requirements set out by the European Commission Detailed Guidance CT-3 2011 including the terminology of adverse events and reactions and the assessment of seriousness, causality and expectedness of an event.

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product "means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions. It is important to note that this is entirely separate to the known side effects listed in the SmPC. It is specifically a temporal relationship between taking the drug, the half-life, and the time of the event or any valid alternative aetiology that would explain the event.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.

Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the reference safety information: • in the case of a product with a marketing authorisation, this could be in the summary of product characteristics (SmPC) for that product, so long as it is being used within its licence. If it is being used off label an assessment of the SmPCs suitability will need to be undertaken. • in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question
Suspected serious adverse reaction (SSAR)	A suspected serious adverse reaction (SSAR), is any serious adverse reaction that is suspected (possibly or probably) to be related to the investigational medicinal product/medical device/intervention.

10.2. Classification of Severity

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

10.3. Classification of Relatedness

Not related	Temporal relationship of the onset of the event, relative to administration of the intervention, is not reasonable or another cause can by itself explain the occurrence of the event.
Unlikely to be related	Temporal relationship of the onset of the event, relative to administration of the intervention, is unlikely and it is likely there is another cause which can by itself explain the occurrence of the event.
Possibly related	Temporal relationship of the onset of the event, relative to administration of the intervention, is reasonable but the event could have been due to another, equally likely cause.
Probably related	Temporal relationship of the onset of the event, relative to administration of the intervention, is reasonable and the event is more likely explained by the intervention than any other cause.
Definitely related	Temporal relationship of the onset of the event, relative to administration of the intervention, is reasonable and there is no other cause to explain the event, or a re-challenge (if feasible) is positive.

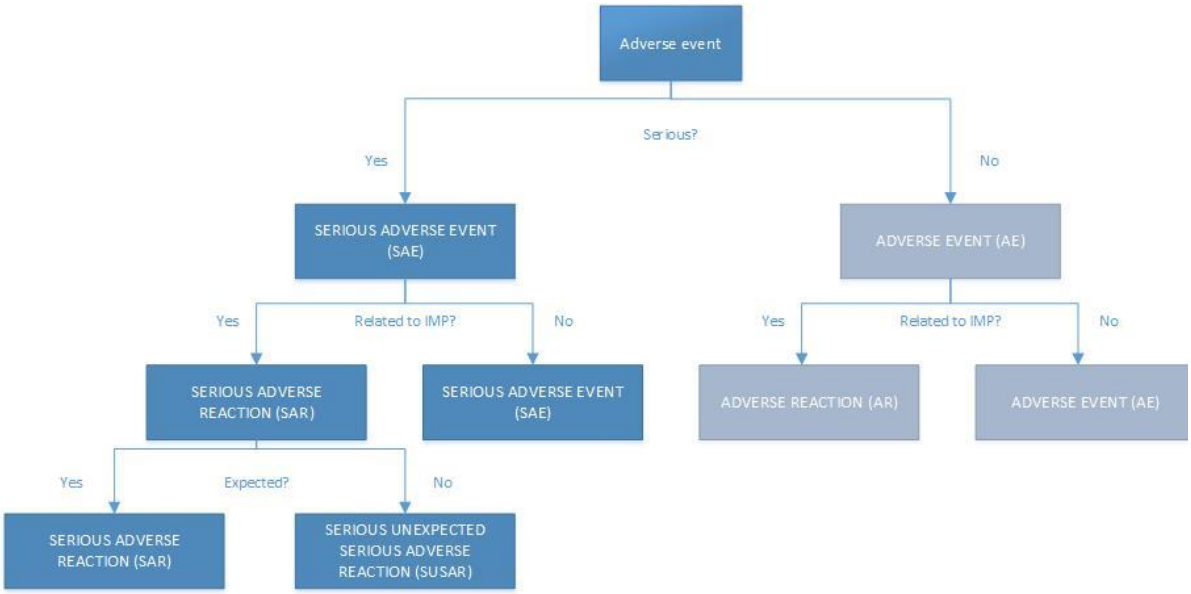
10.4. Classification of Expectedness

Expected	Reaction previously identified and described in the Summary of medicinal Product Characteristics (SmPC).
Unexpected	Reaction not previously described in the Summary of medicinal Product Characteristics (SmPC).

