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Simvastatin as a neuroprotective treatment for Parkinson's disease (PD STAT): Protocol for a double-blind, randomised, placebo-controlled futility study in patients of moderate severity

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ABSTRACT

Introduction: Parkinson's disease (PD) is a progressive neurodegenerative condition affecting approximately 185,000 people in the UK. No drug has been proven to slow disease progression. Epidemiological and pre-clinical data support simvastatin, a widely used cholesterol-lowering drug with a well-established safety profile, having neuroprotective properties. The aim of this study (PD STAT) is to determine whether simvastatin has the potential to slow PD progression. The study is part of the International Linked Clinical Trials (LCT) initiative coordinated by The Cure Parkinson's Trust. This paper describes the protocol for the PD STAT study.

Methods and analysis: PD STAT is a double-blind, randomised, placebo-controlled, multi-centre, parallel group, futility trial in patients with PD of moderate severity. 235 participants have been recruited and randomly allocated in a 1:1 ratio to receive either oral simvastatin or matched placebo. Treatment involves a one month low dose phase (40mg daily), followed by a 23 month high dose phase (80mg daily) and ends with a two month washout period. Participants are reviewed at clinic visits at one month, 6, 12, 18, 24 and 26 months post-baseline, with interim telephone follow-up to monitor for adverse events.

The primary outcome is the change in the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III motor subscale score in the practically defined OFF medication state (OFF state) between baseline and 24 months. Primary analysis will be on an intention to treat basis and will include only those participants who progress to the high dose phase of the study.

Ethics and dissemination: The protocol has been approved by the North East – Newcastle and North Tyneside 2 Research Ethics Committee. The results will be disseminated via research articles in peer-reviewed journals and presentations at local, national and international scientific meetings, as well as disseminated via patient groups, websites and networks. A summary of the study findings will be posted to participants at the end of the study.

Registration: ISRCTN16108482; EudraCT 2015-000148-40; ClinicalTrials.gov NCT02787590

Key words: Parkinson's disease; statin; randomised controlled futility study; neuroprotective effect; MDS-UPDRS

Word count 5538

Strengths and limitations of this study

- Independent, blinded outcome assessors not involved in participant treatment, reduces likelihood of bias in results
- OFF state MDS-UPDRS assessments, the current gold standard for evaluating disease progression
- Standardised training for raters reduces inter-rater variability
- Embedded sub-study to evaluate the participant's trial experience and inform future trial design
- Long duration of study increases risk of drop-out/loss to follow-up

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative condition affecting approximately one person in every 350 in the UK(1). Furthermore, with population growth and an increasingly ageing population, the estimated prevalence and incidence of Parkinson's disease in the UK are increasing. There are currently no

known treatments that slow the rate of neuronal loss or clinical progression in PD. All currently licensed therapies are symptomatic.

Epidemiological and pre-clinical data support a possible neuroprotective role for statins in PD, with statin use being associated with lower PD incidence(2,3). Simvastatin has been shown in various toxin and genetic cell culture and rodent PD models to influence several pathways thought to be of relevance in PD etiopathogenesis, including inflammation and microglial activation, oxidative stress and α-synuclein aggregation(4,5). A beneficial effect of simvastatin on dopamine neuron survival and motor function has been observed in acute(6) and chronic(4) 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mouse models. Additionally, statins may have symptomatic effects on dyskinesia and depression in PD(4). Interestingly, simvastatin has been shown to reduce the rate of brain atrophy in secondary progressive multiple sclerosis(7); it is likely that some of the mechanisms underlying neuronal death are similar in this and other neurodegenerative diseases. This finding therefore lends support to investigating the potential long-term disease-modifying effects of simvastatin in PD. In 2012, the International PD Linked Clinical Trials initiative (LCT) was established by The Cure Parkinson's Trust to identify potential new neuroprotective treatments for PD by repurposing drugs that have been approved, or are in current clinical development, to treat other conditions(8). On the basis that simvastatin has a well-established safety profile(9,10), it was one of the first drugs selected by the LCT committee to be tested in a clinical trial in PD patients to determine its disease-modifying potential.

Clinical trials of potential neuroprotective agents in PD are difficult to design, given the variability in disease phenotype and rate of progression, as well as the potential confounding factor of a symptomatic response. In addition there is no reliable biomarker for assessing disease progression(11). Initially used in oncology trials, a trial with a futility design allows for a relatively short study duration and smaller sample size in comparison with the typical phase II/III trial design(12). The futility design typically has a single treatment arm and tests whether a new treatment exceeds a pre-defined futility threshold(12). In neurological diseases such as PD, the lack of a concurrent control group has led to criticism of subsequent findings from futility trials(13) but it is possible to test for futility using a randomised parallel group design. There is, therefore, increasing interest in the use of futility trials to provide an efficient method for early phase studies to ascertain whether there is sufficient evidence to justify conducting larger, longer and more expensive phase III trials. The PD STAT trial is a phase II futility study, which aims to determine whether simvastatin has potential to reduce the rate of neurodegenerative decline in patients with PD.

Aims and objectives

The aim of the study is to determine whether the cholesterol-lowering drug, simvastatin, has potential as a neuroprotective therapy in PD. The primary objective of the PD STAT study is to determine whether simvastatin is clearly ineffective (futile) in preventing the clinical decline of PD as measured by the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) motor score in patients in the OFF state(14). Secondary objectives are to confirm the safety and tolerability of simvastatin in patients with PD, to distinguish symptomatic effects of simvastatin from disease modifying effects, and to evaluate the impact of simvastatin on activities of daily living, timed motor tests, cognitive ability, mood, behaviour, non-motor symptoms and quality of life in patients with moderate PD using standard validated tools of assessment. The results of this study will help to determine the merits of conducting a larger, definitive phase III study to assess the neuroprotective and/or disease-modifying effectiveness of simvastatin.

METHODS AND ANALYSIS

This protocol is reported in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidance for protocols of clinical trials(15).

Trial design and setting

This is a double-blind, randomised, placebo-controlled, multi-centre, parallel group trial in patients with PD of moderate severity. There are three embedded sub-studies. Participants are individually randomised in a 1:1 ratio to receive either oral simvastatin or matched placebo for 24 months. A one-month low dose phase (40mg daily) is followed by a 23-month high dose phase (80mg daily) and treatment ends with a two-month washout period. Recruitment took place between March 2016 and March 2018, with a target of at least 198 participants progressing successfully to the high dose phase of the study; 26 month follow-up of all participants is expected to be completed by May 2020. The trial design, including scheduled follow-up assessments, is summarised in Figure 1.

A 12-month treatment period was originally considered but it was felt that this might not be long enough to demonstrate any disease modifying effect; hence, participants are each treated for 24 months. Should this futility study have positive results, the additional collection of 12-month outcome data, as well as outcome data collected at the primary endpoint of 24 months, will enable assessment of any potential benefit at 12 months to assist with design of future studies.

The trial is being conducted in 23 NHS Trusts across England. A list of recruiting sites is provided in Appendix A. A local principal investigator (PI), supported by at least two other staff members (e.g. research nurse or PD specialist nurse), leads the conduct of the study at each participating site. Participants are followed up on an outpatient basis at 1 month, 6, 12, 18, 24, and 26 months post baseline (treatment start), with regular interim telephone contact.

Study population

The study population includes patients aged between 40 and 90 years with a diagnosis of idiopathic PD, a modified Hoehn and Yahr stage of ≤3.0 in the ON medication state, and who are on dopaminergic treatment with experience of wearing-off phenomenon (as defined by the nine-item wearing-off questionnaire(16)). Patients are excluded if they have a diagnosis (or suspicion of) another cause for their parkinsonism, or have any prior use, current use, intolerance of or requirement for, statins. A full list of patient inclusion and exclusion criteria is listed in Table 1.

Table 1: Inclusion and Exclusion criteria

Inclusion criteria

1) Diagnosis of idiopathic PD
2) Modified Hoehn and Yahr stage ≤ 3.0 in the ON medication state
3) Age 40-90 years
4) On dopaminergic treatment with wearing-off phenomenon
5) Able to comply with study protocol and willing to attend necessary study visits

Exclusion criteria

1) Diagnosis or suspicion of other cause for parkinsonism
2) Known abnormality on CT or MRI brain imaging considered to be causing symptoms or signs of neurological dysfunction, or considered likely to compromise compliance with study protocol
3) Concurrent dementia defined by a Montreal Cognitive Assessment (MoCA) score <21
4) Concurrent severe depression defined by Montgomery and Asberg Depression Rating Scale (MADRS) score >31
5) Prior intracerebral surgical intervention for PD including deep brain stimulation, lesional surgery, growth factor administration, gene therapy or cell transplantation
6) Already actively participating in a research study that might conflict with this trial
7) Prior or current use of statins as a lipid lowering therapy
8) Intolerance of statins
9) Untreated hypothyroidism
10) End stage renal disease (creatinine clearance <30 mL/min) or history of severe cardiac disease (angina, myocardial infarction or cardiac surgery in preceding two years)
11) Estimated Glomerular Filtration Rate (eGFR) <30 mL/min
12) History of alcoholism or liver impairment
13) Creatine kinase (CK) >1.1 x upper limit of normal (ULN)
14) Aspartate transaminase (AST) or alanine transaminase (ALT) >1.1 x ULN
15) Females who are pregnant or breast feeding or of child-bearing potential and unwilling to use appropriate contraception methods whilst on trial treatment
16) Currently taking any medication contraindicated with simvastatin use
17) Any requirement for statin use
18) Regular participation in endurance or high-impact sports
19) Unable to abstain from consumption of grapefruit-based products

Outcome measures

The primary outcome is the change in MDS-UPDRS part III motor subscale score in the OFF state between baseline and 24 months(14). Secondary outcomes at 12, 24 and 26 months include:

- MDS-UPDRS total score in the practically defined ON state
- MDS-UPDRS part II subscale score in the practically defined ON state
- Timed motor tests – finger tapping and timed walk test (10MWT) in the OFF state, electromagnetic sensor (EMS) assessment in the OFF and ON state
- Montgomery and Asberg Depression Rating Scale (MADRS)
- The Addenbrooke's Cognitive Assessment-III (ACE-III)
- Non-Motor Symptom assessment scale (NMSS)
- Parkinson's disease Questionnaire (PDQ-39)
- Changes in PD medication as measured by levodopa-equivalent dose (LED)
- Cholesterol levels (total, HDL, total/HDL ratio)
- King's PD pain scale (KPPS)
- EuroQoL 5D-5L health status questionnaire (EQ-5D-5L)
- Safety and tolerability of trial medication by adverse events (AEs) review.
- Incidence of diabetes mellitus at 24 months, using a glycated haemoglobin (HbA1c) level of 6.5% (48mmol/mol) as diagnostic of diabetes mellitus(22)

Participant identification and initial telephone screening (T_1)

Potentially suitable patients were identified via clinical lists, research registers, and publicity/word of mouth. Patients who expressed interest in the study were sent a study invitation letter and Participant Information Sheet (PIS). A member of the local research team subsequently telephoned the patient to discuss the study further, ascertain further interest and establish potential eligibility for the study.

