EJS ACT-PD

Edmond J. Safra Accelerating Clinical Trials in Parkinson's disease: A Multi-arm Multi-stage Platform Trial for potential disease modifying approaches

Version:	**V3.0**
Date:	**06th June 2025**
MRC CTU at UCL ID:	**ND002**
ISRCTN #:	**ISRCTN17799294**
CTA #:	**CTA 20363/0473/001-0001**
MREC #:	**25/LO/0039**

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GENERAL INFORMATION

This document was constructed using the MRC CTU at UCL Protocol Template Version 10.0. The CTU endorses the Standard Protocol Items: Recommendations For Interventional Trials (SPIRIT) initiative. It describes the EJS ACT-PD trial, coordinated by the Medical Research Council (MRC) Clinical Trials Unit (CTU) at University College London (UCL), and provides information about procedures for entering participants into it. The protocol should not be used as an aide-memoire or guide for the treatment of other patients. Every care has been taken in drafting this protocol, but corrections or amendments may be necessary. These will be available to the registered investigators in the trial, but sites entering patients for the first time are advised to contact the trial team to confirm they have the most up-to-date version.

COMPLIANCE

The trial will be conducted in compliance with the approved protocol, the Declaration of Helsinki 1996, the principles of Good Clinical Practice (GCP) as laid down by the ICH topic E6 (R2) as amended, the UK Data Protection Act 2018 (DPA number: Z6364106), and the UK Policy Framework for Health and Social Care Research.

The trial will adhere to the conditions and principles of GCP as outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), as amended.

SPONSOR

UCL is the trial Sponsor and has delegated responsibility for the overall management of the EJS ACT-PD trial to the MRC CTU at UCL. Queries relating to UCL sponsorship of this trial should be addressed to Max Parmar, MRC CTU at UCL Director, MRC CTU at UCL, Institute of Clinical Trials & Methodology, 90 High Holborn 2nd Floor, London, WC1V 6LJ.

FUNDING

Funding for EJS ACT-PD has been received from several organisations in the form of a united funding collaboration. These organisations are:

- The Efficacy and Mechanism Evaluation (EME) Programme, an MRC and NIHR partnership
- Cure Parkinson's
- The Michael J Fox Foundation
- Parkinson's UK
- John Black Charitable Foundation
- Gatsby Charitable Foundation
- Van Andel Institute

AUTHORISATIONS AND APPROVALS

This trial was approved by London - Fulham Research Ethics Committee and is, therefore, part of the Noth Thames NIHR Clinical Research network portfolio.

TRIAL REGISTRATION

This trial has been registered with the ISRCTN Clinical Trials Register, where it is identified as ISRCTN17799294.

RANDOMISATIONS
Participants will be randomised at each site via the OpenClinica eDC system after the eligibility criteria has been entered and confirmed.

SAE & NE REPORTING
Within 24 hours of becoming aware of an Serious Adverse Event (SAE) or Notable Event (NE), please report all SAEs and NEs via the OpenClinica eDC system
If you have any issues with entering the SAE/NE or have any questions, please email **mrcctu.ejsactpd@ucl.ac.uk**

Trial Administration

Please direct all queries to the **EJS ACT-PD Trial Team** at **MRC CTU** in the first instance; clinical queries will be passed to the **Clinical Research Fellow** via the Trial Team via mrcctu.ejsactpd@ucl.ac.uk.

Coordinating Site

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NB: throughout this document, “MRC CTU at UCL” is generally abbreviated to “CTU”.

SUMMARY OF TRIAL

SUMMARY INFORMATION TYPE	SUMMARY DETAILS
Acronym	EJS ACT-PD
Long Title of Trial	Edmond J Safra, Accelerating Clinical Trials in Parkinson's Disease (EJS ACT-PD) – a Multi-arm Multi-stage Platform Trial for potential disease modifying approaches.
Version	3.0
Date	06-Jun-2025
MRC CTU at UCL ID	ND002
ISRCTN #	ISRCTN17799294
CTA #	CTA 20363/0473/001-0001
REC #	25/LO/0039
Study Design	A Phase III multi-centre, interventional, multi-arm, multi-stage, randomised, double-blind, placebo-controlled trial to assess the clinical effects and cost-effectiveness of potential disease modifying compounds in a population representative of people with Parkinson's disease (PD) in the UK.
Setting	NHS sites across the UK.
Type of Participants to be Studied	Adults aged over 30 with a clinical diagnosis of PD.
Ancillary Studies/Sub-studies	Partner sub-study Biosamples Sub-study Digital Measures Sub-study Genetics Sub-Study (PD Frontline Collaboration)
Sponsor	University College London
Interventions to be Compared	Arm A: Standard of Care (SoC) plus placebo Arm B: SoC plus telmisartan Arm C: SoC plus terazosin