10.5. Adverse events classification flowchart

For each adverse event the seriousness, relatedness and expectedness will be determined (as per the definitions above) in order to appropriately classify the episode as per Figure 3.

Figure 3 Classification of adverse events flowchart



10.6. Adverse Events (AEs)

Only non-serious adverse events that are assessed as being possibly, probably or definitely related to the IMP (adverse reaction AR), will be reported from the time a signed and dated informed consent form is obtained until completion of the last trial-related procedure. Non-serious adverse events (with the exception of falls) that are **unrelated to the IMP** will not be reported. The expectedness of an adverse reaction shall be determined according to the current approved Summary of medicinal Product Characteristics or Investigators Brochure (IB).

AEs will be recorded by the research team at sites or centrally, in the CRF. It is anticipated that the majority of AE's will be detected via the monthly telephone calls. The central site team will communicate with the local PI and site team if additional information is required to e.g. determine causality. If a patient attends a routine (i.e. non-trial related appointment) and an AE is reported, the site research teams will assess and log this according to the same working instructions. AE's will be reviewed by the DMC at the next booked meeting.

10.7. Serious Adverse Events

Any SAE (regardless of relatedness) will be recorded and reported within 7 days of becoming aware of the event. Hospitalisation for an elective procedure or for a pre-existing condition (prior to study entry) which has not worsened, does not constitute a serious adverse event. All SAEs will be followed until resolution.

Reporting will be performed in accordance with the reporting framework (Appendix 2) for SAE's. All SAE's (SAR, SUSAR, SAE) will be reported to the Sponsor and DMC on a quarterly basis.

10.8. Suspected Unexpected Serious Adverse Reactions (SUSARS)

SUSAR's will be reported to the Sponsor, MHRA, REC and DMC within 15 days or, if life threatening or resultant in death, 7 days.

Occurrences meeting the definition of unexpected serious adverse event (SUSAR) will be reported using the Serious Adverse Event Form, including SAEs spontaneously reported to the Investigator within 30 days after the participant has completed the intervention phase of the trial. University Hospitals Bristol NHS Foundation Trust (UH Bristol), on behalf of the Sponsor, will evaluate any safety information that is spontaneously reported by the CI beyond the time frame specified in the protocol.

10.9. Urgent safety measures

Please refer to the trial specific instructions for Safety Reporting for further details.

10.10. Notification of deaths

All deaths occurring during the intervention phase of the trial or within 28 days after the last dose of trial medication will be reported immediately as soon as the central research team become aware.

10.11. Safety reporting period

The Sponsor Adverse Events Reporting Policy incorporates the requirements of the Medicine for Human Use (Clinical Trials) Regulations 2004. UH Bristol, on behalf of the Sponsor, assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. For each participant the end of safety reporting will be 5 days after removal of the last transdermal patch. Any AE's within this period will follow normal reporting procedure.

10.12. Development Safety Update Reports (DSURs)

The sponsor will submit DSURs once a year throughout the clinical trial, or as necessary to the MHRA and where relevant the Research Ethics Committee. The report will be submitted within 60 days of the Developmental International Birth Date (DIBD) of the trial each year until the trial is declared ended.

11. STATISTICS AND HEALTH ECONOMICS ANALYSIS

11.1. Sample size calculation

The mean falls per month on the log-transformed scale in the placebo group from the feasibility data was 0.3 (SD 1.2) and a 25% reduction in falls on the log-transformed scale is -0.2877, so the mean in the Rivastigmine group is 0.0123 on the log-transformed scale. The correlation is 0.589 (lower bound of the 95% confidence interval for correlation found in feasibility trial) between baseline and follow-up measurements of log-transformed fall rate. Using these values in the ANCOVA sample size calculation, we will have 480 (240 per group) participants to detect a 25% difference in mean fall rate with 90% power. We will recruit 600 people assuming a 20% drop out (n=120).

The sample size calculation is based on an Analysis of Covariance (ANCOVA) approach where any variance between individuals in post-treatment falls rate, which is correlated to the corresponding measure taken at baseline, is removed from the error variance resulting in increased statistical power. With one baseline assessment and one post-treatment assessment of outcome, the standard sample size target is reduced by a factor of (1 - r2), where r2 is the squared Pearson's correlation coefficient. This is a standard approach to sample size calculation for quantitative outcome measures, as detailed in Machin et al 1997 (10).