Consent and screening visit (V_1)

The study schedule is depicted in Table 2. Interested patients deemed to be potentially eligible for the study were invited to attend a local screening appointment. After patients had had any questions answered, those who were willing, and appeared to meet the study eligibility criteria, were asked to provide written informed consent before proceeding with full screening for the study. The written informed consent process was undertaken by the PI or by an appropriately trained member of the research team as delegated by the PI, depending on local arrangements. Initial screening included recording of demographic details, medical history and concomitant medication. Patients completed the wearing-off questionnaire (WOQ-9), MoCA and MADRS with the PI (or authorised delegate) and underwent a physical examination by the PI (or authorised delegate), including assessment of modified Hoehn and Yahr stage. Blood samples for creatine kinase (CK), aspartate transaminase (AST) or alanine transaminase (ALT), estimated glomerular filtration rate (eGFR), cholesterol (HDL, total), urea, electrolytes (sodium, potassium, creatinine), thyroid stimulating hormone (TSH) and glycated haemoglobin (HbA1c) were taken and analysed locally.

Calculation of cardiovascular disease risk score

NICE guidelines recommend that people with an estimated 10‐year risk of cardiovascular disease (CVD) of 10% or more should be prioritised for a full formal risk assessment for consideration of statin therapy(17). QRISK®2 is a commonly used CVD risk calculator that was used in this study to assess whether there may be an underlying requirement for statin therapy.

The QRISK®2 score (considering all risk factors) was calculated for each potential participant after their screening visit, by the Peninsula Clinical Trials Unit at Plymouth University (CTU)(18). A QRISK®2 score <10% permitted entry to the study, assuming all other eligibility criteria were satisfied. Patients with a score ≥10% were advised to discuss the implications with their GP, but were able to be included in the study regardless of whether they consulted their GP or not, providing that they were not subsequently prescribed statin therapy by their GP.

Screening for type 2 diabetes

There is some evidence that long-term use of high doses of simvastatin may be associated with an increased risk of developing insulin resistance and type 2 diabetes mellitus(19,20), although in a recent analysis there was no reported evidence of a significant association at two years in patients taking a prescribed statin(21). To monitor this, patients were screened at baseline and month 24 using a glycated haemoglobin (HbA1c) level of 6.5% (48mmol/mol) as diagnostic of diabetes mellitus(22).

Patients with an existing diagnosis of diabetes were not excluded from study participation. Those presenting with an HbA1c ≥6.5% (≥48mmol/mol) at screening, in the absence of a diabetes diagnosis, were asked to discuss the implications with their GP before proceeding further with the study, and excluded if a statin was prescribed. Patients opting not to consult their GP were considered ineligible for the study, based on the potential requirement for statins in the future.

Table 2: Study schedule

	Study period																
	Screen		Baseline	Post allocation													Wash-out
CONTACTS	T_1	V_1	V_2	T_2	V_3	T_3	T_4	V_4	T_5	T_6	V_5	T_7	T_8	V_6	T_9	T_{10}	V_7	V_8
T – Telephone **V – Clinic Visit**	- 4 weeks	Screen - 2 weeks	Baseline	2 weeks	1 month	2 months	4 months	6 months	8 months	10 months	12 months	14 months	16 months	18 months	20 months	22 months	24 months	26 months
Enrolment:																		
Eligibility screen	X	X																
Informed Consent		X																
Demographics		X																
Randomisation		◆	◆															
Treatment:																		
Prescription			X		X			X			X			X				
Simvastatin/placebo (40mg/day)			◆		◆													
Simvastatin/placebo (80mg/day)					◆												◆	
Assessments (OFF):																		
MDS-UPDRS Part III			X								X						X	X
10 Metre Walk Test			X								X						X	X
Brain (Tap) Test			X								X						X	X
Assessments (ON):																		
Complete MDS-UPDRS			X								X						X	X
ACE-III			X								X						X	X
PDQ-39			X								X						X	X
KPPS			X								X						X	X
EQ-5D-5L			X								X						X	X
LED			X								X						X	X
NMSS			X								X						X	X
MADRS		X									X						X	X
Other:																		
Cholesterol (HDL, Total)		X									X						X	X
HbA1c		X															X	
Adverse event review		◆	◆														◆	◆
Concomitant medication review		◆	◆														◆	◆
Qualitative sub-study[1]		◆	◆														◆	◆
Genetics sub-study[1]											X							
EMS sub-study[1]											X						X	

[1] See embedded sub-studies section

Final eligibility

Following the screening visit, patients who remained eligible and willing to participate in the study were invited to attend a baseline visit approximately two to eight weeks after the screening visit. This interval enabled review of the screening blood results, including time for any subsequent GP discussions, in order to confirm final eligibility for the study. If more than eight weeks had elapsed since the screening visit, all

screening assessments were repeated before proceeding to the baseline visit (nine participants required re-screen on this basis, of whom one was deemed eligible).

Allocation to simvastatin or placebo

Participants were individually randomised to receive simvastatin or matched placebo in a 1:1 ratio. A 24-hour secure web-based randomisation system was created by the CTU in conjunction with an independent statistician and was accessed by research teams at local sites. Allocation used random permuted blocks, with stratification by site and modified Hoehn & Yahr stage (≤2.0 or 2.5-3) in the 'ON' medication state. To maintain concealment, the allocation was not displayed or otherwise accessible to the person undertaking the randomisation process. Following completion of the randomisation process (at some point between the screening and baseline visits, or at the baseline visit itself), a signed prescription is passed to the relevant hospital pharmacy so that the initial one-month supply of trial medication can be dispensed for the baseline visit.

Trial treatment

The trial treatment is an over-encapsulated simvastatin 40mg tablet back-filled with microcrystalline cellulose magnesium stearate, or identically presented matched placebo containing microcrystalline cellulose magnesium stearate only. Capsules are packaged in plastic screw neck bottles with child-resistant, tamper-evident lids. Each bottle contains 100 capsules and has a unique 4-digit number with an expiry date displayed on a label that meets the current regulatory requirements. Participants are provided with a one month supply of trial medication at baseline, a five month supply at the month 1 visit, and a six month supply at months 6, 12 and 18 visits. Participants are asked to return all empty, full or partially used medication bottles at each study visit. These are returned to the local site pharmacy for capsule count as part of the assessment of compliance with study treatment.

Baseline visit (V_2)

Participants attended their baseline visit in the practically defined OFF state (see below) and underwent a series of assessments (see Table 2) before being invited to take their usual PD medications. Further assessments were then undertaken in the ON state (roughly 20 minutes after taking PD medication) before participants were provided with a one month supply of trial medication (40mg daily dose or placebo) for the initial low dose phase. Participants were also provided with a paper-based diary in which to record any dose alterations, concomitant medications or adverse events. The diary was intended to serve as an aide-memoire, with participants being asked to bring their completed diary to each study visit to aid Case Report Form (CRF) completion by the local research team. Participants were advised to contact the local research team promptly should they develop unexplained muscle pain, tenderness or weakness.

Participant follow-up and data collection

Participant follow-up is via a mixture of clinic visits and telephone contacts. Clinic visits are held at one month (V_3), then 6, 12, 18, 24 and 26 months (V_4-V_8) post-baseline. The 12, 24 and 26 month visits require attendance in the OFF state, followed by further assessments on the same day in the 'ON' state after the participant has taken his/her usual PD medication - as for baseline (V_2). Telephone contacts between visits are made at two weeks (T_2), and then at 4, 8, 10, 14, 16, 20, and 22 months (T_3-T_9) to identify any compliance problems, adverse events or changes to participants' routine medication. Additional telephone contacts may be made, as required, at the discretion of the local research team and specifically in the event of abnormal blood results being identified at any stage during the trial.

Practically defined 'OFF' and 'ON' state

Participants are asked to attend baseline, 12, 24 and 26 month study visits in the OFF state, having omitted their routine PD medication. To facilitate attendance, these visits are scheduled in the morning, and

assessments take approximately 30 minutes to complete. Short acting PD medications are omitted from 1800 hours on the day before the clinic visit. Long acting agents are omitted for the entire day before the clinic visit and also on the day of the visit itself. The local research team is able to make arrangements to provide the participant with a prescription for relevant supportive medications (e.g. zopiclone/zolpidem for night sedation, paracetamol for pain relief and/or diazepam for treatment of anxiety) as necessary. Participants may also be prescribed dispersible Madopar as a rescue medication to be taken in the event of severe difficulty with OFF state symptoms, but this would necessitate abandonment of the study visit. The visit can be rescheduled if the patient has been unable to attend in the OFF state. If the further attempt at attending in the OFF state fails, the participant is withdrawn from the study. The delivery of OFF state assessments is challenging, but we are managing this with appropriate interaction with, and training of, study teams, encouraging them to provide support for patients, such as the use of taxis to facilitate visit attendance and the offer of home visits if necessary.

Dose adjustments

If the participant was able to tolerate the initial low dose phase of trial medication for four weeks, the prescription was increased to 80mg daily at the one-month clinic visit. At the 24-month visit, participants stop their trial medication and a two-month washout period follows. The final visit at 26 months will be used to differentiate whether any benefit may have been symptomatic.

Participants who were unable to tolerate the 40mg dose during the first month due to unwanted symptoms, or who fulfilled the stopping criteria (see below), had their trial treatment permanently discontinued but were invited to continue with the study assessments.

During the higher dose maintenance phase, participants who are unable to tolerate the 80mg dose of study medication due to unwanted symptoms (but who do not fulfil the stopping criteria) may have their dose reduced to 40mg daily. Participants may continue on the 40mg dose for the remainder of the trial or, at the discretion of the local PI, may later be re-challenged with the 80mg dose after resolution of their symptoms.

