

PD COMM TRIAL PROTOCOL

A Multi-Centre Randomised Controlled Trial to Compare the Clinical and Cost Effectiveness of Lee Silverman Voice Treatment Versus Standard NHS Speech and Language Therapy Versus Control in Parkinson's Disease



PROTOCOL

VERSION 4.0 14/11/18

This protocol has regard for the HRA guidance

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Funder: National Institute for Health Research Health Technology
Assessment programme (HTA 10/135/02)

Sponsor: University of Birmingham (RG_15-217)

ISRCTN: 12421382

IRAS Ref. No.: 168143

Main REC Ref. No.: 15/WM/0443


**National Institute for
Health Research**



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Protocol development and sign off

Protocol Contributors

This protocol was written by the Trial Management Group of the PD COMM Trial.

Amendments

The following amendments and/or administrative changes have been made to this study since the implementation of the first approved protocol. Amendments section will be updated with each new version of the protocol

Amendment Number	Protocol Version Number	Type of Amendment	Summary of Amendment
<i>Original application</i>	<i>1.0 & 1.1</i>	<i>Substantial</i>	Protocol and participant CRFs. Protocol approved subjected to minor changes. Resubmitted to REC as v1.1 07.12.2015
3	2.0	<i>Substantial</i>	Update of protocol, consent, participant info sheet and questionnaires.
10	4.0	<i>Substantial</i>	Update of protocol, participant & carer consent, participant & carer info sheet and participant CRFs. Creation of letter to accompany PIS (if posting), patient leaflet and poster.

Funder (s)	Financial and non-financial support given:
Funding Scheme	HTA
Funder's reference number	10/135/02

CI Signature Page

This protocol has been approved by:

Trial Name: PD COMM
Protocol Version Number: Version: 4.0
Protocol Version Date: 14/11/2018

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Signature and date:



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Sponsor Statement:

Where the University of Birmingham takes on the Sponsor role for protocol development oversight, the signing of the IRAS form by the Sponsor will serve as confirmation of approval of this protocol.

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This protocol describes the PD COMM Trial only. The protocol should not be used as a guide for the treatment of patients not taking part in the PD COMM Trial. The trial will be conducted in accordance with the protocol, Good Clinical Practice (GCP) and the Research Governance Framework. Every care has been taken in the drafting of this protocol, but future amendments may be necessary, which will receive the required approvals prior to implementation.

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Principal Investigator Signature Page

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I have read and agree to the protocol, as detailed in this document. I agree to adhere to the protocol as outlined and agree that any suggested changes to the protocol must be approved by the Trial Steering Committee prior to seeking approval from the Research Ethics Committee (REC).

I am aware of my responsibilities as an Investigator under the guidelines of Good Clinical Practice (GCP), the Declaration of Helsinki and the trial protocol, and I agree to conduct the trial according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the trial.

PD COMM Trial Protocol Version 4.0 14th November 2018

Principal Investigator

Name	Signature	Date
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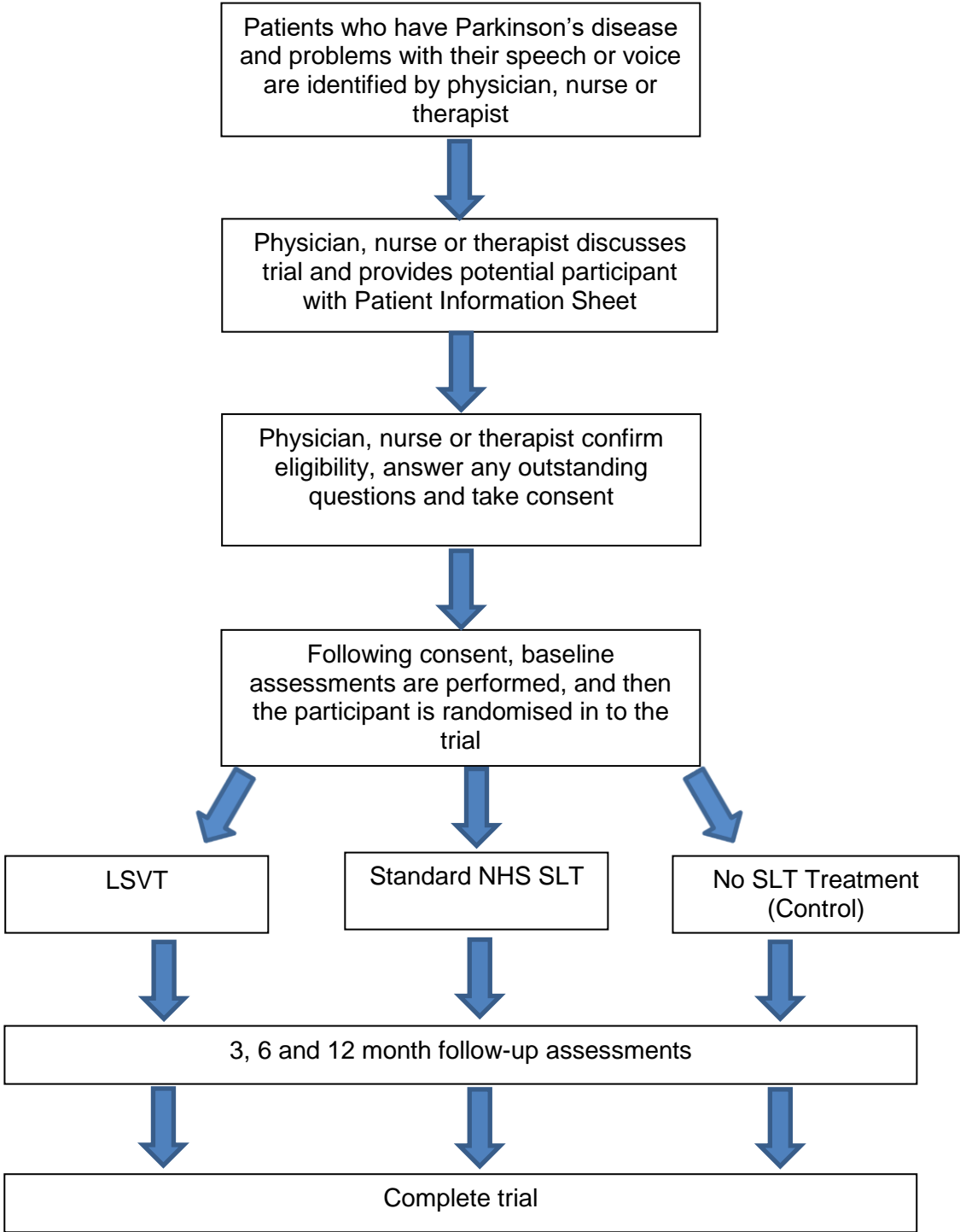
Name of Institution

Each Principal Investigator should sign this page and return a copy of this page to the PD COMM Trial Office

TRIAL SUMMARY

Title	A Multi-Centre Randomised Controlled Trial to Compare the Clinical and Cost-Effectiveness of Lee Silverman Voice Treatment versus Standard NHS Speech and Language Therapy versus Control in Parkinson's Disease (PD COMM).
Trial Design	PD COMM is a phase 3, multicentre, 3-arm unblinded randomised controlled trial to evaluate the effectiveness of two types of speech and language therapy (SLT) compared to no SLT treatment (control) for people with Parkinson's disease (PD) who have self-reported problems with their speech or voice.
Objectives	The primary objective of the trial is to assess the clinical and cost-effectiveness of the two types of SLT versus control for people with PD, but will also compare the two types of SLT (Lee Silverman Voice Treatment (LSVT) versus standard NHS SLT).
Participant Population and Sample Size	Adults of any age with PD who report problems with their speech or voice. The trial is a three arm trial with three comparisons: LSVT versus control, standard NHS SLT versus control and LSVT versus standard NHS SLT. The sample size based on detecting a 10 point difference in Voice Handicap Index total score (SD 26.27; effect size 0.38; 80% power, $\alpha=0.01$) is 546 (including 10% drop-out; 182 per arm).
Outcome Measures	Primary outcome: Voice Handicap Index (VHI) total score at 3 months. Secondary outcomes: Subscales of the VHI, Parkinson's Disease Questionnaire-39; Questionnaire on Acquired Speech Disorders; EuroQol-5D (5 level version); ICECAP-0; Resource Usage; and adverse events. Carer quality of life (Parkinson's Disease Questionnaire - Carers). Assessments will be completed before randomisation and by post at 3, 6 and 12 months after randomisation.
Key Eligibility Criteria	Inclusion criteria: <ol style="list-style-type: none"> 1. Have idiopathic PD defined by the UK PDS Brain Bank Criteria; 2. Person with PD or carer report problems with speech or voice when asked. Exclusion Criteria: <ol style="list-style-type: none"> 1. Dementia as usually defined clinically by the person with PD's physician; 2. Evidence of laryngeal pathology including vocal nodules or a history of vocal strain or previous laryngeal surgery within their medical records or from discussions with client; 3. Received SLT for PD speech or voice related problems in the past 2 years.
Interventions	SLT will be administered either in the community or in an out-patient setting (as per local practice). <ol style="list-style-type: none"> 1. LSVT will be administered in 4 sessions per week for 4 weeks of pre-determined content with homework. 2. NHS SLT will have more variability, but typically will be 1 session per week for 6 to 8 weeks of varying content as determined by participant need.

TRIAL SCHEMA



ACRONYMS

AAC	Augmentative and alternative communication
ABMT	Abbreviated Mental Test
ABPI	Association of the British Pharmaceutical Industry
AE	Adverse Event
BCTU	Birmingham Clinical Trials Unit
CONSORT	Consolidated Standards of Reporting Trials
DMC	Data Monitoring Committee
ENT	Ear, nose and throat
EQ-5D-5L	EuroQol questionnaire
GCP	Good Clinical Practice
GDG	Guideline Development Group
GP	General Practitioner
ICECAP-O	ICEpop CAPability measure for Older people
ICF	Informed Consent Form
ISF	Investigator Site File
LCRN	Local Comprehensive Research Networks
LSVT	Lee Silverman Voice Treatment
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
PD	Parkinson's disease
PDS	Parkinson's Disease Society
PDQ-39	Parkinson's Disease Questionnaire-39
PDQ-Carer	Parkinson's Disease Questionnaire-Carer
PI	Principal Investigator
PIS	Patient information sheet
PPI	Public and patient involvement
PSS	Personal social services
QALY	Quality-adjusted life year
QASD	Questionnaire on Acquired Speech Disorders
R&D	Research and development
RCT	Randomised controlled trial
REC	Research Ethics Committee
RET	Respiratory Therapy Programme
SAE	Serious Adverse Event
SALT	Speech and language therapist
SAP	Statistical Analysis Plan
SLT	Speech and language therapy
SOP	Standard Operating Procedure
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
TIDieR	Template for Intervention Description and Replication
TMG	Trial Management Group
TMF	Trial Master File
TSC	Trial Steering Committee
UK PDS Brain Bank Criteria	United Kingdom Parkinson's Disease Society Brain Bank Criteria
UKCRN	United Kingdom Clinical Research Network
VHI	Voice Handicap Index

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1. Background and Rationale

1.1. Background

Parkinson's disease (PD) is the most common serious movement disorder in the world,(1) affecting approximately 120,000 people in the UK alone.(2) Speech impairments are known to affect a large proportion of the PD population. A systematic review calculated a pooled prevalence estimate from all previous trials, and reported a prevalence of 68% for patient-perceived problems and 71% for listener-rated speech impairment.(3) For those with speech problems, the impact of the impairment is known to be great. In a study of 125 participants with PD by Miller *et al.*,(4) 38% placed speech among their top four concerns, whilst 29% of participants within a trial by Hartelius *et al.*,(5) reported speech problems to be among their greatest present difficulties. Miller *et al.*,(6) conducted in depth interviews with 37 people diagnosed with PD to establish the impact of changes in communication on the lives of the participants. The study noted how changes in communication led to increased physical and mental demands during conversation, an increased reliance on family members and/or carers, and an increased likelihood of reduced participation and social withdrawal. From the perspective of the listener, the speech of people with PD is often noted to sound sad or devoid of emotion, resulting in a potential social barrier to communication.(7) Overall, impairments of speech have been recognised to reduce the quality of life of people with PD.(8;9)

1.2. Existing Research

Two Cochrane reviews of speech and language therapy (SLT) for speech problems in Parkinson's disease were updated and published in 2012. One compared SLT against a placebo or no intervention,(10) and the second compared different SLT techniques.(11) Only randomised controlled trial (RCT) level evidence was included in the reviews.