11.2. Statistical Analysis

Simple descriptive statistics will be used to describe all outcomes measures in both treatment groups. For continuous measures we will describe the mean (SD) for normally distributed variables and the median and interquartile range (IQR) if skewed.

The full analysis set will be all participants providing outcome data, in the treatment group to which they were randomly allocated, under the intention-to-treat (ITT) principle. The per protocol set will be all participants who took any dose of the drug for six months or longer, as randomised. These data will be used only in analyses aimed at estimating the treatment effect in those adhering to their allocation.

The primary outcome analysis is a linear regression model of log transformed fall rates, adjusted for participants' age, cognitive impairment, and fall histories at baseline. This will estimate the treatment effect as a percentage change in average fall rates.

Similar regression models to that used in the primary outcome analysis will be used for the analysis of secondary outcomes as statistically appropriate, including time to event models for outcomes such as mortality. These will be adjusted for participants' age, cognitive impairment, and fall histories at baseline (minimisation variables) and the baseline outcome, as appropriate. Sensitivity analyses will inform the interpretation of the primary outcome analysis only by imputing missing primary outcome data, if appropriate. Additional sensitivity analyses will be performed on primary and secondary outcomes by adjusting for any baseline variables which differ by chance between groups by more than 0.5 standard deviations (continuous variables) or 10% (binary variables).

A more detailed statistical analysis plan will be produced and published before the onset of the analyses.

11.3. Analysis of safety endpoints

We will use descriptive statistics to describe adverse events for participants who took one or more dose(s) of the drug (safety set).

11.4. Economic evaluation

Participant consent will be sought to use data linkage (using e.g. NHS number, date of birth) to access data on their hospital care and cost. We will purchase NHS Digital admitted patient (day case & inpatient), outpatient and A&E hospital episode statistics (HES) datasets covering the estimated 3 years from first participant randomised to 12 months after the last participant is randomised. HES datasets are typically available from NHS Digital 3 months after service use. Brief questions (based on the client service receipt inventory) (11) will be used to assess primary and community care use, medications and informal care via telephone interviews at 1, 3, 6, and 9 months and at the 12-month research clinic visit.

Use of hospital, primary and community care will be costed using national unit costs (12,13). Medication costs will be estimated from the British National Formulary. All unit costs will be taken from or inflated to the most recent available cost year. EQ5D-5L responses will be converted into utility scores using English value sets (14). Utility scores will be combined with ONS mortality data to estimate quality adjusted life years.

A secondary objective is to determine whether rivastigmine patches are cost-effective for use in the NHS. The economic analysis will take an ITT approach with imputation of missing data. In the primary economic analysis, we will estimate the cost per QALY gained of rivastigmine patches within the trial follow up period from the perspective of NHS and social services (to aid comparison with NICE appraisals). Based on the current NICE willingness to pay threshold for a QALY of £20,000 we will calculate the net benefit statistic for each participant and use net benefit regression, adjusting for baseline EQ5D-5L scores and other variables outlined above to estimate the incremental net benefit (and 95% confidence intervals) and determine whether rivastigmine is cost-effective at this threshold. Uncertainty will be explored using cost effectiveness acceptability curves to estimate the probability that rivastigmine is cost-effective at a range of plausible cost-effectiveness thresholds. In secondary analyses we will estimate the cost per fall prevented and expand the perspective of the analysis to include informal care costs, carer quality of life and participant wellbeing measures. If the intervention has a sustained effect in reducing falls and is potentially, but not definitively, cost-effective at 12 months, we will develop a simple extrapolation model to assess cost-effectiveness over a lifetime horizon.

12. DATA MANAGEMENT

12.1. Source Data and documents

When a participant consents to enter the trial, they will have a unique participant identification number allocated. Personal data entered directly onto the password protected database and maintained on a SQL Server database system within the University of Bristol will only be accessible to members of the research team. Any data stored on laptops will be encrypted. Any information that is analysed or transferred outside the EEA will be anonymised. Participants will be asked to consent to their name, email address and phone number being stored on the secure database with the central research team.

Data obtained by paper will also be entered onto the password protected database. Information capable of identifying individuals and the nature of treatment received will be held in the database with passwords restricted to CHIEF-PD trial staff. Information capable of identifying participants will not be removed from University of Bristol or clinical centres or made available in any form to those outside the trial, for the exception of NHS digital for linkage.