Blinding

This is a double-blind study, hence the participants, trial management team, investigator site teams and site pharmacy staff are blind to treatment allocation throughout the trial. In the event of a potential Suspected Unexpected Serious Adverse Reaction (SUSAR) to the trial medication, unblinding will be undertaken by the sponsor in accordance with the regulatory requirements. Unblinding may also be performed at the request of a senior clinician responsible for the care of a trial participant but such requests are likely to occur only in the case of a serious adverse clinical event and are expected to be rare. The Data Monitoring Committee (DMC) is able to review unblinded data as required.

Since the PI and other 'treating' site team members have access to participants' blood results and review all reported adverse events, a separate 'assessing' member of the research team undertakes the MDS-UPDRS and other outcome assessments after appropriate training. The same outcome assessor is used at all visits for an individual participant and sites are requested to identify back-up personnel to cover staff absences and avoid cross-over of 'assessing' and 'treating' team members. Telephone follow-up calls are not to be made by assessors.

Participant monitoring

At each study visit or telephone call, participants are asked about any adverse events experienced and, dependent on reported symptoms, may be asked to provide a blood sample to check CK and/or AST/ALT levels. If a raised AST/ALT is observed in the absence of a CK result, the CK should be checked. Tables 3-5 outline the possible outcomes and any action required.

If the participant reports jaundice or new or unusually severe nausea, malaise or lethargy, an AST/ALT level should be checked (Table 3). If study treatment needs to be stopped temporarily, AST/ALT should be checked again in six weeks' time and action taken in accordance with Table 4.

If the participant reports new or unusually severe muscle pain, tenderness or weakness, the CK level should be checked (Table 5).

Adverse events may also be reported to the research team outside of a participant's scheduled clinic visit, either by the participant, non-study clinician or other informant by contacting the trial centre.

Table 3: AST/ALT monitoring outcomes and action required

Observation	Action required	Repeat observation	Action required
AST/ALT >3xULN	Repeat sample within 1 week.	AST/ALT >4xULN	Stop study treatment temporarily.
		AST/ALT >2xULN but ≤4 x ULN	Repeat again within 3 weeks. If remains >2xULN stop study treatment temporarily.
AST/ALT >2xULN but ≤3xULN	Repeat again within 3 weeks.	AST/ALT >3xULN	Stop study treatment temporarily.
		AST/ALT >2xULN but ≤3xULN	Repeat again within 3 weeks. If remains >2xULN stop study treatment temporarily.

Table 4: AST/ALT monitoring outcomes and action required 6 weeks after temporary stop of study treatment

Observation	Action required	Subsequent action required
AST/ALT >1.5xULN	Stop study treatment permanently.	Repeat every 3 weeks until AST/ALT reverts to normal (i.e. ≤1.5xULN).
AST/ALT ≤1.5xULN	Study treatment can be restarted.	Repeat twice at 3-week intervals. AST/ALT must remain ≤2xULN, otherwise study treatment should be stopped permanently.

Table 5: CK monitoring outcomes and action required

Observation	Action required	Repeat observation	Action required
CK >5xULN	**Stop study treatment permanently.** Repeat sample within 1 week.	Repeat every 3 weeks until CK reverts to normal (i.e. ≤3xULN).	Repeat every 3 weeks until CK reverts to normal (i.e. ≤3xULN).
CK >4xULN but ≤5xULN that cannot be explained (i.e. trauma, heavy exercise etc.)	Repeat sample within 1 week.	CK remains >4xULN but ≤5xULN.	Stop study treatment temporarily. Check CK again in 6 weeks; • If CK >3xULN stop study treatment permanently. • If CK ≤3xULN study treatment can be restarted with 2 further repeats at 3 week intervals (at which CK must remain ≤3xULN otherwise study treatment must be stopped permanently).

Stopping criteria for discontinuation of trial treatment

The defined stopping criteria for the discontinuation of trial medication are:

(1) Abnormalities in CK or ALT/AST fulfilling stopping criteria as outlined above, OR

(2) New severe muscular symptoms (progressive or persistent), not attributable to other cause, which in the opinion of the PI may be related to the study medication even in the absence of abnormal CK.

(3) Onset of a clinical condition for which prescription of a statin is indicated.

Pharmacovigilance

Safety and tolerability of the trial treatment is monitored throughout the study by means of regular clinic visits and interim telephone follow-up review of all participants. All serious adverse events (SAEs) are recorded and reported, whether they are deemed related to the trial treatment or not. Quarterly summaries of all SAEs are provided to the DMC and study sponsor. Any potential Sudden Unexpected Serious Adverse Reaction (SUSAR) will be reported immediately to the sponsor who will have the facility to unblind the treatment allocation independently of the trial team and report onwards as necessary.

Non-serious adverse events deemed possibly, probably or definitely related to trial treatment are also recorded, monitored by the Trial Management Group and reported to the DMC.

Embedded sub-studies

The three embedded sub-studies will be described in more detail in separate publications. The 'Experience of Trial Participation' sub-study aims to develop an understanding of the barriers and facilitators to participating in clinical trials for people living with PD. It includes a quantitative component (feedback surveys) for all participants and a qualitative component (semi-structured interviews and focus groups) in a sample of participants and their carers. Part of this sub-study involves an evaluation of The Cure Parkinson's Trust's Charter for Clinical Trials in Parkinson's, which aims to set standards of practice for both participants

and clinicians involved in clinical trials for PD. All patients approached for the PD STAT study were provided with a copy of this charter and asked to provide feedback on its usefulness.

The 'genetic sub-study' aims to identify the genetic markers that may be associated with PD disease course, severity or variation in treatment responsiveness. PD STAT participants are asked to provide separate written informed consent, followed by collection of two 10mL blood samples, usually at the 12-month clinic visit. One sample is sent to University College London Neurogenetics Department to be stored with other samples in a biobank within the Institute of Neurology. The inherited material (DNA and genes) are extracted from the sample in accordance with the analytical plan agreed by the genetic sub-study investigator and stored in the Cure Parkinson's Trust DNA bank. The second sample is sent to the Genetic Support Services, Culture Collections, Public Health England laboratory for preparation and storage of peripheral blood lymphocytes and potential future cell lines.

The 'electromagnetic sensor measurement' sub-study is an exploratory study conducted in a sub-set of participants. It aims to evaluate the use of electromagnetic sensors (Polhemus Inc.) in the measurement of bradykinesia and tremor and is completed alongside the MDS-UPDRS motor assessments at the 12 and 24-month visits. A participant is required to wear the sensors on the index finger and thumb when performing the assessments, in addition to the visual assessment conducted by the assessor.

Patient and Public Involvement

Patient and Public Involvement (PPI) representatives are members of both the Trial Management Group (TMG) and Trial Steering Committee (TSC). They were involved in the design of the study and reviewed and advised on all participant-facing the study documentation; they will also be closely involved in dissemination of results to participants and patient groups.

Study management

The study sponsor organisation is the University Hospitals Plymouth NHS Foundation Trust, Derriford, Plymouth PL6 5FP. Day to day trial management is administered through the UKCRC-registered Peninsula Clinical Trials Unit (CTU) at Plymouth University. The CTU conducts central and site monitoring in accordance with a risk-based monitoring plan and the study sponsor may audit trial conduct as deemed appropriate.

The TMG, which includes two patient members, meets regularly to monitor and discuss the progress of the trial, and to address any issues that may arise. The TSC, with an independent chair and two other PPI members, meets once or twice a year to oversee the conduct of the trial. An independent DMC, comprising two clinicians and a statistician, meets at similar intervals to the TSC to monitor safety and ethical issues, including any participant drop-outs and overall data completeness. The agreed roles and responsibilities of both committees are set out in written charters.

Data management

Research teams at all sites will ensure that participants' anonymity is maintained on all documents. Data are collected and stored in accordance with the Data Protection Act, 1998 and General Data Protection Regulation, 2018. Within the CTU, pseudonymised paper-based study data are stored in locked filing cabinets within a locked office. Electronic records are stored in a SQL server database, stored on a restricted access, secure server maintained by the University of Plymouth. The study website is encrypted using SSL. Study data are double-data entered on to a password-protected database within the CTU, with copies retained at the relevant study site. Double-entered data are compared for discrepancies using an established procedure to verify data entry. Discrepant data will be verified using the original paper data sheets. Direct access to the trial data is overseen by the CTU, and restricted to members of the research

team and the CTU, with access granted to the sponsor on request. Copies of study data retained at study sites are securely stored for the duration of the study prior to archiving.

Confidentiality

All data are collected and managed in accordance with the General Data Protection Regulation 2018. Each participant has been allocated a unique study number and is identified in all study-related documentation by their study number and initials. All data are entered on a password-protected SQL Server database and encrypted using a stored procedure. After all data cleaning has been performed and the database locked, anonymised data will be exported to the trial statistician.

Sample size

As this study has a futility design, the direction of the hypotheses is different from that in traditional phase II efficacy or effectiveness trials. The study sample size has been calculated based on testing the null hypothesis that simvastatin is not futile, in terms of the primary outcome. If at the end of the study there is evidence to reject the null hypothesis, then simvastatin will be considered to be futile for a phase III study.

The minimum clinically important difference in UPDRS motor score has been estimated to be 2.3-2.7 points(23). The null hypothesis (H_0) in this futility study is that the mean MDS-UPDRS part III change score (between baseline and 24 months) for the simvastatin group is at least 3 points better (i.e. smaller, as higher MDS-UPDRS scores are worse) than the corresponding mean change in the placebo group. The alternative hypothesis (H_A) is that the mean MDS-UPDRS part III change score for the simvastatin group is not at least 3 points better. This can be written mathematically as:

H_0: $\mu_s \leq \mu_p - 3$ vs H_A: $\mu_s > \mu_p - 3$

where μ_s is the expected mean MDS-UPDRS part III change score from baseline to 24 months for the simvastatin group and μ_p is the corresponding expected mean change for the placebo group. Given this hypothesis a one-sided test (and associated significance level, alpha) is appropriate.

In futility studies, the error probabilities are interpreted differently from those in traditional efficacy/effectiveness studies. The type 1 (alpha) error is recommending that an effective treatment should not be considered for a phase III study and the type 2 (beta) error is recommending that an ineffective treatment should be considered for a phase III study(24). Given these different interpretations, alpha and beta are chosen relative to the futility design-based hypotheses: in this study, the one-sided alpha is set at 10% and beta at 20% (i.e. 80% power)(24). Under these design parameters, there is a 20% chance of failing to identify that simvastatin is ineffective.