SLT versus Placebo or No Treatment Cochrane Review

Three RCTs of differing SLT interventions versus no intervention, with a total of 63 PD participants were identified. Ramig *et al.*,(12) (n=29 plus 14 healthy age-matched controls) evaluated standard Lee Silverman Voice Treatment (LSVT) against no treatment. Robertson and Thomson (13) (n=22) and Johnson and Pring (14) (n=12 plus 4 healthy age-matched controls) both compared forms of intensive standard SLT with no treatment, but the two studies varied in SLT dose and delivery.

Ramig *et al.*,(12) evaluated effectiveness through objectively-measured vocal loudness (sound pressure level), reporting a significant improvement in vocal loudness following LSVT both immediately post-therapy and at six month follow-up when comparing baseline to post-intervention changes between trial arms. Robertson and Thomson (13) utilised the Dysarthria Profile to assess outcome, noting a significantly higher score in the intervention group compared to the control group post-therapy. Johnson and Pring (14) reported statistically significant changes in the Frenchay Dysarthria Assessment and vocal loudness for the treatment group when compared with the no treatment arm. The trials used a variety of treatment methods and outcome measures, which meant that in only a couple of instances meta-analysis was possible. Synthesis of Ramig *et al.*(12) and Johnson and Pring (14) was carried out for two outcome measures, although the treatment methods differed, a significant improvement with SLT compared to no therapy for loudness of both reading and monologue speech was shown.

Herd *et al.*,(10) concluded that many of the outcome measures improved following therapy, but due to the small number of participants examined, the low methodological quality of the trials

evaluated, and the possibility of publication bias, the efficacy of SLT for progressive dysarthria in PD against a placebo or no intervention could not be confirmed or refuted.

SLT versus SLT Cochrane Review

To compare different theoretical approaches to SLT provision for people with dysarthria, Herd *et al.*,(11) reviewed six trials with a total of 159 PD participants. Ramig *et al.*,(15) (n=45) compared standard LSVT with a respiratory therapy (RET) programme. The results of this trial were reported through a number of publications.(15-21) Halpern *et al.*,(22) (n=18) also studied LSVT comparing it with LSVT-ARTIC, which used broadly the same techniques as standard LSVT, but with a focus on articulation rather than loudness. LSVT was also studied by Constantinescu *et al.*,(23) (n=34) in a non-inferiority trial investigating the efficacy of online delivery of the techniques compared with standard face-to-face delivery. Scott and Caird (24) (n=26) delivered a standard SLT intervention comparing prosodic exercises with and without the addition of a visual feedback system. Speech rate reduction was the focus of the study by Lowit *et al.*,(25) (n=10) where an in-ear altered auditory feedback device was used with a control arm of standard rate reduction therapy using behavioural techniques. Healy (26) (n=26) also studied two rate reduction techniques, with use of an alphabet chart compared with a pacing board.

All six trials assessed intelligibility and almost all results were not statistically significant. The exception to this was for one of the three types of perceptual ratings of speech recordings made in the study by Halpern *et al.*,(22) for which LSVT gave the greater improvement. All three trials of LSVT (15;22;23;27) recorded loudness measures, with participants showing a greater improvement from LSVT than alternative therapies. Ramig *et al.*,(15) reported that these significant differences were maintained at 12 months after therapy. Objective measures of monotonicity of a monologue also favoured the LSVT method. Constantinescu *et al.*,(23) reported no significant difference between online LSVT and face-to-face delivery in reading and monologue loudness, intelligibility and monotonicity.

Herd *et al.*,(11) concluded that the small number of participants examined, the low methodological quality of the trials evaluated, and the possibility of publication bias resulted in an inability to determine superiority of any one type of SLT over another.

Other systematic reviews have been conducted, but their conclusions concur with the two Cochrane reviews described above that there is insufficient evidence to support or refute SLT for people with PD.(28;29) All reviews have recommended that further large scale RCTs are needed, with longer follow-up periods and should utilise outcome measures that are meaningful to patients.(10;11;28;29)

1.3. Guidelines for SLT in PD and Current Practice

The National Institute for Health and Care Excellence (NICE) guidelines (30) published in June 2006 stated:

“Speech and language therapy should be available for people with PD. Particular consideration should be given to:

- improvement of vocal loudness and pitch range, including speech therapy programmes such as Lee Silverman Voice Treatment (LSVT)
- teaching strategies to optimise speech intelligibility

- ensuring an effective means of communication is maintained throughout the course of the disease, including use of assistive technologies
- review and management to support safety and efficiency of swallowing and to minimise the risk of aspiration.“

In the recommendations, NICE stated:

“The evidence to support the use of speech and language therapy in PD is limited and yet patients feel that it is effective. The provision of this service in the NHS [National Health Service] is patchy with some patients not receiving speech and language therapy when it may be appropriate.

The GDG [Guideline Development Group] recommends a trial that is preceded by survey work to identify current and best practice speech and language therapy for PD in the UK. Similar work has already been performed for physiotherapy and occupational therapy to prepare for analogous trials.

In this pragmatic trial, standard NHS speech and language therapy would be compared with no treatment. Whilst most PD units have access to some speech and language therapy service, this may be insufficient for trial purposes so an NHS subvention would be required.

If speech and language therapy is cost effective, then the provision of service needs to be increased.”

The surveys have now been carried out,(31;32) and a pilot trial has also been undertaken in the UK ((33) see section 1.4). To further guide clinical practice, evidence-based SLT guidelines for people with PD have now also been published.(34)

Many clinicians, patients and carers advocate the use of SLT in PD.(30;35) Despite this, current provision of SLT is low. A survey of over 13,000 people with PD by the Parkinson’s Disease Society (PDS, now Parkinson’s UK) took place in the UK in 2007.(2) Only 37% reported ever receiving SLT.(2) This is higher than the previous reports of 20% in 1997,(36) and 4.4% in 1986,(37) but still falls short of recommendations made in the NICE guidelines,(30) which advocate the availability of SLT for all people with PD.

Published literature regarding the structure, content and delivery of SLT for people with PD in the UK is limited. A survey of 185 UK speech therapists was conducted between 2007 and 2008.(35;38) On average, therapists had an active/current PD caseload of a median of 3 people with PD and had 5 patients on review. Most speech therapists saw people with PD in hospital or out-patient departments, with few providing therapy in community settings. For communication impairments, patients were provided with a median of six 45 minute sessions over a period of 42 days (total dose 4.5 hours). Therapists were recognised to prominently base their assessment on an oral motor exam, with few using formal assessments to explore intelligibility, voice, language and psychosocial impact. Treatment primarily focused upon breathing, voice and speech rate, and a variety of treatment techniques were noted to be used (although this was not elaborated on in the available literature). Further information on SLT provision in the UK was provided in a survey of 123 people with PD and 68 carers by Noble *et al.*(39) For these patients, the duration of therapy varied greatly from one session to a 14 month course, although the majority (42%) had received one session only. Most patients had received therapy on a one-to-one basis (60%) and in a hospital out-patient setting (52%). Both therapists and patients have reported that referral to SLT often takes place later than desired.(35;39)

1.4. Trial Rationale

1.4.1. Justification for Design

NICE recommended that a pragmatic trial of standard NHS SLT compared with no treatment was needed. Since this recommendation was made LSVT has become more widely available, and is now delivered within the NHS.

A pilot trial (PD COMM Pilot) has been performed (33) where people with PD who reported problems with their voice or speech were randomised to either LSVT, standard NHS SLT or no SLT treatment. The data from this pilot trial have informed the design of this RCT (PD COMM) to assess the clinical and cost-effectiveness of these treatments. The pilot trial assessed eligibility, recruitment and retention, participant acceptability and treatment compliance. It also provided data to help inform the sample size and to refine the choice of outcome measures including those used for the economic evaluation.

1.4.2. Choice of Treatment

Guidance on best practice SLT for people with communication impairment as a result of PD can be found in two sources from the Royal College of Speech and Language Therapists.(40;41) When working with people presenting with dysarthria in the context of PD, therapists should be aware of the possibility that the presenting speech disorder is occurring within a more complex presentation profile (potentially including dysphagia). Adequate assessment procedures should be undertaken.

“The choice of therapy approaches is determined by the assessment findings and may involve a physiological, compensatory and/or an augmentative approach. A physiological approach is one which works directly to change specific aspects of the function of the sub-systems i.e. respiratory, resonatory, phonatory, articulatory and prosody. The goals for therapy also differ depending on the assessment findings and may be preventative, facilitative, rehabilitative or supportive.

An explanation of the normal anatomy and physiology of the orofacial tract and speech production will be provided. In addition, an explanation of the causal and maintaining factors that make up the dysarthria will be discussed. Where the aim is to reduce the degree of impairment or increase the physiological support for speech, a physiological approach may be appropriate. This may occur separately or in combination with either or both a compensatory and/or augmentative approach. Where the aim is to minimise the effect of the overall disability and promote intelligibility, various compensatory approaches should be used. These may occur separately or in combination with a compensatory and/or augmentative approach. When speech alone is insufficient to meet the individual’s communication needs, a variety of augmentative strategies should be used.”(40)

“The overall pathway in SLT is diagnostic assessment; followed by formulation of and negotiation of short and long-term goals with all parties involved; episodes of SLT intervention with on-going monitoring of progress towards goals; reassessment at key junctures; planned and measurable discharge and clearly stated workable onwards and sideways referral criteria.”(41)

Therefore, based on the Cochrane reviews of available RCT evidence,(10;11) and the recommendations of national or professional guidelines,(40;41) we remain unclear as to the

optimum theoretical approach, therapy regimen and delivery model for people with dysarthria as a consequence of PD.

1.5. Assessment and Management of Risk

The assessment and management of risk is detailed in the separate PD COMM Risk Assessment document. An on-going evaluation of risk will continue throughout the trial.

2. Aims, Objectives and Outcome Measures

2.1. Aims and Objectives

The primary objective of the trial is to evaluate the clinical and cost-effectiveness of the two types of SLT versus no SLT treatment (control) for people with PD, but the trial will also compare the two types of SLT (LSVT versus standard NHS SLT). Therefore, there will be three comparisons within the trial:

1. LSVT versus control
2. Standard NHS SLT versus control
3. LSVT versus standard NHS SLT

We will assess the clinical effectiveness by using patient reported measures to assess the participant's perception of how their voice impacts on daily activities and participant's perception of their quality of life in people with PD reporting difficulties with speech. We will also assess the quality of life of carers, and a cost-effectiveness analysis will be performed.