Consent forms and clinical letters with personal identifiable data will be stored separately in a locked filing cabinet. Participant details will be anonymised in any publications that result from the trial.

Source data for this trial will consist of paper copies of the consent form, participant completed questionnaires, the patient reported falls diary and drawings from the MoCA assessment as well as the electronic case report forms designed specifically for the study.

12.2. Data collection

Clinical outcomes will be assessed by participant-completed questionnaires at baseline and 12 months (completed at home prior to the face-to-face visit or within clinic at their baseline appointment) as well as telephoning participants monthly to ask to corroborate information returned in the diary each month. Case report forms will be completed at the time of the baseline assessment and treatment phase over 12 months.

We are using standardised outcome instruments. The components and timing of follow-up measures are shown in Table 2.

The database will be set up to prompt the central research team when Participant Questionnaires (PQ) are due.

12.3. Case Report Forms (CRFs)

Case report forms at study centres will be completed using the secure trial database. Questionnaires from participants will be identifiable only by participant trial number and will be returned by the participant by post or via electronic means to the central research team. Any paper copies will be stored in a secure locked cabinet in a locked room.

12.4. Data handling and record keeping

Data will be collected and retained in accordance with the Caldicott Principles, UK Data Protection Act 2018 and General Data Protection Regulation (GDPR).

For this trial, research data will be kept for at least 15 years. Personal data (e.g. name and address, or any data from which a participant might be identified) will not be kept for longer than is required for the purpose for which it has been acquired. Documents will be reviewed by the CI before being destroyed.

12.5. Access to data

For monitoring purposes, the PI will allow monitors from the sponsor (or delegate), persons responsible for the audit, representatives of the REC and other Regulatory Authorities to have direct access to source data/documents.

The Data Manager (in collaboration with the Chief Investigator) will manage access rights to the data set. Prospective new users must demonstrate compliance with legal, data protection and ethical guidelines before any data are released. We anticipate that anonymised trial data will be shared with other researchers to enable international prospective meta-analyses (see section 15.9).

12.6. Archiving

This trial will be sponsored by the University of Bristol (UoB) who are also the data custodian. All research data will be retained in a secure location during the conduct of the trial and for 15 years after the end of the trial, when all paper records will be destroyed by confidential means. An archiving plan will be developed for all trial materials in accordance with the University of Bristol archiving policy.

13. TRIAL MANAGEMENT

13.1. Trial Management Group (TMG)

The TMG will have responsibility for the day-to-day management of the trial and will report to the TSC. The TMG will meet on a regular basis with a core working group of staff having frequent progress meetings. They will link to the network of site research teams to facilitate continuous feedback and early troubleshooting of local site issues that arise.

13.2. Trial Steering Committee (TSC)

Trial Steering Committee (TSC) will be established in conjunction with a Trial Management Group (TMG). Membership, responsibilities and reporting mechanisms of the TSC will be formalised in a TSC charter. The TSC will make recommendations/key decisions during the trial to the TMG and minutes will be sent to the funder. The TSC will comprise Prof C Clarke (University of Birmingham) as Chairperson, Miss N Ives as Independent Statistician and Dr R Campbell and Mr M Bond as patient representatives. In addition, Prof Ben-Shlomo (Lead Epidemiologist) and Dr Henderson (CI) and Dr Metcalfe (Lead Statistician) will represent the TMG, Prof J Close, Prof S Lord (Neuroscience Research Australia) and Ms F Lindop (Derby NHS Trust) are gait and falls experts.

13.3. Data Monitoring Steering Committee (DMC)

The Data Monitoring Committee will meet once prior to recruitment of the first participant and convene prior to the TSC meeting to review the adverse event data and any other ethical aspects that arise and report to the TSC. The DMC will comprise Dr T Quinn (University of Glasgow) as Chairperson, Dr A McConnachie and Dr J Burns as independent members. In addition, Dr E Henderson (CI), Dr Metcalfe (Lead Statistician) (open session only) and Miss D Gaunt (Trial Statistician) (attending both open and closed sessions).

13.4. Patient and Public Involvement (PPI)

People with PD will be involved in every phase of the research trial. This will involve group meetings, specific roles on the trial management group, review of the protocol, participant information, consent and data collection forms and informing dissemination of the research findings to participants.