Based on available data at the time of planning the PD STAT study, the expected mean increase in MDS-UPDRS part III from baseline to 12 months in the placebo group is 2.2 points, with standard deviation 7.3 points(25). Assuming that this increase in MDS-UPDRS part III is linear over time, gives an expected mean increase from baseline to 24 months of 4.4 points in the placebo group, with an assumed slightly inflated standard deviation over this period of 7.5 points.

The null hypothesis H_0: $\mu_s \leq \mu_p - 3$ can be stated equivalently as H_0: $\mu_s - \mu_p \leq -3$. To test this hypothesis, and assuming μ_p is 4.4 points, it is assumed that μ_s is 1.4 points (i.e. 4.4 minus 3). Based on a two-sample t-test with a 10% one-sided alpha, it is estimated that 24-month follow-up data are required from 57 participants per allocated group to provide 80% power to reject the null hypothesis and declare futility.

The initial calculated sample size was inflated twice. Firstly, to allow for a small proportion of participants allocated to the simvastatin group to stop taking the trial medication during the initial 4-week low dose phase. Assuming that this proportion is 15%, the previous sample size is inflated by a factor of $(1–0.15)^{-2}$, to give 79 participants per group(26). Secondly, the sample size was adjusted to allow for a (non-differential) loss to follow-up rate by 24 months of 20%. Accordingly, the sample size was further inflated by a factor of

$(1-0.2)^{-1}$, to give a sample size of 99 participants per group and a total recruitment target of 198 participants.

Statistical analysis

The primary analyses are all pre-specified and a detailed statistical analysis plan will be drafted and agreed by the DMC and signed off by the independent statistician on the TSC, prior to commencement of analyses. The study will be reported following the relevant Consolidated Standards Of Reporting Trials (CONSORT) guidelines(27).There is no planned interim analysis for this study. Primary analyses will be on an intention to treat (ITT) basis. The ITT evaluable sample will include all participants who are randomised and who commence on the higher dose phase of the study. As this is a phase II study, no imputation of missing data is planned for the primary analysis and so the ITT sample for the primary analysis of the primary outcome will include participants with baseline and 24 month MDS-UPDRS part III scores.

The statistical analyses will be undertaken blinded to the allocated group. The primary analysis will be a between-group comparison of mean change in MDS-UPDRS part III from baseline to 24 months. Specifically, a linear regression model will be fitted to MDS-UPDRS part III scores at 24 months, with allocated treatment group, baseline MDS-UPDRS part III score, the stratification variable (modified Hoehn & Yahr stage), gender and age at baseline included as covariates. Scores will be appropriately transformed if necessary. In the primary analysis of the primary outcome, if the p-value from the regression model for the adjusted treatment effect is <0.1, then the null hypothesis that simvastatin is not futile will be rejected and simvastatin will be considered to be futile for a phase III study. For completeness, the two-sided 80% confidence interval for the estimated treatment effect will also be presented, although only the upper bound of the confidence interval is of relevance when assessing for futility. If the upper bound of the confidence interval is lower than -3, there will be evidence to consider simvastatin for a phase III study.

Consideration will be given to a secondary analysis of the primary outcome on a per-protocol basis. If a sufficient number of participants drop back down to the lower dose of simvastatin, consideration will be given to a sub-group analysis of the effect of dose. These, and any other secondary analyses, such as comparing participant characteristics of responders and non-responders, will be discussed with the DMC and included in the agreed statistical analysis plan.

Secondary continuous outcomes will be compared between allocated treatment groups in a similar manner, although will not be statistically tested for futility; instead the focus will be on providing appropriate summary statistics and confidence intervals for the between-group differences. Ordered categorical outcomes will be analysed using ordinal regression analysis. Analysis of adverse events will be on a per-protocol basis.

Ethics and dissemination

The protocol has been approved by the North East – Newcastle and North Tyneside 2 Research Ethics Committee (REC Reference: 15/NE/0324). The trial is conducted in accordance with the study protocol, the principles of the Declaration of Helsinki, International Conference on Harmonisation of Good Clinical Practice (ICH GCP) and the Medicines for Human Use (Clinical Trials) Regulations, 2004. The trial has been adopted by the NIHR Clinical Research Network and has relevant local NHS research approvals. The study is sponsored by University Hospitals Plymouth NHS Trust and managed by the UKCRC-registered Peninsula CTU.

After the end of the study, pseudonymised information collected during the study will be made available to other researchers under an appropriate data sharing agreement, but it will not be possible to identify participants personally from any information shared.

Following analysis of the data, the results will be disseminated through publication of articles in peer-reviewed journals and presentations at local, national and international scientific meetings. A lay summary of the study results will be prepared with assistance from our patient TMG members and made available to study participants, PD charities and relevant support groups for wider dissemination amongst people with

PD and their families. After the end of the study, information collected during the study may be made available as an anonymised participant level dataset to other researchers under an appropriate data sharing agreement.

Discussion

There is currently no neuroprotective agent proven to slow or reverse the progression of PD. This phase II trial is required to inform the decision to progress to a definitive phase III randomised controlled trial evaluating the effectiveness of simvastatin as a neuroprotective agent to treat PD. In addition to this, the study will generate other important outputs related to trial delivery and how trial experience can be improved from the perspective of the participants.

This study has a number of strengths: it starts a shared resource with other studies in the LCT initiative with the pharmacogenetics sub-study, and the EMS sub-study provides a platform for evaluating a novel outcome measure based on wearable technology for neuroprotective studies that can be used to inform future evaluations. PD STAT importantly demonstrates that a multi-centre trial delivery platform exists within the UK to deliver a study of reasonably long duration, engaging PD patients and clinicians, which will strengthen delivery of future similar studies.

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Authors' contributions

CC is the Chief Investigator, provided clinical expertise and was responsible for conception and design of the study.

RW, AW and JZ: provided clinical and scientific expertise and helped with design of the study.

JV: contributed to study design and trial management.

KS: is the trial statistician and provided expertise in the day-to-day running of the trial.

SB and SC: provided statistical expertise in the overall design of the trial.

MW and AF: contributed to study design and PPI input.

VE and DW: were the trial managers, responsible for overseeing the day-to-day running of the trial.

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Disclaimer: The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

Competing interests statement

RW is Director of Research and Development at The Cure Parkinson's Trust.

All other authors declare no conflict of interest.

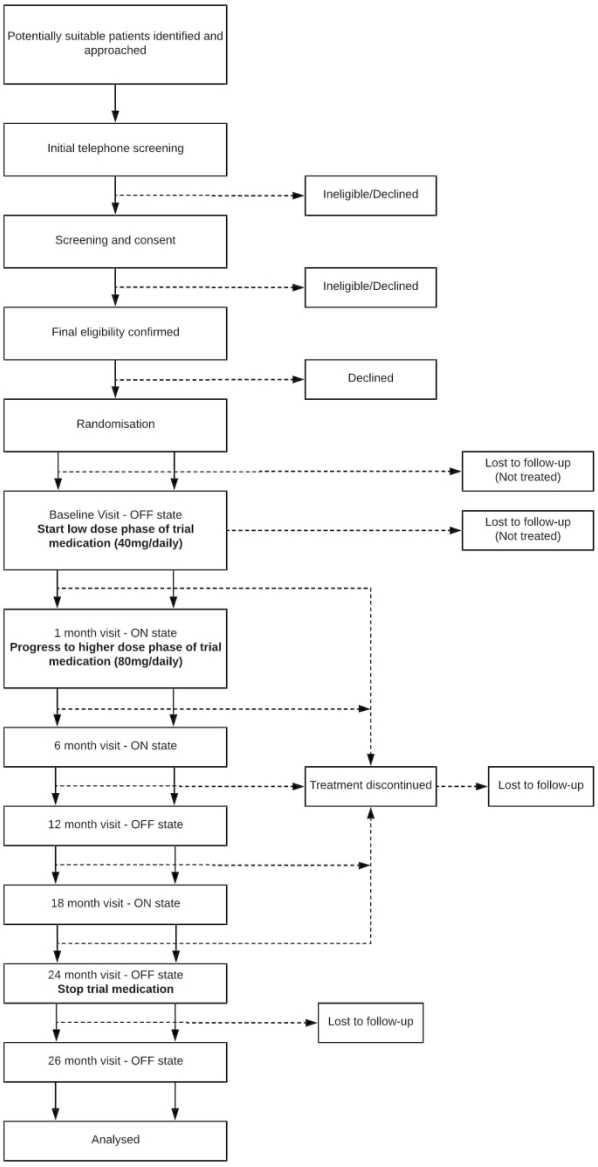

Figure 1: Study Flowchart

155x290mm (300 x 300 DPI)

Appendix A: Recruiting Sites

1. Derriford Hospital, Plymouth
2. Royal Cornwall Hospital, Truro
3. Royal Devon and Exeter Hospital
4. Musgrove Park Hospital, Taunton
5. Yeovil District Hospital
6. Christchurch Hospital, Bournemouth
7. Royal United Hospital, Bath
8. St Peter's Hospital, Chertsey
9. Charing Cross Hospital, London
10. Royal Free Hospital, London
11. Queen's Hospital, Romford
12. John Radcliffe Hospital, Oxford
13. Luton and Dunstable Hospital
14. Addenbrookes Hospital, Cambridge
15. Salford Royal Hospital
16. Fairfield General Hospital, Bury
17. Royal Preston Hospital
18. Leeds General Infirmary
19. Clinical Ageing Research Unit, Newcastle
20. Kings College Hospital, London
21. Royal Hallamshire Hospital, Sheffield
22. Norfolk and Norwich University Hospital
23. Rotherham General Hospital

18Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2

Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	#3	Date and version identifier	N/A
Funding	#4	Sources and types of financial, material, and other support	19
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 19
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	13
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	13
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	13
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant	2-3

		studies (published and unpublished) examining benefits and harms for each intervention	
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3
Objectives	#7	Specific objectives or hypotheses	3
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	3
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	3
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-9
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose	10-12

		change in response to harms, participant request, or improving / worsening disease)	
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	9
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5, 8-9
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	14-15
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A

Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study	9

		instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9-10
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13-14
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of	13

		whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	2,15-16
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	N/A
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6

Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	13
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	19
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13-14
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15-16
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	N/A

Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	13

BMJ Open

Simvastatin as a neuroprotective treatment for Parkinson's disease (PD STAT): Protocol for a double-blind, randomised, placebo-controlled futility study

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Primary Subject Heading:	Neurology
Secondary Subject Heading:	Research methods
Keywords:	Parkinson-s disease < NEUROLOGY, Statin, MDS-UPDRS, Randomised controlled futility study, Neuroprotective effect

Simvastatin as a neuroprotective treatment for Parkinson's disease (PD STAT): Protocol for a double-blind, randomised, placebo-controlled futility study

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ABSTRACT

Introduction: Parkinson's disease (PD) is a progressive neurodegenerative condition affecting approximately 185,000 people in the UK. No drug has been proven to slow disease progression. Epidemiological and pre-clinical data support simvastatin, a widely used cholesterol-lowering drug with a well-established safety profile, having neuroprotective properties. The aim of this study (PD STAT) is to determine whether simvastatin has the potential to slow PD progression. The study is part of the International Linked Clinical Trials (LCT) initiative coordinated by The Cure Parkinson's Trust. This paper describes the protocol for the PD STAT study.