2.2. Outcome Measures

The outcome measures being assessed within the trial include:

- Voice Handicap Index (VHI total score; primary outcome measure)
- Parkinson's Disease Questionnaire-39 (PDQ-39)
- Questionnaire on Acquired Speech Disorders (QASD)
- EuroQoL (EQ-5D-5L)
- ICEpop CAPability measure for Older people (ICECAP-O)
- Resource Usage
- Hoehn and Yahr stage
- Adverse and Serious Adverse Events
- Parkinson's Disease Questionnaire - Carers (PDQ-Carer)

3. Trial Design and Setting

3.1. Trial Design

The PD COMM trial is a multi-centre 3 arm parallel group superiority RCT of LSVT versus standard NHS SLT versus no SLT treatment (control) in 546 people with PD with self-reported problems with their speech or voice. Given the nature of the interventions the trial is not blinded.

The trial protocol has been developed in accordance with the SPIRIT (42) guidelines and will be reported in accordance with the CONSORT (43) guidelines and relevant extensions (e.g. those

for non-pharmacological treatments and complex interventions (TIDieR) (44) and those for a pragmatic trial).

3.2. Trial Setting

Participants will be recruited from their routine out-patient appointments in a geriatric/elderly care, neurology or speech and language therapy secondary care setting. The intervention will typically take place in their local out-patient or community based SLT department. However it may also be provided within environments such as the home or workplace, dependant on patient needs.

4. Eligibility

4.1. Inclusion criteria

The inclusion criteria are deliberately broad to allow the inclusion of a wide spectrum of typical people with PD.

1. People who have idiopathic PD defined by the UK PDS Brain Bank Criteria (45) (Appendix 1). These criteria are in standard use throughout the NHS in the UK and supported by the NICE guidelines.
2. Person with PD or carer report problems with their speech or voice when asked.

4.2. Exclusion criteria

1. Dementia as usually defined clinically by the person with PD's physician.
2. Evidence of laryngeal pathology including vocal nodules or a history of vocal strain or previous laryngeal surgery within their medical records or from discussions with client, as LSVT is not appropriate for this group.(15)
3. Received SLT for PD speech or voice related problems in the past 2 years. This is based on findings by Ramig *et al.*, who reported a detectable treatment effect at 24 months following LSVT.(16)

NB: Individual involvement in the trial is 12 months, but participants randomised to the control group can be referred for SLT at the end of trial (e.g. after 12 months) or, if it becomes medically necessary during the trial (e.g. within 12 months of randomisation).

NB: Should it become apparent after randomisation that a participant has had previous treatment for SLT in the past 2 years, inform the Trials Office immediately. The Trials Office will then provide further advice. The participant should not be withdrawn unless they specifically request it themselves (see section on withdrawal).

4.3. Responsibility for Confirming Eligibility

It is usually the responsibility of the Investigator to confirm eligibility for potential participants, however, given the low risk nature of this trial, this may be delegated to suitably trained individuals e.g. Research Nurse or therapist, if local practice allows and this responsibility has been delegated by the Principal Investigator as captured on the PD COMM Trial site signature and delegation log.

5. Consent

Clinical research nurses and delegated investigators will screen for potential eligible trial participants using the inclusion/exclusion criteria (see Section 4). Potential trial participants will be identified by their neurology or elderly care clinical team when presenting for their routine hospital clinic visits, reflecting the secondary care basis of the proposed research. Patients may be contacted via telephone or letter by a member of their clinical care team (included but not limited to treating consultant, research nurses, speech therapists, etc) to inform them of the trial, prior to, or after their clinic visit should this be felt more practical/appropriate. Patients who fulfil the inclusion criteria will have their eligibility confirmed prior to randomisation by an appropriate person, delegated this role, who has access to and a full understanding of their medical history (see Section 4.3. for details on who can confirm eligibility for the PD COMM trial)

Prospective participants, and their carers if applicable, will be given a full explanation of the trial by the neurologist, geriatrician, research nurse or therapist who usually looks after their care. This will include discussion of the aims of the trial, the treatment options in the trial and the manner of treatment allocation, as well as any anticipated benefits and potential hazards of taking part in the trial. It will be stressed that participation is voluntary and that the participant is free to refuse to take part and may withdraw from the trial at any time. To facilitate this process, the prospective participant and their carer (if applicable) will be given a patient information sheet (PIS) or carer information sheet to read and sufficient time to decide whether they would like to join the trial. The participant and carer will be given the opportunity to ask questions. Given the low risk nature of the trial and the limited mobility of the potential participants, patients can consent on the day they are informed of the trial, or if they prefer they can take the PIS home and decide to return at a later date to join the trial. If the participant has a carer, they will also be invited to join the trial to provide feedback on their quality of life. They will be given a carer information sheet. Patients will be able to join the trial whether or not they have a carer, and whether their carer (assuming they have one) chooses to join the trial.

Once the patient has decided to join the trial, they will then be asked to sign and date the latest version of the informed consent form (ICF). Similarly, for any carers who agree to take part, they will be asked to sign and date a carer ICF.

The participant must give explicit consent for members of the research team and or representatives of the sponsor to be given direct access to the participant's medical records.

It is the responsibility of the Investigator to obtain written informed consent for each participant (both patients and carers) prior to performing any trial related procedures. However, this task may be delegated to suitably trained individuals e.g. research nurses, if local practice allows and this responsibility has been delegated by the Principal Investigator as captured on the PD COMM Trial site signature and delegation log. The investigator or delegates (as per the PD COMM Trial site signature and delegation log) will then sign and date the form. A copy of the ICF will be given to the participant (patient and carer if they also consented to join trial), a copy will be filed in the medical notes, and the original placed in the Investigator Site File (ISF). In addition, if the participant has given explicit consent, a copy of the signed ICF will be sent to the Trials Office for review. Once the participant is entered into the trial, the participant's unique trial identification number will be entered onto the ICF maintained in the ISF.

Details of the informed consent discussions should be recorded in the participant's medical notes. This should include date of discussion, the name of the trial, summary of discussions, version number of the PIS given to the participant and version number of ICF signed and date consent received. Where consent is obtained on the same day that the trial related assessments are due to start, a note should be made in the medical notes as to what time the consent was obtained and what time the procedures started.

Throughout the trial, participants will be encouraged to ask questions and will be reminded that they can withdraw at any time without their clinical care being affected. Since most of the follow-up assessments for the PD COMM trial are through postal questionnaires sent directly to the participant, completion and return of these questionnaires to the Trials Office will be considered as evidence of the participant's willingness to continue in the trial. Where new information becomes available which may affect the participants' decision to continue, participants will be given time to consider this information at their next clinic visit, and if happy to continue will be re-consented. Re-consent will be documented in the medical notes. The participant's right to withdraw from the trial will remain.

Electronic copies of the PIS and ICF (and carer equivalent) will be available from the Trials Office. PIS will be printed on the headed paper of the local institution. Details of all participants approached about the trial will be recorded on the Participant Screening/Enrolment log. The person with PD's general practitioner (GP) will be informed in writing of the person with PD's participation in the trial with the participant's consent.

Although the initial trial procedures will vary from unit to unit, it is likely that research nurses from the Local Comprehensive Research Networks (LCRN) will assist in these processes as shown in Appendix 2.

6. Enrolment and Randomisation

6.1. Enrolment

Participants will be recruited from community or out-patient clinics in elderly care and neurology services in the UK.

6.2. Randomisation

Following informed consent and completion of the baseline assessment and questionnaires, the participant can be randomised into the trial.

In order to ensure SLT availability following consent, randomisation may be deferred – however the participant baseline questionnaire needs to be completed within 2 weeks prior to randomisation, so this should be factored in to any planned delay of a patient's randomisation. A delay to randomisation greater than 3 weeks would also require confirmation from the participant that they still wish to take part in the trial, prior to randomisation and this should be documented in the patient's medical notes. Prior to randomisation, eligibility should also be reconfirmed.

Participants (the people with PD) will be randomised at the level of the individual to either LSVT or standard NHS SLT or no SLT treatment (control) in a 1:1:1 ratio via the Birmingham Clinical Trials Unit (BCTU) secure web-based randomisation system which will ensure concealment of

next treatment allocation. Randomisation will be by a computer-generated programme at the BCTU which will use a minimisation procedure (with a random element). The following minimisation variables will be used: age (≤ 59 , 60-70, >70 years); disease severity measured using the Hoehn & Yahr staging (1.0 to 2.5, 3 to 5) and severity of speech measured using the VHI total score (≤ 33 , mild 34-44, moderate 45-61, severe >61). To avoid any possibility of the treatment allocation becoming predictable, a random factor will be included within the algorithm, whereby for a proportion of the allocations, true randomisation will be implemented rather by using the minimisation algorithm.

A telephone randomisation service is available (9am – 5pm weekdays, except bank holidays and University of Birmingham closed days) if the site is having local difficulty with internet access. Informed consent must be obtained before randomisation is performed.

Once a participant is randomised, they will be given a unique trial identifier. If randomised online a computer-generated program will generate an email confirming the trial number and treatment allocation. If randomised by phone, the telephone randomiser at BCTU will generate the confirmation email.

Those entering participants into the PD COMM trial (as per the PD COMM Trial site signature and delegation log) should be aware of the availability of SLT before randomising participants into the trial in order to minimise the delay between randomisation and the start of treatment. All participants randomised to one of the SLT arms should have their initial session as soon as possible. **Treatment for those on the standard NHS arm should begin within 4 weeks of randomisation. Treatment for those on the LSVT arm should begin within 7 weeks** (extra time for this arm is to allow for a possible ENT referral prior to beginning treatment). Treatment may be provided at a health care site different to the hospital the participant was randomised to (dependant on local practice).

6.3. Informing the participant's GP

Once the participant has been randomised into the trial, their GP should be informed of their involvement *in the PD COMM trial, provided the participant has approved to this optional consent on the consent form*. A GP notification letter is provided within the Investigator Site File. *This should be completed with the relevant participant's details and then be sent to the GP as soon as possible post randomisation.*

6.4. Blinding

Given the nature of the interventions this trial is not blinded.

7. Trial Interventions

7.1. Lee Silverman Voice Treatment

The focus of LSVT is to “think loud”; improving phonation and vocal loudness through better vocal fold adduction.(15) The intervention will replicate the dose and content recommended by the originators and delivered in clinical practice and previous “standard” LSVT trials.

The LSVT intervention consists of four 50 minute sessions per week delivered over four weeks.(15) Each session follows a similar structure: 25 minutes of repeated and intensive

maximum effort drills, and 25 minutes of high effort speech production tasks.(15) Participants will also be set 5 to 10 minutes of home-based practice tasks on treatment days, and up to 30 minutes of home-based practice tasks on non-treatment days.(27)

The content of the intervention will consist of repeated repetitions of sustained “ah” phonation, maximum fundamental frequency range high and low pitch glides, and functional sentence repetition for the first half of each session, and exercises using speech production hierarchy that progresses throughout the duration of the treatment programme (single word, phrases, sentences, paragraph reading, conversation) during the second half of the sessions.(27) Throughout all of the sessions, the focus of the intervention will be to “think loud”, maintaining the vocal loudness produced during vowel phonation throughout all other task during the treatment.(15)

7.2. Standard NHS Speech and Language Therapy

The intensity, content and dose of standard NHS SLT is poorly defined within the published literature. For this reason, the standard therapy arm will encompass all local practice standard NHS SLT techniques that are not LSVT as per the LSVT Protocol. Treatment will be individualised to suit each participant’s needs. The standard NHS SLT may include interventions aimed at rehabilitating the underlying impairments of dysarthria, behavioural compensatory strategies and augmentative and alternative communication (AAC) strategies aimed at improving communicative function and participation.(46) The participant’s family/carer(s) will be involved as appropriate.