14. MONITORING, AUDIT & INSPECTION

14.1. Monitoring

The trial will be monitored and audited in accordance with the Sponsor's policy, which is consistent with the UK Policy Framework for Health and Social Care Research and the Medicines for Human Use (Clinical Trials) Regulations 2004. All trial related documents will be made available on request for monitoring and audit by the sponsor, the relevant REC and for inspection by MHRA and other licensing bodies.

The University of Bristol holds a Service Level Agreement (SLA) with UH Bristol. Under the Agreement UH Bristol undertakes to monitor and carry out pharmacovigilance for certain UoB sponsored studies. These activities should be carried out in accordance with the SLA, the identified risks, subsequent proposed monitoring and the trial's specific Monitoring Plan.

A Trial Monitoring Plan will be developed by the Sponsor and agreed by the TMG and CI based on the trial risk assessment which may include on site monitoring. This will be dependent on a documented risk assessment of the trial.

The sponsor usually delegates some of the monitoring to the central research team. The following checks would be typical:

- That written informed consent has been properly documented
- that data collected are consistent with adherence to the trial protocol
- that CRFs are only being completed by authorised persons
- that SAE recording and reporting procedures are being followed correctly
- that no key data are missing
- that data is valid
- review of recruitment rates, withdrawals and losses to follow up.

On a regular basis we will monitor the percentage of PD patients that meet the eligibility criteria and report the percentage of participants who consent. To assess the generalisability of the participants, the characteristics of consenting participants and non-consenting will be compared. We will also report to the DMC if requested, preliminary data on event rates observed in the trial population: SAE rates and dropout rates.

14.2. Protocol compliance

There will be no prospective, planned deviations or waivers to the protocol. Accidental protocol deviations will be documented and reported to the CI and Sponsor immediately. They will also be reported to the DMC. In the event of systematic protocol deviations, investigation and remedial action will be taken in liaison with the CI, DMC and the TMG.

A serious protocol breach will be reported to the NHS R & I and Sponsor as soon as possible. The sponsor will determine the seriousness of the breach and whether onward reporting to the REC and MHRA is necessary.

14.3. 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 will be notified immediately of any case where the above definition applies during the trial conduct phase. They will assess the seriousness of any breach as per the appropriate trial specific instructions.

15. ETHICAL AND REGULATORY CONSIDERATIONS

15.1. Governance and legislation

This trial will be conducted in accordance with:

- The Medicine for Human Use (Clinical Trial) Regulations 2004
- Medicines and Healthcare Products Regulatory Agency (MHRA)
- International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines
- UK Policy Framework for Health and Social Care Research
- Data Protection Act 2018
- General Data Protection Regulation

Any amendments to the trial documents must be approved by the sponsor prior to submission to the REC.

Before any site can enrol participants into the trial, the CI or designee will obtain confirmation of capacity and capability for each site in-line with HRA processes along with other documentation required for the sponsor to grant sites with a greenlight letter.

For all amendments the CI or designee will confirm with the Sponsor, the HRA (+/- REC) and sites' R&D departments that permissions are ongoing.

This research trial will be run in accordance with ICH GCP. ICH GCP is an international ethical and scientific quality standard for designing, conducting, recording and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that originated in the Declaration of Helsinki and that the clinical trial data are credible.

15.2. Research Ethics Committee (REC) review and reports

Ethics review of the protocol for the trial and other trial related Participant facing documents (e.g. PIB and consent form) will be carried out by a UK Research Ethics Committee (REC). Any amendments to these documents, after a favourable opinion from the REC/HRA has been given, will be submitted to the REC/HRA for approval prior to implementation.

All correspondence with the REC will be retained in the Trial Master File (TMF)/Investigator Site File (ISF). An annual progress report will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. The CI will notify the REC of the end of the trial and if the trial is ended prematurely (including the reasons for the premature termination). Within one year after the end of the trial, the CI will submit a final report with the results, including any publications/abstracts, to the REC.

ICH GCP training will be carried out by certain staff members depending on their delegated responsibilities within the trial, the level of training required will be determined according to the NIHR Delegation and Training Decision Aid. Informed consent to participate in the trial will be sought and obtained according to ICH GCP guidelines.

15.3. MHRA review and reports

MHRA review of the protocol for the trial and other trial related documents relating to the IMP/placebo will be carried out by MHRA. Clinical Trial Authorisation (CTA) will be obtained.