Methods and analysis: PD STAT is a double-blind, randomised, placebo-controlled, multi-centre, parallel group, futility trial in patients with PD of mild-moderate severity. 235 participants have been recruited and randomly allocated in a 1:1 ratio to receive either oral simvastatin or matched placebo. Treatment involves a one month low dose phase (40mg daily), followed by a 23 month high dose phase (80mg daily) and ends with a two month washout period. Participants are reviewed at clinic visits at one month, 6, 12, 18, 24 and 26 months post-baseline, with interim telephone follow-up to monitor for adverse events.

The primary outcome is the change in the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III motor subscale score in the practically defined OFF medication state (OFF state) between baseline and 24 months. Primary analysis will be on a modified intention to treat basis and will include only those participants who progress to the high dose phase of the study.

Ethics and dissemination: The protocol has been approved by the North East – Newcastle and North Tyneside 2 Research Ethics Committee. The results will be disseminated via research articles in peer-reviewed journals and presentations at local, national and international scientific meetings, as well as disseminated via patient groups, websites and networks. A summary of the study findings will be posted to participants at the end of the study.

Registration: ISRCTN16108482 (prospectively registered); EudraCT 2015-000148-40; ClinicalTrials.gov NCT02787590

Key words: Parkinson's disease; statin; randomised controlled futility study; neuroprotective effect; MDS-UPDRS

Word count 5575

Strengths and limitations of this study

- Independent, blinded outcome assessors not involved in participant treatment, reduces likelihood of bias in results
- OFF state MDS-UPDRS assessments, the current gold standard for evaluating disease progression
- Standardised training for raters reduces inter-rater variability
- Embedded sub-study to evaluate the participant's trial experience and inform future trial design
- Long duration of study increases risk of drop-out/loss to follow-up

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative condition affecting approximately one person in every 350 in the UK(1). Furthermore, with population growth and an increasingly ageing population, the estimated prevalence and incidence of Parkinson's disease in the UK are increasing. There are currently no

known treatments that slow the rate of neuronal loss or clinical progression in PD. All currently licensed therapies are symptomatic.

Epidemiological and pre-clinical data support a possible neuroprotective role for statins in PD, with statin use being associated with lower PD incidence(2,3). Simvastatin has been shown in various toxin and genetic cell culture and rodent PD models to influence several pathways thought to be of relevance in PD etiopathogenesis, including inflammation and microglial activation, oxidative stress and α-synuclein aggregation(4,5). A beneficial effect of simvastatin on dopamine neuron survival and motor function has been observed in acute(6) and chronic(4) 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mouse models. Additionally, statins may have symptomatic effects on dyskinesia and depression in PD(4). Interestingly, simvastatin has been shown to reduce the rate of brain atrophy in secondary progressive multiple sclerosis(7); it is likely that some of the mechanisms underlying neuronal death are similar in this and other neurodegenerative diseases. This finding therefore lends support to investigating the potential long-term disease-modifying effects of simvastatin in PD. In 2012, the International PD Linked Clinical Trials initiative (LCT) was established by The Cure Parkinson's Trust to identify potential new neuroprotective treatments for PD by repurposing drugs that have been approved, or are in current clinical development, to treat other conditions(8). On the basis that simvastatin has a well-established safety profile(9,10), it was one of the first drugs selected by the LCT committee to be tested in a clinical trial in PD patients to determine its disease-modifying potential.

Clinical trials of potential neuroprotective agents in PD are difficult to design, given the variability in disease phenotype and rate of progression, as well as the potential confounding factor of a symptomatic response. In addition there is no reliable biomarker for assessing disease progression(11). Initially used in oncology trials, a trial with a futility design allows for a relatively short study duration and smaller sample size in comparison with the typical phase II/III trial design(12). The futility design typically has a single treatment arm and tests whether a new treatment exceeds a pre-defined futility threshold(12). In neurological diseases such as PD, the lack of a concurrent control group has led to criticism of subsequent findings from futility trials(13) but it is possible to test for futility using a randomised parallel group design. There is, therefore, increasing interest in the use of futility trials to provide an efficient method for early phase studies to ascertain whether there is sufficient evidence to justify conducting larger, longer and more expensive phase III trials. The PD STAT trial is a phase II futility study, which aims to determine whether simvastatin has potential to reduce the rate of neurodegenerative decline in patients with PD.

Aims and objectives

The aim of the study is to determine whether the cholesterol-lowering drug, simvastatin, has potential as a neuroprotective therapy in PD. The primary objective of the PD STAT study is to determine whether simvastatin is clearly ineffective (futile) in preventing the clinical decline of PD as measured by the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) motor score in patients in the OFF state(14). Secondary objectives are to confirm the safety and tolerability of simvastatin in patients with PD, to distinguish symptomatic effects of simvastatin from disease modifying effects, and to evaluate the impact of simvastatin on activities of daily living, timed motor tests, cognitive ability, mood, behaviour, non-motor symptoms and quality of life in patients with moderate PD using standard validated tools of assessment. The results of this study will help to determine the merits of conducting a larger, definitive phase III study to assess the neuroprotective and/or disease-modifying effectiveness of simvastatin.

METHODS AND ANALYSIS

This protocol is reported in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidance for protocols of clinical trials(15).

Trial design and setting

This is a double-blind, randomised, placebo-controlled, multi-centre, parallel group trial in patients with PD of moderate severity. There are three embedded sub-studies. Participants are individually randomised in a 1:1 ratio to receive either oral simvastatin or matched placebo for 24 months. A one-month low dose phase (40mg daily) is followed by a 23-month high dose phase (80mg daily) and treatment ends with a two-month washout period. Recruitment took place between March 2016 and March 2018, with a target of at least 198 participants progressing successfully to the high dose phase of the study; 26 month follow-up of all participants is expected to be completed by May 2020. The trial design, including scheduled follow-up assessments, is summarised in Figure 1.

A 12-month treatment period was originally considered but it was felt that this might not be long enough to demonstrate any disease modifying effect; hence, participants are each treated for 24 months. Should this futility study have positive results, the additional collection of 12-month outcome data, as well as outcome data collected at the primary endpoint of 24 months, will enable assessment of any potential benefit at 12 months to assist with design of future studies.

The trial is being conducted in 23 NHS Trusts across England. A list of recruiting sites is provided in Appendix A. A local principal investigator (PI), supported by at least two other staff members (e.g. research nurse or PD specialist nurse), leads the conduct of the study at each participating site. Participants are followed up on an outpatient basis at 1 month, 6, 12, 18, 24, and 26 months post baseline (treatment start), with regular interim telephone contact.

Study population

The study population includes patients aged between 40 and 90 years with a diagnosis of idiopathic PD, a modified Hoehn and Yahr stage of ≤3.0 in the ON medication state, and who are on dopaminergic treatment with experience of wearing-off phenomenon (as defined by the nine-item wearing-off questionnaire(16)). Patients are excluded if they have a diagnosis (or suspicion of) another cause for their parkinsonism, or have any prior use, current use, intolerance of or requirement for, statins. A full list of patient inclusion and exclusion criteria is listed in Table 1.

Table 1: Inclusion and Exclusion criteria

Inclusion criteria

1) Diagnosis of idiopathic PD
2) Modified Hoehn and Yahr stage ≤ 3.0 in the ON medication state
3) Age 40-90 years
4) On dopaminergic treatment with wearing-off phenomenon
5) Able to comply with study protocol and willing to attend necessary study visits

Exclusion criteria

1) Diagnosis or suspicion of other cause for parkinsonism
2) Known abnormality on CT or MRI brain imaging considered to be causing symptoms or signs of neurological dysfunction, or considered likely to compromise compliance with study protocol
3) Concurrent dementia defined by a Montreal Cognitive Assessment (MoCA) score <21
4) Concurrent severe depression defined by Montgomery and Asberg Depression Rating Scale (MADRS) score >31
5) Prior intracerebral surgical intervention for PD including deep brain stimulation, lesional surgery, growth factor administration, gene therapy or cell transplantation
6) Already actively participating in a research study that might conflict with this trial
7) Prior or current use of statins as a lipid lowering therapy
8) Intolerance of statins
9) Untreated hypothyroidism
10) End stage renal disease (creatinine clearance <30 mL/min) or history of severe cardiac disease (angina, myocardial infarction or cardiac surgery in preceding two years)
11) Estimated Glomerular Filtration Rate (eGFR) <30 mL/min
12) History of alcoholism or liver impairment
13) Creatine kinase (CK) >1.1 x upper limit of normal (ULN)
14) Aspartate transaminase (AST) or alanine transaminase (ALT) >1.1 x ULN
15) Females who are pregnant or breast feeding or of child-bearing potential and unwilling to use appropriate contraception methods whilst on trial treatment
16) Currently taking any medication contraindicated with simvastatin use
17) Any requirement for statin use
18) Regular participation in endurance or high-impact sports
19) Unable to abstain from consumption of grapefruit-based products

Outcome measures

The primary outcome is the change in MDS-UPDRS part III motor subscale score in the OFF state between baseline and 24 months(14). Secondary outcomes at 12, 24 and 26 months include:

- MDS-UPDRS total score in the practically defined ON state
- MDS-UPDRS part II subscale score in the practically defined ON state
- Timed motor tests – finger tapping and timed walk test (10MWT) in the OFF state, electromagnetic sensor (EMS) assessment in the OFF and ON state
- Montgomery and Asberg Depression Rating Scale (MADRS)
- The Addenbrooke's Cognitive Assessment-III (ACE-III)
- Non-Motor Symptom assessment scale (NMSS)
- Parkinson's disease Questionnaire (PDQ-39)
- Changes in PD medication as measured by levodopa-equivalent dose (LED)
- Cholesterol levels (total, HDL, total/HDL ratio)
- King's PD pain scale (KPPS)
- EuroQoL 5D-5L health status questionnaire (EQ-5D-5L)
- Safety and tolerability of trial medication by adverse events (AEs) review.
- Incidence of diabetes mellitus at 24 months, using a glycated haemoglobin (HbA1c) level of 6.5% (48mmol/mol) as diagnostic of diabetes mellitus(17)

Participant identification and initial telephone screening (T_1)

Potentially suitable patients were identified via clinical lists, research registers, and publicity/word of mouth. Patients who expressed interest in the study were sent a study invitation letter and Participant Information Sheet (PIS). A member of the local research team subsequently telephoned the patient to discuss the study further, ascertain further interest and establish potential eligibility for the study.