- Treatments targeted at impairment level may include exercises focused on improving capacity, control and co-ordination of respiration, techniques for improving phonation intensity and co-ordination with respiration (but not LSVT), and exercises to improve the range, strength and speed of the articulatory muscles.(13;14)
- Behavioural therapy may include interventions aimed at reducing prosodic abnormality (24;47) such as exercises targeting pitch, intonation, stress patterns, and volume variation,(13;14;24;47;48) and techniques to address the overall rate of speech (13;14) including the use of therapeutic devices such as pacing boards (49;50).
- AAC strategies such as topic and alphabet supplementation through communication books and boards may be employed,(46) along with AAC devices such as voice amplifiers, delayed auditory feedback systems and masking devices.(51-53)

The practice of pitch limiting voice treatment (54) may also be utilised within the standard SLT intervention.

The above methods may include techniques used in LSVT e.g. vocal intensity exercises, but will be distinct by the individualised treatment, other SLT strategies, intensity of delivery and dose.

Dose and frequency will be determined by the participant’s individual needs, but the duration is unlikely to exceed twelve weeks of treatment. It is most likely to reflect the median dose as reported in a survey of current UK SLT practice for PD by Miller *et al.*,(31) of 6 sessions delivered over 42 days. The PD COMM Pilot trial found the median dose to be 6 sessions (range 1 – 14) over an average of 9.6 weeks (standard deviation 6.1 weeks).

7.3. Control arm

The control arm will be no SLT treatment for speech or voice (participants may still be treated for dysphagia). The people with PD randomised to the control arm will consent to not having SLT during their 12 months participation in the PD COMM trial. Since there is insufficient evidence to prove or disprove the benefit of SLT in PD, equipoise still exists. Therefore, it is ethical to randomise between SLT and no SLT.

Investigators should, however, remain vigilant throughout the 12 months of the trial for people with PD randomised to the control group, who have deteriorated to the point of needing therapy urgently. Should this occur, SLT should be provided without delay by the usual local NHS services. This mechanism will act as a safety net for the people in the control arm.

People with PD will be encouraged to be fully compliant with their randomised treatment allocation; however, some may have SLT arranged by health or social care providers not associated with the trial (e.g. social services). Since this may lead to a dilution of the intervention effect, at each assessment participants in the control arm will be asked whether they have received any SLT.

At the end of the trial after the participant has completed their 12 month assessments (both patient and clinical assessments), those in the control arm can be referred for SLT by their usual care specialist through local NHS referral pathways.

7.4. Recording the Intervention Delivered in the SLT arms

In order to monitor intervention delivery, therapists providing the SLT interventions will complete a SLT Initial Interview Log and then a SLT Treatment Record Form after each treatment session for all participants randomised to SLT. The initial interview will include the Abbreviated Mental Test (AMT).⁽⁵⁵⁾ These forms will be used to monitor participant adherence (e.g. missed or cancelled appointments), and therapist adherence to the protocols for these programmes. In addition, for the standard NHS SLT intervention, the forms will be used to further explore what standard SLT delivered within the NHS entails.

7.5. Home-based Practice for the SLT arms

Participants randomised to either of the SLT treatment arms will complete brief home-based therapy diaries to determine the level of home-based practice recommended and undertaken by participants outside of the therapy sessions. These diaries will be reviewed by therapists and then returned to BCTU by the therapists.

8. Trial Procedures and Assessments

8.1. Summary of Assessments

Table 1: Assessment schedule

<i>Measure</i>		<i>Completed by</i>	<i>Assessment time</i>			
			<i>Baseline</i>	<i>3 months</i>	<i>6 months</i>	<i>12 months</i>
Randomisation Form		Clinician	✓			
Clinical data: Entry	Education & living arrangements	Clinician	✓			

Form or 12 month CRF	Height	Clinician	✓			
	Weight	Clinician	✓			✓
	PD Medication	Clinician	✓			✓
	Hoehn and Yahr stage	Clinician	✓			✓
VHI	Participant	✓	✓	✓	✓	✓
PDQ-39	Participant	✓	✓	✓	✓	✓
QASD	Participant	✓	✓	✓	✓	✓
EQ-5D-5L	Participant	✓	✓	✓	✓	✓
ICECAP-O	Participant	✓	✓	✓	✓	✓
Resource Usage Questionnaire	Participant		✓	✓	✓	✓
Transition Item	Participant & Carer			✓		
PDQ-Carer	Carer	✓	✓	✓	✓	✓
Adverse Event Log	Clinician			✓*		
Initial Interview Log (first session only) and Treatment Record Form (all sessions)	Speech & Language Therapist			✓**		
Home-Based Therapy Diary	Participant			✓***		

* Only required for participants randomised to a treatment arm.

**Following each therapy session for participants in the two SLT treatment arms only.

*** Completed at home by the participant as recommended in their SLT therapy session.

8.2. Schedule of Assessments

Assessments will be made following informed consent, and prior to randomisation (baseline assessment), and then at 3 months (i.e. after treatment if in the SLT arms), 6 and 12 months after randomisation (note: schedule is different for participant completed and clinical assessments – see Table 1). Participant-completed assessments at 3, 6 and 12 months will be obtained by post and returned to BCTU by post. The participant will have clinical assessments at baseline and then again at 12 months after randomisation.

Baseline: Following consent, the randomisation form and the clinical case report form (CRF; Entry Form) will be completed by the clinician or suitably trained delegate (as documented in the PD COMM Trial site signature and delegation log). The participant will complete the VHI, PDQ-39, QASD, EQ-5D-5L, and ICECAP-O questionnaires. The carer will complete the PDQ-Carer questionnaire.

3 months post-randomisation: The participant will complete the VHI, PDQ-39, QASD EQ-5D-5L, ICECAP-O and Resource Usage questionnaires and the Transition Item. The carer will complete the PDQ-Carer questionnaire and the Transition Item.

6 months post-randomisation: The participant will complete the VHI, PDQ-39, QASD EQ-5D-5L, ICECAP-O and Resource Usage questionnaires. The carer will complete the PDQ-Carer questionnaire.

12 months post-randomisation: The participant will complete the VHI, PDQ-39, QASD EQ-5D-5L, ICECAP-O and Resource Usage questionnaires. The carer will complete the PDQ-Carer questionnaire. The participant will have a clinical assessment and the 12 month clinical CRF will be completed by the clinician or suitably trained delegate (as documented in the PD COMM Trial site signature and delegation log).

For participants randomised to either of the SLT intervention arms of the trial, the therapists will complete an Initial Interview Log and treatment record forms and the participants will complete home-based therapy diaries.

8.3. Trial Procedures

8.3.1. Hoehn & Yahr

The **Hoehn and Yahr stage** (56) (Appendix 3) is a clinician-rated measure of disease severity in PD. It is a standard staging scale for PD that is required to document the severity of PD in the participant population.

8.3.2. Voice Handicap Index

Effectiveness of communication is being measured using the **Voice Handicap Index**.⁽⁵⁷⁾ The VHI is a valid and reliable tool which is completed by the participant. It has previously been used as an outcome measure in an extended LSVT trial for PD,⁽²⁷⁾ and also in the PD COMM Pilot trial. ⁽³³⁾ It comprises of 30 questions divided into emotional, functional and physical subscales.⁽⁵⁷⁾ It aims to assess the psychosocial consequences of voice disorders, and can be used to gain an overall perception of effectiveness of voice-related communication. The VHI total score ranges from zero to 120 (with 0 being the best score and 120 the worst score). The subscales range from zero to 40.

8.3.3. Parkinson's Disease Questionnaire-39

Quality of life is being measured using the **Parkinson's Disease Questionnaire-39**.⁽⁵⁸⁾ This is a validated, health-related quality of life measure specific to PD,⁽⁵⁸⁾ and is the most widely used disease-specific quality of life rating scale for PD. It is completed by the participant. It comprises of 39 questions divided into the following dimensions: mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication and bodily discomfort. The PDQ-39 summary index and each of the individual dimensions provide a score that can be converted into a 0-100 metric where 0=no problem at all and 100=worst or maximum level of problem.

8.3.4. Questionnaire on Acquired Speech Disorders

Participation restriction related to speech and communication will be assessed using the self-reported Questionnaire on Acquired Speech Disorders.⁽⁵⁹⁾ The Questionnaire on Acquired Speech Disorders questionnaire comprises of 30 questions which are scored zero to 3 giving a total score that ranges from zero to 90, where lower scores are better.

8.3.5. EuroQoL-5D (5 level version)

The **EQ-5D-5L(60) (61)** is a well-established standardised instrument for use as a measure of health outcome. It provides a simple descriptive profile and a single index value for health status. It is completed by the participant, and comprises of the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension can take one of five responses: no problems, slight problems, moderate problems, severe problems or extreme problems. There is also a 100 point visual analogue scale. It is often used together with resource usage questionnaires (see below) to provide data to inform the cost-effectiveness analysis.

8.3.6. ICECAP-O

The **ICECAP-O** (ICEpop CAPability measure for Older people) is a measure of capability in older people for use in economic evaluations.(62) Unlike most profile measures used in economic evaluations, the ICECAP-O focuses on well-being defined in a broader sense, rather than health. It is completed by the participant. The measure covers attributes of well-being that were found to be important to older people in the UK. It comprises of five attributes: attachment (love and friendship); security (thinking about the future without concern); role (doing things that make you feel valued); enjoyment (enjoyment and pleasure); and control (independence).

8.3.7. Resource Usage Questionnaire

Developed for use in the PD COMM Pilot, this trial and disease-specific **Resource Usage questionnaire** will be used to collect information on participant resource usage data. The questionnaire includes items on primary care and secondary care healthcare utilisation, including the use of therapy services, and out-patient appointments. Further questions relate to use of social services, including provision of meals and formal care. Finally, information will be collected on time off work, participants out of pocket costs (e.g. travel, medication) and costs incurred by informal carers, in order to inform analysis from a societal perspective.

8.3.8. Transition Item

The transition item is a single question asked at the 3 month time point to the participant and carer: “Compared to 3 months ago (when you joined the trial), has your ability to communicate using speech changed?” with 7 levels of response ranging from “much worse” to “much better” or “Compared to 3 months ago (when your partner/family member /friend joined the trial), has his/her ability to communicate using speech changed” is used for the participant and carer respectively. It measures whether the participant or carer has noticed any change in communication by voice or speech since the participant (with PD) entered the trial. The Transition Item will be used to calculate Minimally Clinical Important Differences (MCID) in other questionnaires, specifically the VHI.

8.3.9. Parkinson’s Disease Questionnaire - Carer

Carer quality of life will be measured using the **Parkinson’s Disease Questionnaire - Carer**.(63) This is the first disease-specific measure of quality of life for carers of people with PD, and is a validated and reliable tool. It is completed by the carer and comprises of 29 questions with 5

responses (Never/ Occasionally/ Sometimes/ Often/ Always). It is made up of four discrete scales: social and personal activities (12 items); anxiety and depression (6 items); self-care (5 items); and stress (6 items). The raw score of each scale can be calculated and converted to a 0-100 metric where 0=no problem at all and 100=worst or maximum level of problem. The sum of the scale scores can provide a single figure used to assess the overall quality of life of the individual questioned.