After the initial CTA has been approved, any amendments (which effect the safety (physical or mental integrity) of the participants, the scientific value of the study, the conduct or management of the study or the quality or safety of any IMP) will constitute a substantial amendment and a request to the MHRA for approval will be submitted.

All correspondence with the MHRA will be retained in the Trial Master File (TMF)/Investigator Site File (ISF).

In addition to the expedited reporting required for Suspected Unexpected Serious Adverse Reactions (SUSARs), a Development Safety Update Report (DSUR) will be submitted to the MHRA, once a year throughout the clinical trial or on request until the end of the trial is declared. The annual safety report should take into account all new available safety information received during the reporting period and assess the safety of subjects included in the study.

The sponsor will submit an end of trial summary results to EudraCT as per the commission's guidelines on posting and publication of result-related information within one year of the end of study declaration being submitted

15.4. Amendments

HRA approval will be sought alongside the REC and MHRA approval process.

Under the Medicines for Human Use (Clinical Trials) Regulations 2004, the sponsor may make a non-substantial amendment at any time during a trial. If the sponsor wishes to make a substantial amendment to the CTA (Clinical Trial Authorisation) or the documents that supported the original application for the CTA, the sponsor must submit a valid notice of amendment to the licencing authority (MHRA) for consideration. If the sponsor wishes to make a substantial amendment to the REC application or the supporting documents, the sponsor must submit a valid notice of amendment to the REC for consideration. The MHRA and/or the REC will provide a response regarding the amendment within 35 days of receipt of the notice. It is the sponsor's responsibility to decide whether an amendment is substantial or non-substantial for the purposes of submission to the MHRA and/or REC.

15.5. Peer review

The proposal for this trial has been peer-reviewed through the NIHR HTA peer-review process, which includes independent expert and lay reviewers.

15.6. Regulatory compliance

The trial will comply with the necessary regulations (MHRA, CTA, etc.) and will gain sponsor and HRA approval. The trial will not commence until a CTA is obtained from the MHRA and Favourable REC opinion and HRA approval have been provided. The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments.

15.7. Poor quality data, notification of serious breaches to GCP and/or the protocol

Poor quality data

The quality of the trial data will be monitored throughout the trial (see 14.1) and data completeness will be reported to the DMC and TSC, and any cause for concern over data quality will be highlighted and an action plan put in place.

15.8. Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall trial management

The research team and all PIs must disclose any ownership interests that may be related to products, services, or interventions considered for use in the trial or that may be significantly affected by the trial. Competing interests will be reported in all publications and in the final report.

15.9. Indemnity

The necessary trial insurance is provided by the Sponsor. The PIB provides a statement regarding indemnity for negligent and non-negligent harm.

15.10. Access to the final trial dataset

Anonymous research data will be stored securely and kept for future analysis. Members of the TMG will develop a data sharing policy consistent with UoB policy. Data will be kept anonymous on research data facility storage (RDSF). Requests for access to data must be via a written confidentiality and data sharing agreements (DSA) available from the RDSF website which will be confirmed by the CI (or appointed nominee).

The DSA should cover limitations of use, transfer to 3rd parties, data storage and acknowledgements. The person applying for use of the data will be scrutinised for appropriate eligibility by members of the research team.

16. DISSEMINATION POLICY

A plan for disseminating the trial results will be developed by the TMG.

The main results of the trial will be published in a high impact peer-reviewed journal. Initial findings will be submitted to relevant national and international meetings. Innovative methods of dissemination will be explored such as videos, YouTube clips and blogs to accompany scientific papers that are accessible to patients as well as providing a lay summary.

For participants of the trial, the dissemination routes which were utilised in the phase 2 trial will be mirrored by providing regular trial newsletters. PPI work has established that the demographics of the patients that participate are such that they tend to prefer paper updates as opposed to online material. However, updates will be provided through a variety of mediums including a live Twitter feed and regular updates on the web page. Research newsletters hosted by Parkinson's UK, such as 'Progress', will be utilised to reach people living with PD, as well as providing updates to newsletters that are distributed to those registered on the databases which will also be utilised during the recruitment phase (PRODeNDRoN (14) and Parkinson's Research Network).

On completion of the trial a final report will be prepared for the Funder (NHR HTA) and once approved, made publicly available on their website.