Consent and screening visit (V_1)

The study schedule is depicted in Table 2. Interested patients deemed to be potentially eligible for the study were invited to attend a local screening appointment. After patients had had any questions answered, those who were willing, and appeared to meet the study eligibility criteria, were asked to provide written informed consent before proceeding with full screening for the study. The written informed consent process was undertaken by the PI or by an appropriately trained member of the research team as delegated by the PI, depending on local arrangements. Initial screening included recording of demographic details, medical history and concomitant medication. Patients completed the wearing-off questionnaire (WOQ-9), MoCA and MADRS with the PI (or authorised delegate) and underwent a physical examination by the PI (or authorised delegate), including assessment of modified Hoehn and Yahr stage. Blood samples for creatine kinase (CK), aspartate transaminase (AST) or alanine transaminase (ALT), estimated glomerular filtration rate (eGFR), cholesterol (HDL, total), urea, electrolytes (sodium, potassium, creatinine), thyroid stimulating hormone (TSH) and glycated haemoglobin (HbA1c) were taken and analysed locally.

Calculation of cardiovascular disease risk score

NICE guidelines recommend that people with an estimated 10‐year risk of cardiovascular disease (CVD) of 10% or more should be prioritised for a full formal risk assessment for consideration of statin therapy(17). QRISK®2 is a commonly used CVD risk calculator that was used in this study to assess whether there may be an underlying requirement for statin therapy.

The QRISK®2 score (considering all risk factors) was calculated for each potential participant after their screening visit, by the Peninsula Clinical Trials Unit at Plymouth University (CTU)(18). A QRISK®2 score <10% permitted entry to the study, assuming all other eligibility criteria were satisfied. Patients with a score ≥10% were advised to discuss the implications with their GP, but were able to be included in the study regardless of whether they consulted their GP or not, providing that they were not subsequently prescribed statin therapy by their GP.

Screening for type 2 diabetes

There is some evidence that long-term use of high doses of simvastatin may be associated with an increased risk of developing insulin resistance and type 2 diabetes mellitus(19,20), although in a recent analysis there was no reported evidence of a significant association at two years in patients taking a prescribed statin(21). To monitor this, patients were screened at baseline and month 24 using a glycated haemoglobin (HbA1c) level of 6.5% (48mmol/mol) as diagnostic of diabetes mellitus(22).

Patients with an existing diagnosis of diabetes were not excluded from study participation. Those presenting with an HbA1c ≥6.5% (≥48mmol/mol) at screening, in the absence of a diabetes diagnosis, were asked to discuss the implications with their GP before proceeding further with the study, and excluded if a statin was prescribed. Patients opting not to consult their GP were considered ineligible for the study, based on the potential requirement for statins in the future.

Table 2: Study schedule

	Study period																
	Screen		Baseline	Post allocation													Wash-out
CONTACTS	T_1	V_1	V_2	T_2	V_3	T_3	T_4	V_4	T_5	T_6	V_5	T_7	T_8	V_6	T_9	T_{10}	V_7	V_8
T – Telephone **V – Clinic Visit**	- 4 weeks	Screening	Baseline	2 weeks	1 month	2 months	4 months	6 months	8 months	10 months	12 months	14 months	16 months	18 months	20 months	22 months	24 months	26 months
Enrolment:																		
Eligibility screen	X	X																
Informed Consent		X																
Demographics		X																
Randomisation		◆	◆															
Treatment:																		
Prescription			X		X			X			X			X				
Simvastatin/placebo (40mg/day)			◆		◆													
Simvastatin/placebo (80mg/day)					◆												◆	
Assessments (OFF):																		
MDS-UPDRS Part III			X								X						X	X
10 Metre Walk Test			X								X						X	X
Brain (Tap) Test			X								X						X	X
Assessments (ON):																		
Complete MDS-UPDRS			X								X						X	X
ACE-III			X								X						X	X
PDQ-39			X								X						X	X
KPPS			X								X						X	X
EQ-5D-5L			X								X						X	X
LED			X								X						X	X
NMSS			X								X						X	X
MADRS		X									X						X	X
Other:																		
Cholesterol (HDL, Total)		X									X						X	X
HbA1c		X															X	
Adverse event review		◆																◆
Concomitant medication review		◆																◆
Qualitative sub-study[1]		◆																◆
Genetics sub-study[1]											X							
EMS sub-study[1]											X						X	

[1] See embedded sub-studies section

Final eligibility

Following the screening visit, patients who remained eligible and willing to participate in the study were invited to attend a baseline visit approximately two to eight weeks after the screening visit. This interval enabled review of the screening blood results, including time for any subsequent GP discussions, in order to confirm final eligibility for the study. If more than eight weeks had elapsed since the screening visit, all

screening assessments were repeated before proceeding to the baseline visit (nine participants required re-screen on this basis, of whom one was deemed eligible).

Allocation to simvastatin or placebo

Participants were individually randomised to receive simvastatin or matched placebo in a 1:1 ratio. A 24-hour secure web-based randomisation system was created by the CTU in conjunction with an independent statistician and was accessed by research teams at local sites. Allocation used random permuted blocks, with stratification by site and modified Hoehn & Yahr stage (≤2.0 or 2.5-3) in the 'ON' medication state. To maintain concealment, the allocation was not displayed or otherwise accessible to the person undertaking the randomisation process. Following completion of the randomisation process (at some point between the screening and baseline visits, or at the baseline visit itself), a signed prescription is passed to the relevant hospital pharmacy so that the initial one-month supply of trial medication can be dispensed for the baseline visit.

Trial treatment

The trial treatment is an over-encapsulated simvastatin 40mg tablet back-filled with microcrystalline cellulose magnesium stearate, or identically presented matched placebo containing microcrystalline cellulose magnesium stearate only. Capsules are packaged in plastic screw neck bottles with child-resistant, tamper-evident lids. Each bottle contains 100 capsules and has a unique 4-digit number with an expiry date displayed on a label that meets the current regulatory requirements. Participants are provided with a one month supply of trial medication at baseline, a five month supply at the month 1 visit, and a six month supply at months 6, 12 and 18 visits. Participants are asked to return all empty, full or partially used medication bottles at each study visit. These are returned to the local site pharmacy for capsule count as part of the assessment of compliance with study treatment.

Baseline visit (V_2)

Participants attended their baseline visit in the practically defined OFF state (see below) and underwent a series of assessments (see Table 2) before being invited to take their usual PD medications. Further assessments were then undertaken in the ON state (roughly 20 minutes after taking PD medication) before participants were provided with a one month supply of trial medication (40mg daily dose or placebo) for the initial low dose phase. Participants were also provided with a paper-based diary in which to record any dose alterations, concomitant medications or adverse events. The diary was intended to serve as an aide-memoire, with participants being asked to bring their completed diary to each study visit to aid Case Report Form (CRF) completion by the local research team. Participants were advised to contact the local research team promptly should they develop unexplained muscle pain, tenderness or weakness.

Participant follow-up and data collection

Participant follow-up is via a mixture of clinic visits and telephone contacts. Clinic visits are held at one month (V_3), then 6, 12, 18, 24 and 26 months (V_4-V_8) post-baseline. The 12, 24 and 26 month visits require attendance in the OFF state, followed by further assessments on the same day in the 'ON' state after the participant has taken his/her usual PD medication - as for baseline (V_2). Telephone contacts between visits are made at two weeks (T_2), and then at 4, 8, 10, 14, 16, 20, and 22 months (T_3-T_9) to identify any compliance problems, adverse events or changes to participants' routine medication. Additional telephone contacts may be made, as required, at the discretion of the local research team and specifically in the event of abnormal blood results being identified at any stage during the trial.

Practically defined 'OFF' and 'ON' state

Participants are asked to attend baseline, 12, 24 and 26 month study visits in the OFF state, having omitted their routine PD medication. To facilitate attendance, these visits are scheduled in the morning, and

assessments take approximately 30 minutes to complete. Short acting PD medications are omitted from 1800 hours on the day before the clinic visit. Long acting agents are omitted for the entire day before the clinic visit and also on the day of the visit itself. The local research team is able to make arrangements to provide the participant with a prescription for relevant supportive medications (e.g. zopiclone/zolpidem for night sedation, paracetamol for pain relief and/or diazepam for treatment of anxiety) as necessary. Participants may also be prescribed dispersible Madopar as a rescue medication to be taken in the event of severe difficulty with OFF state symptoms, but this would necessitate abandonment of the study visit. The visit can be rescheduled if the patient has been unable to attend in the OFF state. If the further attempt at attending in the OFF state fails, the participant is withdrawn from the study. The delivery of OFF state assessments is challenging, but we are managing this with appropriate interaction with, and training of, study teams, encouraging them to provide support for patients, such as the use of taxis to facilitate visit attendance and the offer of home visits if necessary.

Dose adjustments

If the participant was able to tolerate the initial low dose phase of trial medication for four weeks, the prescription was increased to 80mg daily at the one-month clinic visit. At the 24-month visit, participants stop their trial medication and a two-month washout period follows. The final visit at 26 months will be used to differentiate whether any benefit may have been symptomatic.

Participants who were unable to tolerate the 40mg dose during the first month due to unwanted symptoms, or who fulfilled the stopping criteria (see below), had their trial treatment permanently discontinued but were invited to continue with the study assessments.