8.3.10. Other Data Collected

Participants' name, address, date of birth, gender, date of PD diagnosis, height, weight, Hoehn and Yahr stage, PD medication, living arrangements (e.g. alone, with a spouse or partner), level of education and smoking status will be collected on the Randomisation and Entry Forms at baseline. The participants' weight and PD Medication will be collected alongside the Hoehn and Yahr stage at 12 months as part of the 12 month clinical CRF.

8.4. Treatment Dose & Fidelity

8.4.1. SLT Initial Interview Log and SLT Treatment Record Forms

The speech and language therapists will complete an Initial Interview Log and Intervention Record Forms for all participants receiving SLT.

8.4.4. Therapy Notes

It is expected that as part of standard practice, therapists will keep a record of their therapy notes for each participant treated. Upon trial treatment completion, a pseudo-anonymised (ie patient only identified by trial number) version of these will be sent by the site to the Trials Office. These will in turn be sent from the Trials Office to University of Glasgow, to be used in the treatment dose and fidelity analysis.

8.5. Process Evaluation

In order to evaluate the fidelity of implementation of PD COMM interventions a process evaluation will be carried out alongside PD COMM. The process evaluation team will employ a number of approaches to data collection:

8.5.1. Qualitative interviews with PD COMM patient participants

Qualitative interviews, led by Bangor University, will be conducted with a purposive sample of participants in each of the three trial arms. Sampling will ensure engagement of trial participants with different age, disease severity, and the presence of a family carer. Interviews will draw on an interview spine underpinned by the Normalization Process Theory (NPT) (64). Focusing on the work associated with assimilating new interventions into pre-existing norms and routines, the use of this theoretical perspective will enable the differentiation of managing life with PD in general, and speech and language therapy interventions in particular. Participants will be asked to consent to being contacted after their 3 month assessment to be invited to be interviewed by the qualitative team. Interviews will take place between the 3 and 6 month assessment time points.

8.5.2. Qualitative interviews with PD COMM therapists

Semi structured in-depth interviews will be conducted with speech and language therapists (SALTs) and therapy assistants delivering the two SLT treatment arms, and will explore implementation from the therapists' perspectives. Interviews are expected to last a maximum of an hour and will be audio recorded. Interviews will be carried out at two time points: midway through therapists' anticipated involvement in the trial, and at the end of their involvement. The interviews will be carried out over the phone at a convenient date and time.

8.5.3. Critical incident reports

All PD COMM therapists will be asked to record key reflections using a critical incident technique. Data will be collected in the form of 'critical incident reports', and will follow a reflective cycle (65). SALTs and SALT assistants will be asked to complete these reports throughout their involvement in the trial.

8.5.4. Therapists questionnaire

All SALTs and SALT assistants involved in the trial will be asked to complete an online questionnaire at two time points: prior to the start of intervention delivery and after they have treated their last PD COMM participant. Guided by the NPT constructs (64) this questionnaire will include three sections with a series of Likert scale questions which will explore therapists' role within their service, previous experience as SALTs and SALT assistants delivering LSVT and NHS standard therapy, information on relevant training and therapists' expectations in regards to their ability to carry out their research role.

The analysis of process evaluation data will focus on the practical implementation of the trial interventions, including how these were tailored to individual patient and other circumstances. The analysis of qualitative data, and its integration with quantitative data on intervention provision, will be performed between researchers at Bangor University (Professor Christopher Burton), Glasgow Caledonian University (Professor Marian Brady), University College London (Dr Christina Smith) and King's College London (Professor Cath Sackley).

8.6. Withdrawal

Non-compliance with trial treatment does not constitute the participant's withdrawal from the trial. If the participant is non-compliant, inform the Trials Office and continue to capture trial data as instructed.

At any time during their trial involvement, should a participant clearly express the desire to withdraw from the trial, as per Good Clinical Practice they are free to do so. It is useful if a reason can be ascertained as to why the participant wishes to withdraw, however they are not required to provide one.

Please note, partial withdrawal is an option, so it should be discussed with the participant what they wish to withdraw from – for instance a participant may wish to continue with treatment, but no longer wants to complete the questionnaires. Examples of types of partial and complete withdrawal are as follows:

Partial withdrawal examples include:

- The participant would like to withdraw from trial treatment, but is willing to complete questionnaires, HBT diaries and for clinical data to continue to be supplied in accordance with the assessments schedule.
- The participant would like to withdraw from trial treatment and completing questionnaires and HBT diaries but is willing for clinical data to continue to be supplied in accordance with the assessments schedule.
- The participant would like to withdraw from completing questionnaires, but is willing to receive trial treatment and for clinical data to be supplied in accordance with the assessments schedule.

Note: Possible types of partial withdrawal are not limited to the above examples, if in doubt contact the Trials Office.

Complete withdrawal examples:

- The participant would like to withdraw from trial treatment and is not willing to be followed up in any way for the purposes of the trial and for no further data to be collected (ie does not want to receive treatment, complete questionnaires and HBT dairies or for clinical data to be supplied).
- The participant would like to withdraw from trial treatment and is not willing to be followed up in any way for the purposes of the trial and for no further data to be collected (ie does not want to receive treatment, complete questionnaires and HBT dairies or for clinical data to be supplied). The participant is also unwilling for any of their data already collected to be used in future trial analysis.

Note: There are only two types of complete withdrawal (as listed above), the difference being whether the participant is willing for data collected prior to their withdrawal to be used in trial analysis.

Regardless of the level of withdrawal, inform the Trials Office via the use of a Change of Status form. The details of withdrawal (date, reason (if available) and type of withdrawal) should be clearly documented in the source data.

9. Death

All deaths should be reported to the PD COMM Trial Office on the Change of Status form immediately on becoming aware, so that no correspondence (ie questionnaires or queries) are sent to the participant or carer. Only deaths related to vocal strain or vocal abuse should be reported as an SAE. For SAE reporting guidance, see the adverse event reporting section.

10. Adverse Event Reporting

The collection and reporting of adverse events (AEs) and Serious Adverse Events (SAEs) will be in accordance with Good Clinical Practice (GCP) and the Research Governance Framework 2005.

Safety will be assessed continuously throughout the trial. Safety monitoring has been delegated by the Sponsor (University of Birmingham) to the BCTU. There are no Investigational Medicinal

Products being used as part of the PD COMM trial. A risk assessment of the PD COMM trial has been performed with the SLT interventions considered to be of low risk.

There may be a small increased risk of vocal strain or abuse, and this is stated clearly in the PIS. Every effort will be made to minimise the risk of vocal strain or abuse. Speech and language therapists are trained to identify and rehabilitate vocal strain so, if present, the therapist will be quick to identify and address it. No other risks are expected to arise from taking part in the trial. It is therefore reasonable to **collect only targeted AEs related to vocal strain or abuse**. No SAEs are anticipated as a unique consequence of participation in PD COMM, but reporting requirements are clearly outlined in this section.

10.1. Adverse Events

The standard AE definition is as below:

AE: Any untoward medical occurrence in a trial patient to whom a research treatment or procedure has been administered, including occurrences which are not necessarily caused by or related to that treatment or procedure.

AEs are commonly encountered in people with PD. However, very few are likely to be related to the SLT. As the adverse events seen in this population are well known, **only AEs relating to vocal strain or abuse will be reported**.

For participants on a therapy arm, any vocal strain or abuse believed to be associated with treatment will be identified by the therapists at the participants' therapy session. These AEs should be captured on the AE log (see section 10.4.1). BCTU will also check that no vocal strain or abuse has occurred following participants reporting out-patients appointments with ear, nose and throat (ENT) specialists on Resource Usage forms. The therapy notes will be checked and compared with the SLT treatment forms and AE Log for quality assurance.

Participants that are randomised to the control arm will have their AEs checked via the Resource Usage form - should the participant indicate they had an ENT referral, the Trials Office will query with site to clarify whether this was an SAE. At the 12 month clinical visit, the medical professional will also check whether any AEs have occurred since entering the trial,

10.2. Serious Adverse Events

The definition of an SAE is an untoward event that:

- results in death;
- is life-threatening*;
- requires hospitalisation** or prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity;
- or, is otherwise considered medically significant by the Investigator

*The term "life-threatening" refers to an event in which the patient 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.

** Patients must be formally admitted – waiting in out-patients or A&E does not constitute an SAE (even though this can sometimes be overnight). Similarly, planned hospitalisations that clearly are not related to the condition under investigation or hospitalisations/prolongation of hospitalisation due to social reasons should not be considered as SAEs.

Investigators will only report AEs associated with vocal strain or abuse that meet the definition of an SAE (section 10.4.2 for reporting procedures at site), SAEs that are expected and do not require reporting on an SAE form are listed in section 10.2.2.

10.2.1. Events that do not require expedited (immediate) reporting

SAEs that are not related to vocal strain or abuse are excluded from expedited notification during the course of the trial and do not need to be reported to the Trials Office – see section 10.2.2. The only exception to this guidance is death – see section 9. Death.

10.2.2. Events that do not require reporting on a Serious Adverse Event Form

The following are expected SAEs for the purpose of the trial and should not be reported on an SAE form:

- Hospital admissions to control symptoms of any medications;
- SAEs that are related to a pre-existing condition;
- SAEs that are related to symptoms or progression of the participant's condition under study;
- Death as a result of the participant's standard treatment or from a pre-existing medical condition;

The above events are examples, this is not an exhaustive list. These SAEs are not considered related to the trial intervention and are therefore excluded from notification to the PD-COMM Trial Office as SAEs. These events should continue to be recorded in the medical records according to local practice.

Investigators should only report SAEs which are attributable to the trial protocol.

10.3. Reporting period

Treatment related AEs associated with vocal strain or abuse will be documented and reported from the date of commencement of protocol defined SLT treatment until 30 days after the administration of the last treatment. AEs associated with vocal strain or abuse that are not considered treatment related (ie AEs experienced on the control arm) will be reported from randomisation until 12 months post randomisation via the resource usage questionnaire.

10.4. Reporting Procedure – At Site

10.4.1. Adverse Events

Treatment related AEs should be reported on the AE Log. The participant will also be asked if they experienced any AEs on the resource usage form. These will be returned to the PD COMM Trial Office by post.

10.4.2. Serious Adverse Events

SAEs which do not meet the criteria of 'expected' and are considered related to the trial intervention will be notifiable to the PD-COMM Trial Office **immediately and within 24 hours of becoming aware of the event**. On becoming aware that a participant has experienced a trial

related SAE, the Investigator (or delegate) must complete, date and sign an SAE Form. The form should be faxed to the PD COMM Trial Office using one of the numbers listed below. The Investigator will also be asked to provide a categorisation of seriousness and causality (see section 10.4.2.1).

Fax SAE Forms to the Trials Office
and inform trial team of fax submission, via telephone or email
(please see page 3 for contact details).

For SAE Forms completed by a member of the site trial team other than the Principal Investigator (PI), the PI will be required to countersign the original SAE Form to confirm agreement with the causality and seriousness/severity assessments. The form should then be returned to the Trials Office and a copy kept in the Site File.

Investigators should also report SAEs to their own Trust in accordance with local practice.

10.4.2.1 Causality assessment

AEs defined as serious and which require reporting as an SAE should be reported on an SAE Form. The PI will be asked to define the causality and the severity of the AE.

Causality (relatedness) will be categorised according to the following coding system:

- 1=Unrelated to trial treatment or procedure
- 2=Unlikely to be related to trial treatment or procedure
- 3=Possibly related to trial treatment or procedure
- 4=Probably related to trial treatment or procedure
- 5=Definitely related to trial treatment or procedure

Table 2 provides a definition for each relatedness category.

Table 2: Definitions of relatedness.