17. REFERENCES

1. Sarter M, Albin RL, Kucinski A, Lustig C. Where attention falls: Increased risk of falls from the converging impact of cortical cholinergic and midbrain dopamine loss on striatal function. Exp Neurol [Internet]. 2014 Jul 31;257:120–9. Available from: http://dx.doi.org/10.1016/j.expneurol.2014.04.032
2. Chung KA, Lobb BM, Nutt JG, Horak FB. Effects of a central cholinesterase inhibitor on reducing falls in Parkinson disease. Neurology [Internet]. 2010 Oct 5 [cited 2011 Aug 12];75(14):1263–9. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3013493&tool=pmcentrez&rendertype=abstract
3. Henderson EJ, Lord SR, Brodie MA, Gaunt DM, Lawrence AD, Close JCT, et al. Rivastigmine for gait stability in patients with Parkinson's disease (ReSPonD): a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Neurol [Internet]. 2016;15(3):249–58. Available from: http://linkinghub.elsevier.com/retrieve/pii/S1474442215003890
4. Li Z, Yu Z, Zhang J, Wang J, Sun C, Wang P, et al. Impact of rivastigmine on cognitive dysfunction and falling in Parkinson's disease patients. Eur Neurol. 2015;74:86–91.
5. Lamb SE, Jørstad-Stein EC, Hauer K, Becker C. Development of a common outcome data set for fall injury prevention trials: the Prevention of Falls Network Europe consensus. J Am Geriatr Soc [Internet]. 2005 Sep 1 [cited 2011 Aug 7];53(9):1618–22. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16137297
6. Emre M, Aarsland D, Brown R, Burn DJ, Duyckaerts C, Mizuno Y, et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. Mov Disord [Internet]. 2007 Sep 15 [cited 2011 Jun 11];22(12):1689–707. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17542011
7. Manor Y, Giladi N, Cohen A, Fliss DM, Cohen JT. Validation of a swallowing disturbance questionnaire for detecting dysphagia in patients with Parkinson's disease. Mov Disord [Internet]. 2007 Oct 15 [cited 2018 Nov 1];22(13):1917–21. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17588237
8. Y. Xin, J. Lewsey, R. Gray, C.E. Clarke EM. Broadening the evaluative scope of quality of life in Parkinson's: Testing the construct validity of the ICECAP-O instrument. Mov Disord. 2016;31(suppl 2).
9. Goranitis I, Coast J, Al-Janabi H. An investigation into the construct validity of the Carer Experience Scale (CES). Qual Life Res. 2014;23(6):1743–52.
10. Machin D, Campbell MJ, Tan SB, Tan SH. Sample Size Tables for Clinical Studies [Internet]. Oxford, UK: Wiley-Blackwell; 2008 [cited 2017 May 21]. Available from: http://doi.wiley.com/10.1002/9781444300710
11. Thornicroft G, et al. CSRI (Client Services Receipt Inventory) European version. Int outcome Meas Ment Heal. 2006;(November):1–8.
12. PSSRU | Unit Costs of Health and Social Care 2016 [Internet]. [cited 2017 Jan 17]. Available from: http://www.pssru.ac.uk/project-pages/unit-costs/2016/index.php
13. NHS reference costs - GOV.UK [Internet]. [cited 2017 Jan 17]. Available from:

https://www.gov.uk/government/collections/nhs-reference-costs

14. Devlin N, Shah K, Feng Y, Mulhern B, Hout B van. Valuing health-related quality of life : An EQ-5D-5L value set for England. Off Heal Econ. 2016;16(1):1–22.

15. Kobylecki C, Shiderova I, Michou E. Relationship between dysphagia severity and gai disturbance in Parkinson's disease 2018: 1569 2018 International Congress of the International Parkinson and Movement Society, Hong Kong.

16. Cohen JT, Manor Y (2011) Swallowing disturbance questionnaire for detecting dysphagia *Laryngoscope* 121(7): 1383-1387

1. APPENDIX 1: CARER STUDY

Assessment of the effect of cholinesterase inhibitor treatment versus placebo on those caring for a person with Parkinson's disease.

1.1. Trial Design

A nested sub-study within the multicentre, phase III, RCT of the ChEi rivastigmine versus placebo to prevent falls in PD.

1.2. Primary objective

To determine the effect of cholinesterase inhibitor or placebo treatment on those caring for people with Parkinson's disease who are enrolled in the phase III CHIEF-PD study.