During the higher dose maintenance phase, participants who are unable to tolerate the 80mg dose of study medication due to unwanted symptoms (but who do not fulfil the stopping criteria) may have their dose reduced to 40mg daily. Participants may continue on the 40mg dose for the remainder of the trial or, at the discretion of the local PI, may later be re-challenged with the 80mg dose after resolution of their symptoms.

Blinding

This is a double-blind study, hence the participants, trial management team, investigator site teams and site pharmacy staff are blind to treatment allocation throughout the trial. In the event of a potential Suspected Unexpected Serious Adverse Reaction (SUSAR) to the trial medication, unblinding will be undertaken by the sponsor in accordance with the regulatory requirements. Unblinding may also be performed at the request of a senior clinician responsible for the care of a trial participant but such requests are likely to occur only in the case of a serious adverse clinical event and are expected to be rare. The Data Monitoring Committee (DMC) is able to review unblinded data as required.

Since the PI and other 'treating' site team members have access to participants' blood results and review all reported adverse events, a separate 'assessing' member of the research team undertakes the MDS-UPDRS and other outcome assessments after appropriate training. The same outcome assessor is used at all visits for an individual participant and sites are requested to identify back-up personnel to cover staff absences and avoid cross-over of 'assessing' and 'treating' team members. Telephone follow-up calls are not to be made by assessors.

Participant monitoring

At each study visit or telephone call, participants are asked about any adverse events experienced and, dependent on reported symptoms, may be asked to provide a blood sample to check CK and/or AST/ALT levels. If a raised AST/ALT is observed in the absence of a CK result, the CK should be checked. Tables 3-5 outline the possible outcomes and any action required.

If the participant reports jaundice or new or unusually severe nausea, malaise or lethargy, an AST/ALT level should be checked (Table 3). If study treatment needs to be stopped temporarily, AST/ALT should be checked again in six weeks' time and action taken in accordance with Table 4.

If the participant reports new or unusually severe muscle pain, tenderness or weakness, the CK level should be checked (Table 5).

Adverse events may also be reported to the research team outside of a participant's scheduled clinic visit, either by the participant, non-study clinician or other informant by contacting the trial centre.

Table 3: AST/ALT monitoring outcomes and action required

Observation	Action required	Repeat observation	Action required
AST/ALT >3xULN	Repeat sample within 1 week.	AST/ALT >4xULN	Stop study treatment temporarily.
		AST/ALT >2xULN but ≤4 x ULN	Repeat again within 3 weeks. If remains >2xULN stop study treatment temporarily.
AST/ALT >2xULN but ≤3xULN	Repeat again within 3 weeks.	AST/ALT >3xULN	Stop study treatment temporarily.
		AST/ALT >2xULN but ≤3xULN	Repeat again within 3 weeks. If remains >2xULN stop study treatment temporarily.

Table 4: AST/ALT monitoring outcomes and action required 6 weeks after temporary stop of study treatment

Observation	Action required	Subsequent action required
AST/ALT >1.5xULN	Stop study treatment permanently.	Repeat every 3 weeks until AST/ALT reverts to normal (i.e. ≤1.5xULN).
AST/ALT ≤1.5xULN	Study treatment can be restarted.	Repeat twice at 3-week intervals. AST/ALT must remain ≤2xULN, otherwise study treatment should be stopped permanently.

Table 5: CK monitoring outcomes and action required

Observation	Action required	Repeat observation	Action required
CK >5xULN	**Stop study treatment permanently.** Repeat sample within 1 week.	Repeat every 3 weeks until CK reverts to normal (i.e. ≤3xULN).	Repeat every 3 weeks until CK reverts to normal (i.e. ≤3xULN).
CK >4xULN but ≤5xULN that cannot be explained (i.e. trauma, heavy exercise etc.)	Repeat sample within 1 week.	CK remains >4xULN but ≤5xULN.	Stop study treatment temporarily. Check CK again in 6 weeks; • If CK >3xULN stop study treatment permanently. • If CK ≤3xULN study treatment can be restarted with 2 further repeats at 3 week intervals (at which CK must remain ≤3xULN otherwise study treatment must be stopped permanently).

Stopping criteria for discontinuation of trial treatment

The defined stopping criteria for the discontinuation of trial medication are:

(1) Abnormalities in CK or ALT/AST fulfilling stopping criteria as outlined above, OR

(2) New severe muscular symptoms (progressive or persistent), not attributable to other cause, which in the opinion of the PI may be related to the study medication even in the absence of abnormal CK.

(3) Onset of a clinical condition for which prescription of a statin is indicated.

Pharmacovigilance

Safety and tolerability of the trial treatment is monitored throughout the study by means of regular clinic visits and interim telephone follow-up review of all participants. All serious adverse events (SAEs) are recorded and reported, whether they are deemed related to the trial treatment or not. Quarterly summaries of all SAEs are provided to the DMC and study sponsor. Any potential Suspected Unexpected Serious Adverse Reaction (SUSAR) will be reported immediately to the sponsor who will have the facility to unblind the treatment allocation independently of the trial team and report onwards as necessary.

Non-serious adverse events deemed possibly, probably or definitely related to trial treatment are also recorded, monitored by the Trial Management Group and reported to the DMC.

Embedded sub-studies

The three embedded sub-studies will be described in more detail in separate publications. The 'Experience of Trial Participation' sub-study aims to develop an understanding of the barriers and facilitators to participating in clinical trials for people living with PD. It includes a quantitative component (feedback surveys) for all participants and a qualitative component (semi-structured interviews and focus groups) in a sample of participants and their carers. Part of this sub-study involves an evaluation of The Cure Parkinson's Trust's Charter for Clinical Trials in Parkinson's, which aims to set standards of practice for both participants

and clinicians involved in clinical trials for PD. All patients approached for the PD STAT study were provided with a copy of this charter and asked to provide feedback on its usefulness.

The 'genetic sub-study' aims to identify the genetic markers that may be associated with PD disease course, severity or variation in treatment responsiveness. PD STAT participants are asked to provide separate written informed consent, followed by collection of two 10mL blood samples, usually at the 12-month clinic visit. One sample is sent to University College London Neurogenetics Department to be stored with other samples in a biobank within the Institute of Neurology. The inherited material (DNA and genes) are extracted from the sample in accordance with the analytical plan agreed by the genetic sub-study investigator and stored in the Cure Parkinson's Trust DNA bank. The second sample is sent to the Genetic Support Services, Culture Collections, Public Health England laboratory for preparation and storage of peripheral blood lymphocytes and potential future cell lines.

The 'electromagnetic sensor measurement' sub-study is an exploratory study conducted in a sub-set of participants. It aims to evaluate the use of electromagnetic sensors (Polhemus Inc.) in the measurement of bradykinesia and tremor and is completed alongside the MDS-UPDRS motor assessments at the 12 and 24-month visits. A participant is required to wear the sensors on the index finger and thumb when performing the assessments, in addition to the visual assessment conducted by the assessor.

Patient and Public Involvement

Patient and Public Involvement (PPI) representatives are members of both the Trial Management Group (TMG) and Trial Steering Committee (TSC). They were involved in the design of the study and reviewed and advised on all participant-facing study documentation; they will also be closely involved in dissemination of results to participants and patient groups.

Study management

The study sponsor organisation is the University Hospitals Plymouth NHS Foundation Trust, Derriford, Plymouth PL6 5FP. Day to day trial management is administered through the UKCRC-registered Peninsula Clinical Trials Unit (CTU) at Plymouth University. The CTU conducts central and site monitoring in accordance with a risk-based monitoring plan and the study sponsor may audit trial conduct as deemed appropriate.

The TMG, which includes two patient members, meets regularly to monitor and discuss the progress of the trial, and to address any issues that may arise. The TSC, with an independent chair and two other PPI members, meets once or twice a year to oversee the conduct of the trial. An independent DMC, comprising two clinicians and a statistician, meets at similar intervals to the TSC to monitor safety and ethical issues, including any participant drop-outs and overall data completeness. The agreed roles and responsibilities of both committees are set out in written charters.

Data management

Research teams at all sites will ensure that participants' anonymity is maintained for all documents. Data are collected and stored in accordance with the Data Protection Act, 1998 and General Data Protection Regulation, 2018. Within the CTU, pseudonymised paper-based study data are stored in locked filing cabinets within a locked office. Electronic records are stored in a SQL server database, stored on a restricted access, secure server maintained by the University of Plymouth. The study website is encrypted using SSL. Study data are double-data entered on to a password-protected database within the CTU, with copies retained at the relevant study site. Double-entered data are compared for discrepancies using an established procedure to verify data entry. Discrepant data are verified using the original paper data sheets. Direct access to the trial data is overseen by the CTU, and restricted to members of the research

team and the CTU, with access granted to the sponsor on request. Copies of study data retained at study sites are securely stored for the duration of the study prior to archiving.

Confidentiality

All data are collected and managed in accordance with the General Data Protection Regulation 2018. Each participant has been allocated a unique study number and is identified in all study-related documentation by their study number and initials. All data are entered on a password-protected SQL Server database and encrypted using a stored procedure. After all data cleaning has been performed and the database locked, anonymised data will be exported to the trial statistician.

Sample size

As this study has a futility design, the direction of the hypotheses is different from that in traditional phase II efficacy or effectiveness trials. The study sample size has been calculated based on testing the null hypothesis that simvastatin is not futile, in terms of the primary outcome. If at the end of the study there is evidence to reject the null hypothesis, then simvastatin will be considered to be futile for a phase III study.

The minimum clinically important difference in UPDRS motor score has been estimated to be 2.3-2.7 points(23). The null hypothesis (H_0) in this futility study is that the mean MDS-UPDRS part III change score (between baseline and 24 months) for the simvastatin group is at least 3 points better (i.e. smaller, as higher MDS-UPDRS scores are worse) than the corresponding mean change in the placebo group. The alternative hypothesis (H_A) is that the mean MDS-UPDRS part III change score for the simvastatin group is not at least 3 points better. This can be written mathematically as:

H_0: $\mu_s \leq \mu_p - 3$ vs H_A: $\mu_s > \mu_p - 3$

where μ_s is the expected mean MDS-UPDRS part III change score from baseline to 24 months for the simvastatin group and μ_p is the corresponding expected mean change for the placebo group. Given this hypothesis a one-sided test (and associated significance level, alpha) is appropriate.