Category	Definition	Causality
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out	Related
Probably	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely	
Possibly	There is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after administration of LSVTLSTiohexolLSVT). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant events or medication)	
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of LSVTLSTiohexolLSVT). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant events or medication)	Unrelated
Unrelated	There is no evidence of any causal relationship	

10.4.2.2 Assessment of Expectedness

Expectedness will be assessed by the CI or designee using this study protocol as the reference document. Table 3 gives definitions of expectedness with respect to SAEs.

Table 3: Definitions of expectedness

Category	Definition
Expected	An adverse event that is classed in nature as serious and which is consistent with known information about the study related procedures or that is clearly defined in this protocol
Unexpected	An adverse event that is classed in nature as serious and which is <u>not</u> consistent with known information about the study related procedures

10.4.2.3 Provision of follow-up information

Participants should be followed up until resolution or stabilisation of the event. Follow-up information should be provided on a new SAE Form, making sure to include the SAE reference number, provided by the Trials Unit upon receipt of the initial SAE.

10.5. Reporting Procedure – PD COMM Trials Office

On receipt the Trials Office will allocate each vocal abuse SAE a unique reference number which will be forwarded to the site as proof of receipt within 1 working day. The SAE reference number will be quoted on all correspondence and follow-up reports regarding the SAE.

On receipt of an SAE Form, seriousness and causality (relatedness to the trial intervention) will be assessed independently by the Clinical Lead (Prof Carl Clarke or delegate where necessary).

Further information may be immediately requested from the clinical team at site. The Clinical Lead will not overrule the causality or seriousness assessment given by the site PI, but may add additional comment on these.

An SAE judged to have a reasonable causal relationship with the trial treatment will be regarded as a related SAE. The Clinical Lead or delegate will assess all related SAEs for expectedness. If the event is unexpected (i.e. is not defined in the protocol as an expected event) it will be classified as **an unexpected and related SAE**.

10.6. Reporting to Research Ethics Committee (REC)

10.6.1. Unexpected and Related Serious Adverse Events

SAEs categorised by a PI or the Clinical Lead as both suspected to be related to trial participation and “unexpected” will be subject to expedited reporting to the REC by the PD COMM Trial Office within 15 days after the Trial Office has been notified. A copy will also be sent to the University of Birmingham Research Governance Team at the same time.

The PD COMM Trial Office (on behalf of the CI) will inform all PIs of relevant information about SAEs that could adversely affect the safety of participants.

10.6.2. Other safety issues identified during the course of the trial

The REC will be notified immediately if a significant safety issue is identified during the course of the trial.

The University of Birmingham Research Governance Team will also be informed at the time that the REC is informed.

10.7. Investigators

Details of all Unexpected and Related SAEs and any other safety issue which arises during the course of the trial will be reported to Principal Investigators. A copy of any such correspondence should be filed in the Site File.

10.8. Data Monitoring Committee

The Independent Data Monitoring Committee (DMC) will review all vocal AEs and SAEs.

11. Data Handling and Record Keeping

11.1. Source Data

In order to allow for the accurate reconstruction of the trial and clinical management of the subject, source data will be accessible and maintained.

For all participant completed questionnaires including home-based practice diaries, the questionnaire is the source document.

For all Clinical CRF data, the medical records or research notes are the source data.

For all records of the SLT interventions, the therapy notes are the source data.

11.2. CRF Completion

Clinical CRFs must be completed, signed/dated and returned to the PD COMM Trial Office by the Principal Investigator or an authorised member of the site research team (as delegated on the PD COMM Trial site signature & delegation log) within 4 weeks of the time points listed in Table 1. Similarly, we would expect to receive all therapist forms within 4 weeks of a participant completing therapy. Entries on paper CRFs should be made in ballpoint pen, in black ink, and must be legible. Any errors should be crossed out with a single stroke, the correction inserted and the change initialled and dated. If it is not obvious why a change has been made, an explanation should be written next to the change. Data reported on each CRF should be consistent with the related source data and any discrepancies should be explained. If information is not known, this must be clearly indicated on the CRF. All sections should be completed; all missing and ambiguous data will be queried by the trial team at BCTU. In all cases it remains the responsibility of the site's Principal Investigator to ensure that the CRF has been completed correctly and that the data are accurate. Copies of the CRFs at site should be archived with the ISF.

Further information on CRF completion can be found in the CRF completion guidelines.

Given the typical age range of the participant population, help in reading, interpreting and writing answers to the participant/carer questionnaires may be needed. This is acceptable, but should only be provided where required and answers should always be reflective of participant/carer views.

11.3. CRF and Data Management

CRF version numbers may be updated by the PD COMM Trial Office, as appropriate, throughout the duration of the trial. Whilst this will not constitute a protocol amendment, new versions of the CRFs must be implemented by participating sites immediately on receipt. Changes to Participant questionnaires or the PIS or ICF (for either the participant or carer) will require a substantial amendment prior to their implementation.

The Trial Office will be in regular contact with the site research teams to check on progress and address any queries that they may have. The Trial Office will check incoming CRFs for compliance with the protocol, data consistency, missing data and timing. Sites will be asked for missing data or clarification of inconsistencies or discrepancies. Participant Questionnaire booklets will be reviewed on receipt at the PD COMM Trial Office at BCTU, and inconsistent and/or missing data will be queried. To ensure that participants do not feel harassed, a single letter will be sent to participants outlining the discrepancy and/or missing data and requesting this information. Occasionally participants may be telephoned to request or clarify missing or ambiguous data queries (where participants have consented to be telephoned), again the trial team will not speak to the participants on more than one occasion regarding a missing /ambiguous set of data.

All data will be entered onto the PD COMM trial database by suitably trained staff as soon as feasible once it has arrived in the trial office, this includes amended data following data queries, as per internal data management guidelines. Data (paper documents) will be stored in lockable filing cabinets in a secure, swipe access part of the University of Birmingham. Electronic databases for trial data will have limited access to BCTU members of staff working on the trial – access will be password protected. Investigators and delegates will have access to the web-based randomisation system. The database will have ranges applied to data items where suitable and the interim statistical analyses will include missing and unusual data searches.

11.4. Process evaluation

The treatment dose and fidelity will be assessed by the Collaborative group based at the Universities of Bangor, Glasgow Caledonian, University College London and King's College London.

Patient participants joining the trial will be informed of the option to be interviewed after the three month assessment to provide feedback and inform the fidelity of the intervention. Contact details and selection variables of participants who agree to be contacted on the main PD COMM trial consent form (point 9) will be collected and held by the University of Birmingham and forwarded when required, to the process evaluation team at Bangor University. An additional qualitative participant information sheet and consent form will be posted to participants selected to be invited to take part in the process evaluation which will take the form of a single, no longer than 30 minute face to face or phone interview. The Research officer at Bangor University will arrange interviews with the participants. Participants will be able to withdraw their consent to being interviewed without withdrawing from the PD COMM trial or affecting their care.

The University of Birmingham will provide written information to all SALTs and SALT assistants who have been recruited into the PD COMM trial explaining the aims of the trial and process evaluation. PD COMM therapists will be asked to consent to take part in the qualitative interviews and they will be invited to complete critical record forms and the online Therapists questionnaire.

Completed consent forms for the qualitative interviews, along with the data obtained from these, the online therapist questionnaires and critical record forms will be held separately and securely by Bangor University.

Copies of SLT Initial Interview Logs and SLT Treatment Record Forms together with therapy notes will be pseudo-anonymised (ie patient only identified only by trial number) and forwarded to collaborators at Glasgow Caledonian University and King's College London for analysis of the quantitative treatment data led by Professor Marian Brady. These data will then be integrated into the qualitative data being undertaken by the qualitative group at Bangor University, led by Professor Christopher Burton. Recordings of interviews and data from clinical incident reports and therapist questionnaires will be retained by Bangor University. Transcripts identifiable by Trial number (patients) or site will be available to the PD COMM investigators.

11.5. Archiving

At the completion of the trial, the data held by BCTU will be retained for at least 20 years in accordance with the University of Birmingham Standard Operating Procedure (SOP). This may be in a secure on site store at the University of Birmingham or a GCP compliant Archiving facility.

It is the responsibility of the Principal Investigator to ensure all essential trial documentation and source documents (e.g. signed ICF, ISF, participant's hospital notes, copies of CRFs etc.) at their site are securely retained for at least 20 years.

Information from Scottish sites held at Glasgow Caledonian University will be archived at Glasgow Caledonian University.

Interview recordings and transcripts will be held by the University of Bangor and pseudo-anonymous (ie patient only identifiable by trial number) copies of the therapy dataset may be archived at Glasgow Caledonian University and the Universities of Bangor, University College London and King's College London or a GCP compliant Archiving facility for at least 20 years.

11.6. Confidentiality

All data will be handled in accordance with the General Data Protection Regulation and Data Protection Act 2018.

The PD COMM trial will collect personal data about participants. Participants will be informed about the transfer of this information to the trial office at the BCTU, and will be asked to consent to this. The data will be entered onto a secure computer database. Any data to be processed outside the BCTU will be at least be pseudo-anonymised (ie patient only identified by trial number).

For Scottish sites, Patient identifiable information may also be held at Glasgow Caledonian University, as part of their coordination of recruitment in Scotland.

All personal information obtained for the trial will be held securely and treated as strictly confidential. Intervention staff will be asked to indicate if they agree to their contact details to be shared across the study team in order to facilitate on-going engagement in the trial, including education and training, professional development, and the opportunity to engage in additional research activities.

12. Quality Control and Quality Assurance

12.1. Site Set up and Initiation

All participating Principal Investigators will be asked to sign the necessary agreements and supply a current CV to the Trials Office. All members of the site research team will also be required to sign a PD COMM Trial site signature and delegation log. Prior to commencing recruitment, all sites will undergo a process of initiation and will have completed GCP training. Key members of the site research team will be required to attend either a meeting or a teleconference covering aspects of the trial design, protocol procedures, Adverse Event reporting, collection and reporting of data and record keeping. Sites will be provided with an ISF containing essential documentation, instructions, and other documentation required for the conduct of the trial. The Trials Office must be informed immediately of any change in the site research team.

12.2. Monitoring

Monitoring will be carried out as required following a risk assessment and as documented in the monitoring plan. Given the low risk nature of the trial, central monitoring will be routine and additional on-site monitoring may be triggered:

Central monitoring: The Trials Office will be in regular contact with the site research team to check on progress and address any queries that they may have. The Trials Office will check incoming CRFs for compliance with the protocol, data consistency, missing data and timing. Sites will be asked for missing data or clarification of inconsistencies or discrepancies.

Additional on-site monitoring visits may be triggered, for example by poor CRF return, poor data quality, low SAE reporting rates, excessive number of participant withdrawals or deviations. If a monitoring visit is required, the Trials Office will contact the site to arrange a date for the proposed visit and will provide the site with written confirmation. Investigators will allow appropriately trained Trials Office staff access to source documents as requested.

12.3. Audit and Inspection

The Principal Investigator will permit trial-related monitoring, quality checks, audits and ethical reviews at their site, providing direct access to source data/documents. The Principal Investigator will comply with these visits and any required follow up.