1.3. Definition of a carer

For purposes of this trial a carer is defined as an individual who undertakes informal or formal care responsibility for the participant.

1.4. Outcome

Total CES score at 12 months

1.5. Participants

Individuals who meets the definition of a carer who are caring for an individual(s) who are enrolled in CHIEF-PD.

1.6. Recruitment

Carers will be approached only with the agreement of the participant and be consented separately. If carers do not wish to, or is unable to consent to take part, the patient is still eligible to participate in the trial.

1.7. Trial population and size

Up to 600 carers recruited via their contact with people with Parkinson's Disease.

1.8. Number of study sites

Please see Section 4

1.9. Consent

Consent will be obtained by the site research team once the person with Parkinson's disease has been enrolled and randomised.

1.10. Intervention

The collection of sociodemographic data (name, gender, date of birth, address, ethnicity, GP details) and the Carer Experience Scale (CES) at time 0 and 12 months. It is anticipated that the questions will be mostly self-completed although the trained site researchers are positioned to facilitate this if required.

1.11. Enrolment duration

12 months

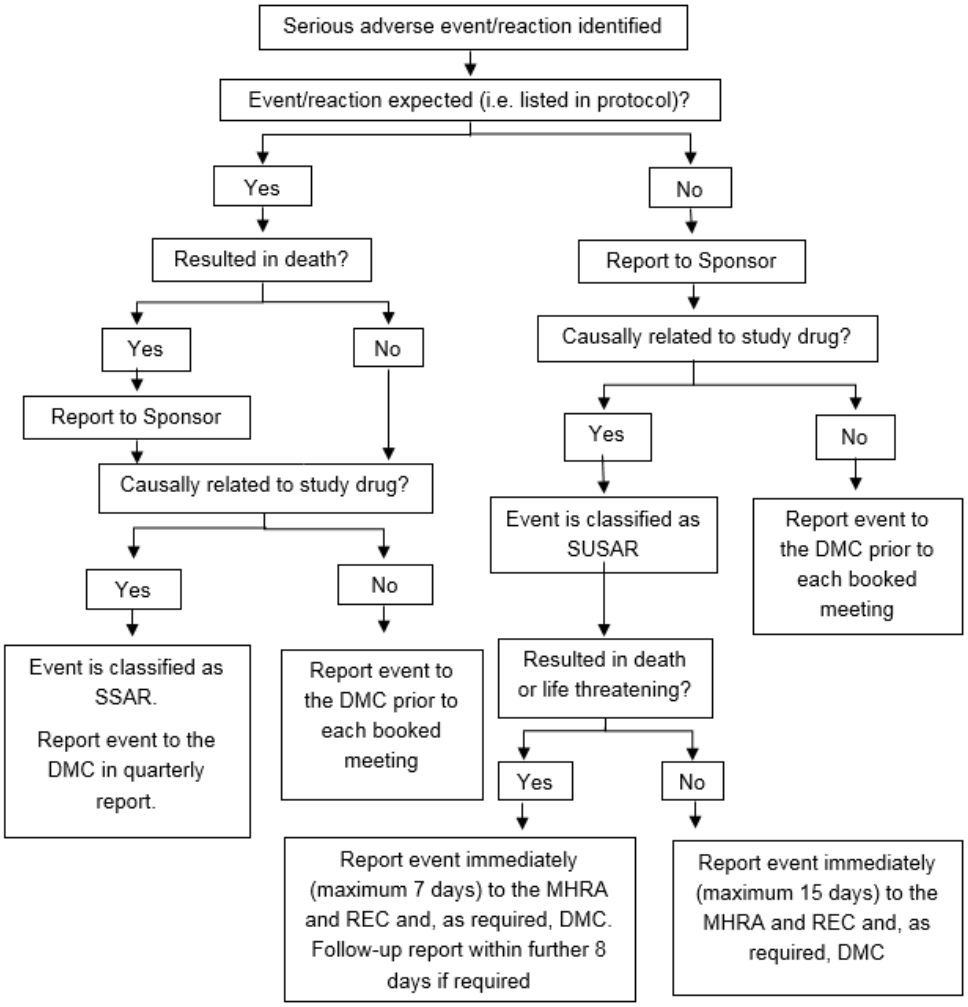
1.12. Study duration

12 months

1.13. Ethical considerations

As per Section 16

2. APPENDIX 2



Reporting framework for Serious Adverse Events reporting flowchart