In futility studies, the error probabilities are interpreted differently from those in traditional efficacy/effectiveness studies. The type 1 (alpha) error is recommending that an effective treatment should not be considered for a phase III study and the type 2 (beta) error is recommending that an ineffective treatment should be considered for a phase III study(24). Given these different interpretations, alpha and beta are chosen relative to the futility design-based hypotheses: in this study, the one-sided alpha is set at 10% and beta at 20% (i.e. 80% power)(24). Under these design parameters, there is a 20% chance of failing to identify that simvastatin is ineffective.

Based on available data at the time of planning the PD STAT study, the expected mean increase in MDS-UPDRS part III from baseline to 12 months in the placebo group is 2.2 points, with standard deviation 7.3 points(25). Assuming that this increase in MDS-UPDRS part III is linear over time, gives an expected mean increase from baseline to 24 months of 4.4 points in the placebo group, with an assumed slightly inflated standard deviation over this period of 7.5 points.

The null hypothesis H_0: $\mu_s \leq \mu_p - 3$ can be stated equivalently as H_0: $\mu_s - \mu_p \leq -3$. To test this hypothesis, and assuming μ_p is 4.4 points, it is assumed that μ_s is 1.4 points (i.e. 4.4 minus 3). Based on a two-sample t-test with a 10% one-sided alpha, it is estimated that 24-month follow-up data are required from 57 participants per allocated group to provide 80% power to reject the null hypothesis and declare futility.

The initial calculated sample size was inflated twice. Firstly, to allow for a small proportion of participants allocated to the simvastatin group to stop taking the trial medication during the initial 4-week low dose phase. Assuming that this proportion is 15%, the previous sample size is inflated by a factor of $(1–0.15)^{-2}$, to give 79 participants per group(26). Secondly, the sample size was adjusted to allow for a (non-differential) loss to follow-up rate by 24 months of 20%. Accordingly, the sample size was further inflated by a factor of

$(1-0.2)^{-1}$, to give a sample size of 99 participants per group and a total recruitment target of 198 participants.

Statistical analysis

The primary analyses are all pre-specified and a detailed statistical analysis plan will be drafted and agreed by the DMC and signed off by the independent statistician on the TSC, prior to commencement of analyses. The study will be reported following the principles of Consolidated Standards Of Reporting Trials (CONSORT) guidelines(27-31).There is no planned interim analysis for this study. Primary analyses will be on an intention to treat (ITT) basis. The ITT evaluable sample will include all participants who are randomised and who commence on the higher dose phase of the study. As this is a phase II study, no imputation of missing data is planned for the primary analysis and so the ITT sample for the primary analysis of the primary outcome will include participants with baseline and 24 month MDS-UPDRS part III scores.

The statistical analyses will be undertaken blinded to the allocated group. The primary analysis will be a between-group comparison of mean change in MDS-UPDRS part III from baseline to 24 months. Specifically, a linear regression model will be fitted to MDS-UPDRS part III scores at 24 months, with allocated treatment group, baseline MDS-UPDRS part III score, the stratification variable (modified Hoehn & Yahr stage), gender and age at baseline included as covariates. Scores will be appropriately transformed if necessary. In the primary analysis of the primary outcome, if the p-value from the regression model for the adjusted treatment effect is <0.1, then the null hypothesis that simvastatin is not futile will be rejected and simvastatin will be considered to be futile for a phase III study. For completeness, the two-sided 80% confidence interval for the estimated treatment effect will also be presented, although only the upper bound of the confidence interval is of relevance when assessing for futility. If the upper bound of the confidence interval is lower than -3, there will be evidence to consider simvastatin for a phase III study.

Consideration will be given to a secondary analysis of the primary outcome on a per-protocol basis. If a sufficient number of participants drop back down to the lower dose of simvastatin, consideration will be given to a sub-group analysis of the effect of dose. These, and any other secondary analyses, such as comparing participant characteristics of responders and non-responders, will be discussed with the DMC and included in the agreed statistical analysis plan.

Secondary continuous outcomes will be compared between allocated treatment groups in a similar manner, although will not be statistically tested for futility; instead the focus will be on providing appropriate summary statistics and confidence intervals for the between-group differences. Ordered categorical outcomes will be analysed using ordinal regression analysis. Analysis of adverse events will be on a per-protocol basis.

Ethics and dissemination

The protocol has been approved by the North East – Newcastle and North Tyneside 2 Research Ethics Committee (REC Reference: 15/NE/0324). The trial is conducted in accordance with the study protocol, the principles of the Declaration of Helsinki, International Conference on Harmonisation of Good Clinical Practice (ICH GCP) and the Medicines for Human Use (Clinical Trials) Regulations, 2004. The trial has been adopted by the NIHR Clinical Research Network and has relevant local NHS research approvals. The study is sponsored by University Hospitals Plymouth NHS Trust and managed by the UKCRC-registered Peninsula CTU.

After the end of the study, pseudonymised information collected during the study will be made available to other researchers under an appropriate data sharing agreement, but it will not be possible to identify participants personally from any information shared.

Following analysis of the data, the results will be disseminated through publication of articles in peer-reviewed journals and presentations at local, national and international scientific meetings. A lay summary of the study results will be prepared with assistance from our patient TMG members and made available to study participants, PD charities and relevant support groups for wider dissemination amongst people with

PD and their families. After the end of the study, information collected during the study may be made available as an anonymised participant level dataset to other researchers under an appropriate data sharing agreement.

Discussion

There is currently no neuroprotective agent proven to slow or reverse the progression of PD. This phase II trial is required to inform the decision to progress to a definitive phase III randomised controlled trial evaluating the effectiveness of simvastatin as a neuroprotective agent to treat PD. In addition to this, the study will generate other important outputs related to trial delivery and how trial experience can be improved from the perspective of the participants.

This study has a number of strengths: it starts a shared resource with other studies in the LCT initiative with the pharmacogenetics sub-study, and the EMS sub-study provides a platform for evaluating a novel outcome measure based on wearable technology for neuroprotective studies that can be used to inform future evaluations. PD STAT importantly demonstrates that a multi-centre trial delivery platform exists within the UK to deliver a study of reasonably long duration, engaging PD patients and clinicians, which will strengthen delivery of future similar studies.

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Authors' contributions

CC is the Chief Investigator, provided clinical expertise and was responsible for conception and design of the study.

RW, AW and JZ: provided clinical and scientific expertise and helped with design of the study.

JV: contributed to study design and trial management.

SC and KS: are the trial statisticians and provided expertise in the day-to-day running of the trial.

SB and SC: provided statistical expertise in the overall design of the trial.

MW and AF: contributed to study design and PPI input.

VE and DW: were the trial managers, responsible for overseeing the day-to-day running of the trial.

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Data availability statement: After the end of the study, pseudonymised information collected during the study will be made available to other researchers under an appropriate data sharing agreement. De-identified data will be made available upon reasonable request.

Disclaimer: The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

Competing interests statement

RW is Director of Research and Development at The Cure Parkinson's Trust.

All other authors declare no conflict of interest.

Figure 1: Scheduled follow-up assessments

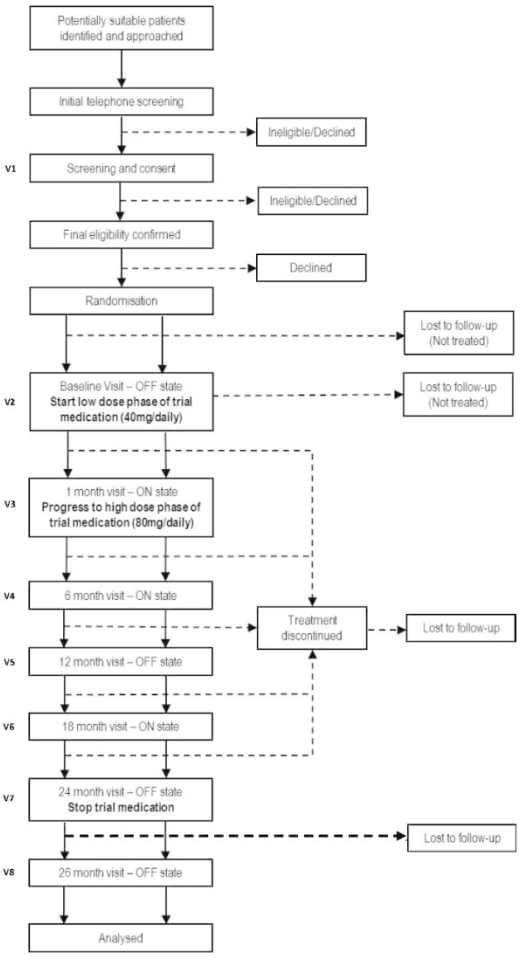

Figure 1: Scheduled follow-up assessments

210x297mm (154 x 154 DPI)

Appendix A: Recruiting Sites

1. Derriford Hospital, Plymouth
2. Royal Cornwall Hospital, Truro
3. Royal Devon and Exeter Hospital
4. Musgrove Park Hospital, Taunton
5. Yeovil District Hospital
6. Christchurch Hospital, Bournemouth
7. Royal United Hospital, Bath
8. St Peter's Hospital, Chertsey
9. Charing Cross Hospital, London
10. Royal Free Hospital, London
11. Queen's Hospital, Romford
12. John Radcliffe Hospital, Oxford
13. Luton and Dunstable Hospital
14. Addenbrookes Hospital, Cambridge
15. Salford Royal Hospital
16. Fairfield General Hospital, Bury
17. Royal Preston Hospital
18. Leeds General Infirmary
19. Clinical Ageing Research Unit, Newcastle
20. Kings College Hospital, London
21. Royal Hallamshire Hospital, Sheffield
22. Norfolk and Norwich University Hospital
23. Rotherham General Hospital

18Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2

Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	#3	Date and version identifier	N/A
Funding	#4	Sources and types of financial, material, and other support	19
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 19
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	13
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	13
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	13
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant	2-3

		studies (published and unpublished) examining benefits and harms for each intervention	
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3
Objectives	#7	Specific objectives or hypotheses	3
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	3
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	3
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-9
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose	10-12

		change in response to harms, participant request, or improving / worsening disease)	
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	9
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5, 8-9
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	14-15
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A

Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study	9

		instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9-10
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13-14
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of	13

		whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	2,15-16
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	N/A
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6

Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	13
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	19
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13-14
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15-16
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	N/A

Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	13