12.4. Notification of Serious Breaches

The Sponsor is responsible for notifying the REC of any serious breach of the conditions and principles of GCP in connection with that trial or the protocol relating to that trial. Sites are therefore requested to notify the Trials Office of any suspected trial-related serious breach of GCP and/or the trial protocol. Where the Trials Office is investigating whether or not a serious breach has occurred, sites are also requested to cooperate with the Trials Office in providing sufficient information to report the breach to the REC where required and in undertaking any corrective and/or preventive action.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment. Any major problems identified during monitoring may be reported to PD COMM stakeholders e.g. Trial Management Group, Trial Steering Committee (TSC), and the REC. This includes reporting serious breaches of GCP and/or the trial protocol to the REC. A copy is also sent to the University of Birmingham Clinical Research Compliance Team at the time of reporting to the REC.

13. End of Trial Definition

The end of trial will be 6 months after the last data capture. The Trials Office will notify the REC that the trial has ended and a summary of the clinical trial report will be provided within 12 months of the end of trial.

A copy of the end of trial notification as well as the summary report is also sent to the University of Birmingham Research Governance Team at the time of sending these are sent to the REC.

14. Statistical Considerations

14.1. Definition of Outcome Measures

See also section 8.3.

The outcome measures for the PD COMM trial include the following:

- Participant self-reported questionnaires: VHI (VHI total score, primary outcome measure), PDQ-39, Questionnaire on Acquired Speech Disorders, EQ-5D-5L, ICECAP-O and Resource Usage questionnaire;
- Clinician reported: Hoehn & Yahr stage, AE and SAEs;
- Carer self-reported questionnaire: PDQ-Carer.

14.1.1. Primary Outcome Measure

The primary outcome measure is the **total score of the VHI** at 3 months. The VHI consists of 30 questions and provides a total score which ranges from 0 to 120 (with 0 being the best score and 120 the worst score).

14.1.2. Secondary Outcome Measures

Participant-related:

- Subscales of the VHI: emotional, functional, and physical subscales (scores range from 0 to 40);
- PDQ-39 summary index and the eight individual dimensions of the PDQ-39: mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication and bodily discomfort. For each, the score ranges from 0 to 100 (where 0=no problem at all and 100=worst or maximum level of problem);
- Questionnaire on Acquired Speech Disorders (score ranges from 0 to 90, with lower scores better);
- EQ-5D-5L (score ranges from -0.59 to 1, with high scores better);
- EQ-5D visual analogue scale (score ranges from 0 to 100, with lower scores better);
- ICECAP-O (score ranges from 0 to 1, with high scores better);
- Hoehn and Yahr stage;
- Adverse and Serious Adverse Events.

Carer-related:

- PDQ-Carer overall score and the four scales: social and personal activities, anxiety and depression, self-care and stress. For each, the score ranges from 0 to 100 (where 0=no problem at all and 100=worst or maximum level of problem). The sum of the scale scores can provide a single figure used to assess the overall quality of life of the individual questioned.

14.2. Analysis of Outcome Measures

A separate Statistical Analysis Plan (SAP) for the PD COMM trial will provide a detailed description of the planned analyses for the trial. A brief outline of these analyses is provided below.

The primary objective of the trial is to compare the two types of SLT versus no SLT treatment (control) for people with PD, but it will also compare the two types of SLT. Therefore, there are three comparisons being undertaken within this trial:

- LSVT versus control
- Standard NHS SLT versus control
- LSVT versus Standard NHS SLT.

All the above comparisons will be analysed in the same way unless otherwise stated.

All primary analyses (for both the primary and secondary outcomes) will be by intention to treat. Participants will be analysed in the treatment group to which they were randomised, and all participants shall be included whether or not they received the allocated treatment. This is to avoid any potential bias in the analysis. For all tests, summary statistics (e.g. mean differences) will be reported along with 95% confidence intervals and p-values from two-sided tests. A p-value of <0.01 will be considered statistically significant, as per the sample size calculations to take into account the multiple treatment comparisons being undertaken.

14.2.1. Primary Outcome Analysis

The primary outcome measure is the VHI total score at 3 months. A linear regression model will be used to estimate differences in the VHI total score at 3 months between the two arms of interest, with the VHI baseline score and the minimisation variables age and severity of PD (Hoehn & Yahr) included in the model as covariates.

14.2.2. Secondary Outcome Analyses

The majority of the secondary outcome measures (e.g. PDQ-39) are continuous measurements and will be analysed in a similar way to that described for the primary analysis: a linear regression analysis adjusting for relevant baseline score and all of the minimisation variables (baseline VHI, age and severity of PD). As per the primary outcome, the primary analysis for the secondary outcomes will be based on the 3 month data.

To assess whether any treatment effect is maintained, participant and carer completed questionnaires are also being collected at 6 and 12 months post-randomisation. Data collected at 6 and 12 months will be analysed using the same methods as described above. Further analysis using a repeated measures model will also be performed using all data over the 3, 6 and 12 month assessment points.

Adverse events and safety data will be summarised descriptively by treatment arm, and the number of events and percentage of participants experiencing any adverse event reported. It is not expected that there will be many adverse events as a result of the intervention, but the number of participants reporting an adverse event will be compared using a Chi-squared test, with relative risks and 95% confidence intervals reported (if appropriate).

14.2.3. Missing Data and Sensitivity Analyses

Every attempt will be made to collect complete data on all participants. In particular, participants will continue to be followed up even after protocol treatment violation. The questionnaire total and/or subscales cannot be calculated for participants who have incomplete questionnaires, so

these participants will be excluded from the relevant primary analysis, except for the PDQ-39, where missing domains will be imputed using the expectation algorithm.⁽⁶⁶⁾ Sensitivity analyses may be performed to investigate the impact of any missing data for the primary outcome. Sensitivity analyses may also include a per-protocol analysis where only those participants who complied with their randomised treatment allocation are included in the analysis. More details regarding the sensitivity analyses will be provided in the SAP.

14.2.4. Planned Subgroup Analyses

Subgroup analyses will be performed to assess whether there are differences in treatment effect by the minimisation variables: age; baseline voice severity (as measured by VHI); and PD severity (as measured by Hoehn & Yahr). The trial is not powered to detect differences in treatment effect in these subgroups and therefore these analyses will be treated as purely hypothesis generating.

14.2.5. Planned Interim Analyses

Interim analyses of efficacy and safety will be provided in strict confidence to the DMC at least annually, or as per a timetable agreed by the DMC prior to trial commencement (see Section 16.5 for further details on trial data monitoring including the use of pragmatic stopping criteria).

14.2.6. Final Analyses

The final analyses will start once the last patient randomised has completed their 12 month assessment.

14.2. Sample Size Calculations

The primary outcome is the mean difference in the VHI total score at 3 months across the three comparisons: LSVT versus control; standard NHS SLT versus control; and LSVT versus standard NHS SLT. The MCID for the VHI has not been established in PD patients. Therefore, data from the PD COMM pilot trial was used to inform the sample size calculations for this trial. In the PD COMM pilot trial, a difference of around 10 points in VHI total score was observed at 3 months between SLT and control for both of the SLT (standard NHS and LSVT) versus control comparisons. To detect a 10 point difference in VHI total score between arms at 3 months (using a 2-sided t-test and the upper standard deviation of 26.27 obtained from the VHI baseline data from the pilot trial; effect size 0.38), with 80% power and $\alpha=0.01$, we need 163 participants per arm. Allowing for 10% drop-out will require 182 participants per arm, so 546 participants in total.

15. Health Economics Analysis

The aim of the economic evaluation is to estimate the cost-effectiveness of LSVT or standard NHS SLT compared to no SLT treatment (control) in PD. The base-case economic evaluation will be undertaken from the UK NHS and personal social services (PSS) perspective, with further analysis from a broader societal perspective, over 12 months follow up.

Firstly, a cost-consequence analysis will present a disaggregated list of all costs and outcomes by trial arm. Subsequently, a cost-effectiveness analysis will use the primary outcome (VHI) to calculate the cost per unit improvement in VHI score, and a cost-utility analysis will use responses from the EQ-5D-5L to calculate cost per quality-adjusted life year (QALY) gained. Resource use

data will be collected on PD-related medication, primary care and secondary care healthcare utilisation, including the use of therapy services, and use of social services including formal care. Further information will be collected on time off work, participant out of pocket costs and costs incurred by informal carers, in order to inform analysis from a societal perspective. The cost of delivering the LSVT intervention and NHS SLT, including length and number of sessions and any training required will be determined within the trial. Data will be collected using a participants-completed resource utilisation questionnaire (at 3, 6 and 12 months) and the therapist-completed Initial Interview Logs and Treatment Record Forms. Unit costs from routine sources (e.g. PSSRU,(67) NHS Reference costs) will be applied to resource use data. Health related quality of life will be assessed using the EQ-5D-5L (61) collected at baseline, 3, 6 and 12 months, in order to calculate QALYs. The ICECAP-O (62) will be used to capture changes in participants' capabilities, allowing a broader assessment of benefits to patients.

Cost data is likely to have a skewed distribution, the nature of the distribution of costs will be explored, and if the data is not normally distributed, a non-parametric comparison of means (using bootstrapping will be undertaken). QALYs will be calculated using responses to the EQ-5D-5L, using the "area under the curve" approach. Incremental cost-effectiveness and cost-utility analyses will be undertaken to estimate the incremental cost per unit of outcome gained, adjusting for baseline covariates. Both deterministic and probability sensitivity analysis will be undertaken and cost-effectiveness acceptability curves will be produced to reflect the probability the intervention will be cost-effective at different willingness to pay thresholds, in terms of cost per unit of outcome gained.

16. Trial Organisational Structures

16.1. Sponsor

The University of Birmingham is the trial Sponsor.

16.2. Trials Office

The trial will be run from the PD COMM Trial Office in BCTU at the University of Birmingham. For Scottish sites, a coordinating centre in Glasgow Caledonian University will provide additional support in recruiting participants.

16.3. Trial Management Group (TMG)

The TMG will comprise the CI, other lead investigators (clinical and non-clinical) and members of the BCTU. The TMG will be responsible for the day-to-day running and management of PD COMM. It will convene at least every 3 months, and more frequently when required.

16.4. Trial Steering Committee (TSC)

The role of the TSC is to provide the overall supervision of the trial. The TSC will monitor trial progress and conduct and advise on scientific credibility. The TSC will consider and act, as appropriate, upon the recommendations of the DMC, and ultimately carries the responsibility for deciding whether the trial needs to be stopped on grounds of safety or efficacy. Further details of the remit and role of the TSC are available in the TSC Charter.

16.5. Data Monitoring Committee (DMC)

An independent DMC will be established to oversee the safety of participants in the trial. The DMC will meet prior to the trial opening to enrolment, and then meet at least annually, or as per a timetable agreed by the DMC prior to trial commencement. The DMC will operate in accordance with the trial specific DMC charter. Data analyses will be supplied in confidence to the DMC, which will be asked to give advice on whether the accumulated data from the trial, together with the results from other relevant research, justifies the continuing recruitment of further participants.

The DMC may consider recommending the discontinuation of the trial if the recruitment rate or data quality are unacceptable, or if any issues are identified which may compromise participant safety. The trial would also stop early if interim analyses showed differences between treatments that were deemed to be convincing to the clinical community. Alternatively, new evidence might emerge from other sources that any one treatment is definitely more, or less, effective than any other. To protect against this, during the main period of recruitment to the trial, interim analyses of the primary outcome and adverse events will be supplied, in strict confidence, to the independent DMC, along with updates on results of other related studies, and any other analyses that the DMC may request. The DMC will advise the chair of the TSC if, in their view, any of the randomised comparisons in the trial have provided both (a) “proof beyond reasonable doubt”¹ that for all, or for some, types of patient one particular treatment is definitely indicated or definitely contraindicated in terms of a net difference in the major endpoints, and (b) evidence that might reasonably be expected to influence the patient management of many clinicians who are already aware of the other main trial results. The TSC can then decide whether to close or modify any part of the trial. Unless this happens, however, the TMG, TSC, the investigators and all of the central administrative staff (except the statisticians who supply the confidential analyses) will remain unaware of the interim results.

16.6. Service Users

Patient and carer involvement will be incorporated at all levels of this trial. A group of patients and carers recruited from Parkinson UK were involved in the design of the study and members of the Patient and Public Involvement (PPI) group are part of the TSC. Patient and carer involvement will not be a stand-alone activity, but an integral part of all stages of the trial. Patients and carers will be directly involved as research ‘partners’ and not just as ‘data providers’ (using the INVOLVE guidance). All support for patient and carer involvement in the PD COMM trial will be provided by BCTU.

16.7. Network Support

This trial is supported by the Parkinson’s UK and the LCRN Division 4: Neurology.

¹ Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but a difference of at least $p < 0.001$ (similar to a Haybittle-Peto stopping boundary) in an interim analysis of a major endpoint may be needed to justify halting, or modifying, the study prematurely. If this criterion were to be adopted, it would have the practical advantage that the exact number of interim analyses would be of little importance, so no fixed schedule is proposed.

16.8. Local Centre Organisation

16.8.1. Training

Training will be provided for the Speech and Language therapists where necessary. Furthermore, all sites will be offered site initiation visits to ensure the smooth running of the trial at each individual site. If the central monitoring reveals issues, or at the request of the site, further training on trial procedures will be available on an ongoing basis.

16.8.2. Staffing

Each centre will nominate one clinician to act as **Principal Investigator**. He/she will be responsible for the local management of the trial and for dealing with any local governance issues throughout the trial. He/she will make arrangements with their hospital and/or primary care trust managers to provide SLT facilities for the PD COMM trial.

Each centre will develop its own model for providing the **Therapists** required to deliver the trial intervention. However, these therapists are likely to be drawn from existing staff, so they will have experience in working with people with PD. This experience will be supplemented by specific training on the trial and the therapy interventions.

16.9. Finance

The National Institute for Health Research (NIHR) Health Technology Assessment Programme is funding this trial (project number 10/135/02). The trial will be automatically adopted by the NIHR United Kingdom Clinical Research Network (UKCRN) who will provide NHS service support.

17. Ethical Considerations

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, June 1964, amended at the 48th World Medical Association General Assembly, Somerset West, Republic of South Africa, October 1996 (website: <http://www.wma.net/en/30publications/10policies/b3/index.html>).

The trial will be conducted in accordance with the Research Governance Framework for Health and Social Care, the General Data Protection Regulation and Data Protection Act 2018 and Guidelines for Good Clinical Practice (GCP). The protocol will be submitted to and approved by the REC prior to circulation.

Before any participants are enrolled into the trial, the Principal Investigator at each site is required to obtain local Research and Development (R&D) approval. Sites will not be permitted to enrol participants until written confirmation of R&D approval is received by the Principal Investigator.

It is the responsibility of the Principal Investigator to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual participants.

18. Confidentiality and Data Protection

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the General Data Protection Regulation and Data Protection Act 2018.

With the participants' permission, the BCTU Neurosciences Team will hold participants name, date of birth and address to enable them to know the age of participants and to be able to post questionnaires to them. Participants will always be identified using only their unique trial identification number, initials and date of birth on the CRF, and on any correspondence between the Trials Office and the participating site. Participants will print and sign self-report questionnaires.

For Scottish sites, patient identifiable information will be held at Glasgow Caledonian University, as part of their coordination of recruitment in Scotland.

For the process evaluation (section 10.4), patient identifiable information will be held at Bangor University as part of their coordination of the process evaluation.

The Investigator must maintain documents not for submission to the Trials Office (e.g. Participant Identification Logs) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, provided that participant confidentiality is protected.

The Trials Office will maintain the confidentiality of all participants' data and will not disclose information by which participants may be identified to any third party. Representatives of the PD COMM Trials Office and Sponsor may be required to have access to participant's notes for quality assurance purposes, but participants should be reassured that their confidentiality will be respected at all times.

19. Insurance and Indemnity

The University of Birmingham has in place Clinical Trials indemnity coverage for this trial which provides cover to the University for harm which comes about through the University's, or its staff's, negligence in relation to the design or management of the trial and may alternatively, and at the University's discretion provide cover for non-negligent harm to participants.

With respect to the conduct of the trial at Site and other clinical care of the patient, responsibility for the care of the patients remains with the NHS organisation responsible for the Clinical Site and is therefore indemnified through the NHS Litigation Authority.

The University of Birmingham is independent of any pharmaceutical company, and as such it is not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for participant compensation.

20. Dissemination and Publication Policy

Regular newsletters sent out to collaborators and participants to keep them informed of trial progress and disseminate results. Regular collaborator meetings will be held to report on progress of the trial and to address any problems encountered in the conduct of the trial.

The CI will coordinate dissemination of data from PD COMM. All publications and presentations, including abstracts, relating to the main trial will be authorised by the PD COMM TMG and will follow the NIHR funders guidance on publications (see <http://www.nihr.ac.uk/policy-and-standards/publishing-research-findings.htm>). The results of the analysis will be published in the name of the PD COMM Collaborative Group in a peer reviewed journal (provided that this does not conflict with the journal's policy). All contributors to the trial will be listed, with their contribution identified. Trial participants will be sent a summary of the final results of the trial, which will contain a reference to the full paper. All applications from groups wanting to use PD COMM data to undertake original analyses will be submitted to the TMG for consideration before release. To safeguard the scientific integrity of PD COMM, trial data will not be presented in public before the main results are published without the prior consent of the TMG.

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22. Appendices

Appendix 1: United Kingdom Parkinson's Disease Society Brain Bank Diagnostic Criteria⁴⁴

STEP 1 Diagnosis of Parkinsonian syndrome:

Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions) and at least one of the following:

- a) Muscular rigidity
- b) 4-6 Hz rest tremor
- c) Postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction.

STEP 2 Exclusion criteria for Parkinson's disease:

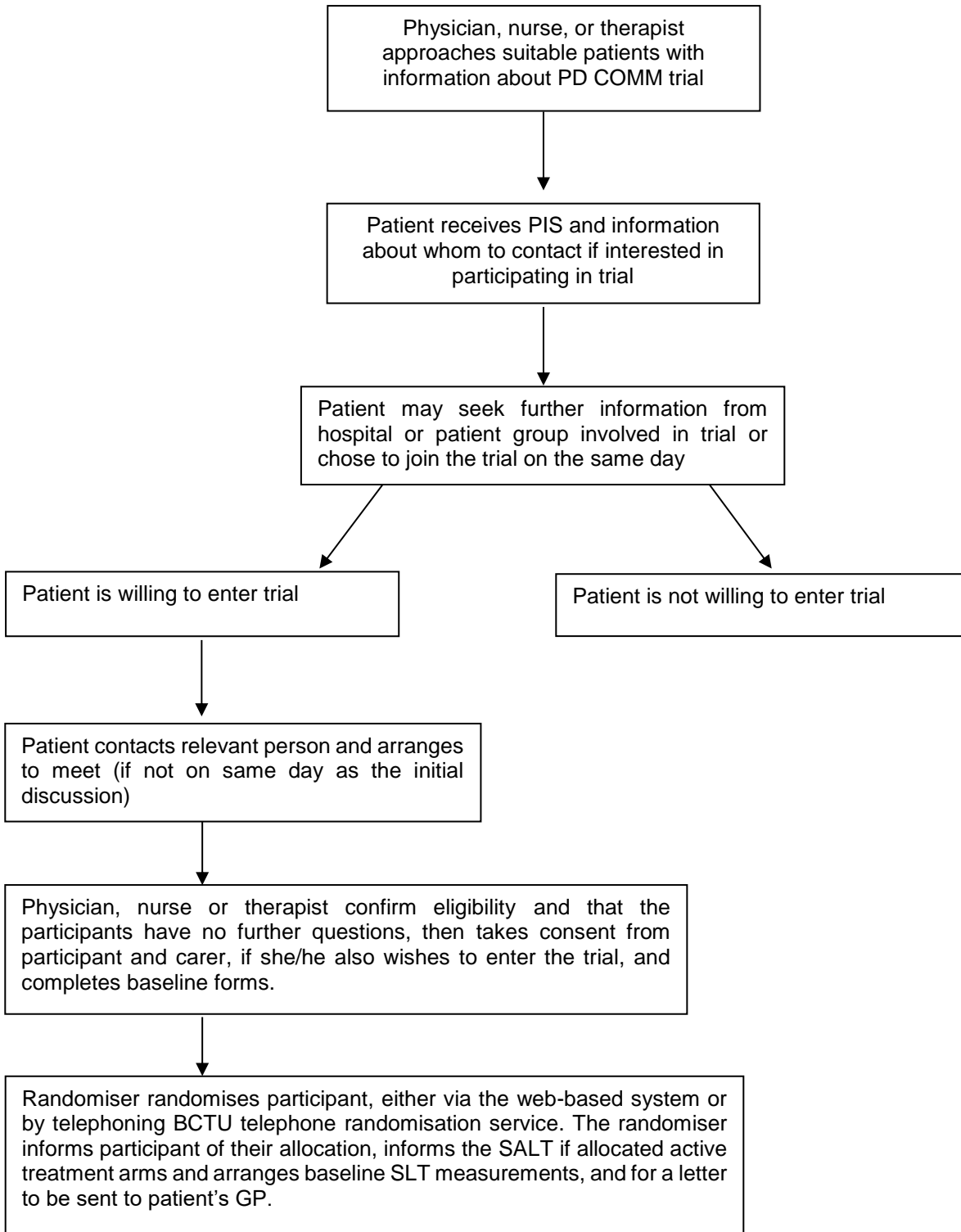
History of repeated strokes with stepwise progression of Parkinsonian features
History of repeated head injury
History of definite encephalitis
Oculogyric crises
Neuroleptic treatment at onset of symptoms
More than one affected relative
Sustained remission
Strictly unilateral features after three years
Supranuclear gaze palsy
Cerebellar signs
Early severe autonomic involvement
Early severe dementia with disturbances of memory, language and praxis
Babinski sign (Plantar Reflex)
Presence of a cerebral tumour or communicating hydrocephalus on CT scan
Negative response to large doses of levodopa (if malabsorption excluded)
MPTP exposure

STEP 3 Supportive prospective positive criteria for Parkinson's disease; three or more required for diagnosis of definite Parkinson's disease:

Unilateral onset
Rest tremor present
Progressive disorder
Persistent asymmetry affecting the side of onset most
Excellent response (70-100%) to levodopa
Severe levodopa-induced chorea
Levodopa response for 5 years or more
Clinical course of 10 years or more

Appendix 2: Flow Diagram of Randomisation Process

Randomisers should be aware of availability of Speech and Language therapy before randomising participants into the trial to minimise delay between randomisation and the start of treatment: all participants randomised to Speech and Language therapy should have initial session as soon as possible and ideally within 4 weeks of randomisation



Appendix 3: Hoehn and Yahr Stage⁵⁶

Stage 1.0	Unilateral involvement only
Stage 1.5	Unilateral and axial involvement
Stage 2.0	Bilateral involvement without impairment of balance
Stage 2.5	Mild bilateral involvement with recovery on retropulsion (pull) test
Stage 3.0	Mild to moderate bilateral involvement, some postural instability but physically independent
Stage 4.0	Severe disability, still able to walk and to stand unassisted
Stage 5.0	Wheelchair bound or bedridden unless aided.