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Definitions of stages	**Interim analyses (activity):** **Stage 1 analysis:** will compare the effect of active intervention arms on disease progression, compared to placebo. This will take place when approximately 133 participants in each arm have reached 52 weeks post first dose of study medication. **Stage 2 analysis:** will compare the effect of active intervention arms on disease progression, compared to placebo. This will take place when approximately 200 participants in each arm have reached 78 weeks post first dose of study medication. **Primary analyses (efficacy):** **Stage 3 analysis (early efficacy):** treatments that passed both the stage 1 and stage 2 analyses will proceed with recruitment and follow up to the primary analyses to be assessed for effect. The stage 3 analysis will compare the effect of active interventions on disease progression, compared to placebo. This will take place when 266 participants in each arm have reached 104 weeks post first dose of study medication using a very small alpha criterion (probability of false positive). **Stage 4 analysis (final efficacy):** If the stage 3 analysis does not show efficacy, then a stage 4 primary analysis will compare the effect of active intervention arms on disease progression, compared to placebo. This will take place when approximately 266 participants in each arm have reached 156 weeks post first dose of study medication.
Study Hypothesis	Selected treatments that target key neurodegenerative / neuroprotective pathways in PD will slow disease progression compared to placebo.
Stages 1 and 2: **Interim Measure(s)**	Evidence in support of a possible reduction in disease progression as measured by the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Parts I, II & (remote) III combined with inverse variance weighting (see **Table 11**).
Stage 3 and final: **Primary Outcome Measure(s)**	Difference in rate of disease progression between the active treatment and placebo arms as measured by the MDS-UPDRS Parts I and II combined with equal weighting.
Stage 3 and final: **Secondary Outcome Measure(s)**	**Clinician reported measures:** ● Hoehn and Yahr Scale (H&Y) ● Montreal Cognitive Assessment (MoCA) ● Parkinson's disease medication use as measured by levodopa-equivalent daily dose (LEDD) ● Part III of the MDS-UPDRS in the ON medication state (remote elements only) ● Part IV of the MDS-UPDRS in the ON medication state

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	● Clinical Global Impression Scale (CGI) – Severity of illness (CGI-S) and Measure of clinical change (CGI-C). **Participant reported measures:** Difference in impact of Parkinson's disease between active treatment and placebo arms as measured by: ● The severity of depression as assessed by the Patient Health Questionnaire (PHQ-9) ● Disease-specific quality of life as assessed by the Parkinson's Disease Questionnaire (PDQ-8) ● Carers quality-of-life questionnaire for parkinsonism (PQoL Carers) Capability, quality of life and resource use in active treatment and placebo arms as measured by: ● Capability as assessed by the ICEpop CAPability measure for Older people (ICECAP-O) ● Generic health-related quality of life as assessed by the EuroQol five-dimension questionnaire (EQ-5D-5L) ● Use of health and social care resources, as assessed by the resource use questionnaire (which includes modified Client Service Receipt Inventory (CSRI) and modified iMTA Valuation of Informal Care Questionnaire (iVICQ)) ● Carer generic health-related quality of life as assessed by the EQ-5D-5L **Safety and tolerability:** ● Suicidal ideation as assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS) ● Adverse events/ Serious Adverse Events ● Treatment compliance ● Trial withdrawal and treatment discontinuation rates **Participant experience of trial participation:** ● Participant experience before, during and after trial participation as assessed by an amended Study Participant Feedback Questionnaire (SPFQ) ●
Stage 3 and final: **Exploratory Outcome Measure(s)**	Difference in rate of disease progression between active treatment and placebo arms as measured by: ● Reduction in time to reach selected clinical milestones deemed important and meaningful to people with Parkinson's (e.g., falls, cognitive decline). Long-term impact of treatment on mortality, dependent on access to routine healthcare datasets (at primary analysis and 10 year follow up time points) ● Impact of participant expectation of treatment response as measured by the participant expectations questionnaire
Health economic analysis	Pairwise cost-utility analysis (CUA) to calculate mean incremental cost per quality-adjusted life-year (QALY) gained when using active treatment pathway vs. SoC pathway over the time horizon of the

SUMMARY INFORMATION TYPE	SUMMARY DETAILS
	active treatment arm's follow-up period. QALYs will be calculated from utility scores calculated from EQ-5D-5L responses at baseline (week 0) and 13, 26, 52, 78, 104, 130, 156 weeks, and early termination visit. Costs of health and social care resources will be calculated from the perspective of the NHS and Personal Social Services using the modified CSRI and iVICQ (baseline (week 0), 26, 52, 78, 104, 130 and 156 weeks, , each time covering the preceding 6 months) to capture resource use information from participants, and other CRFs to capture intervention and concomitant medication use. This could be done for a treatment arm at any of stages 1, 2, 3 and 4 listed above, depending on when and why recruitment to the treatment arm is stopped. Secondary analyses will be performed considering PDQ-8 mapping to utility scores for QALYs, ICECAP-O for capability-adjusted life-years (CALYs), and including care partner QALYs from carer-completed EQ-5D-5L, and using wider cost perspectives, including out-of-pocket costs, private care costs, use of care home and respite care services, and paid/unpaid or informal care as captured by the resource use questionnaire. Multi-arm analyses will be performed where appropriate, potentially using network meta analysis, reporting net monetary benefit at a range of cost-effectiveness thresholds.
Randomisation	Eligibility and consent will be verified before each participant is randomised. Participants will be randomised at each site via the online trial database, accessible to authorised members of the research teams at recruiting sites. Participants will be randomised equally (e.g., 1:1:1) to each of the active treatment arms they are eligible for, or placebo. The following stratification factors of (i) biological sex; (ii) site tier; (iii) age; and (iv) Hoehn & Yahr stage will be applied at randomisation. If participants are ineligible for a specific research arm, they can be assessed for eligibility and randomised to other arms for which they are eligible. Any proposed arm-specific reasons for exclusions will be carefully reviewed to determine their likelihood to bias the rate of disease progression as judged by the primary outcome. This will determine whether: 1) Introduced bias can be accounted for in the trial analysis 2) An arm-specific placebo "sub-cohort" must be analysed
Number of Participants to be Studied	The trial will recruit a total of 1,200 participants across 2 active treatment arms and one shared placebo arm (n = 400 participants per arm). Additional active treatment arms will be added from approximately 12 months onwards with an estimated target recruitment of 400 participants per arm. Participants will be randomised across all

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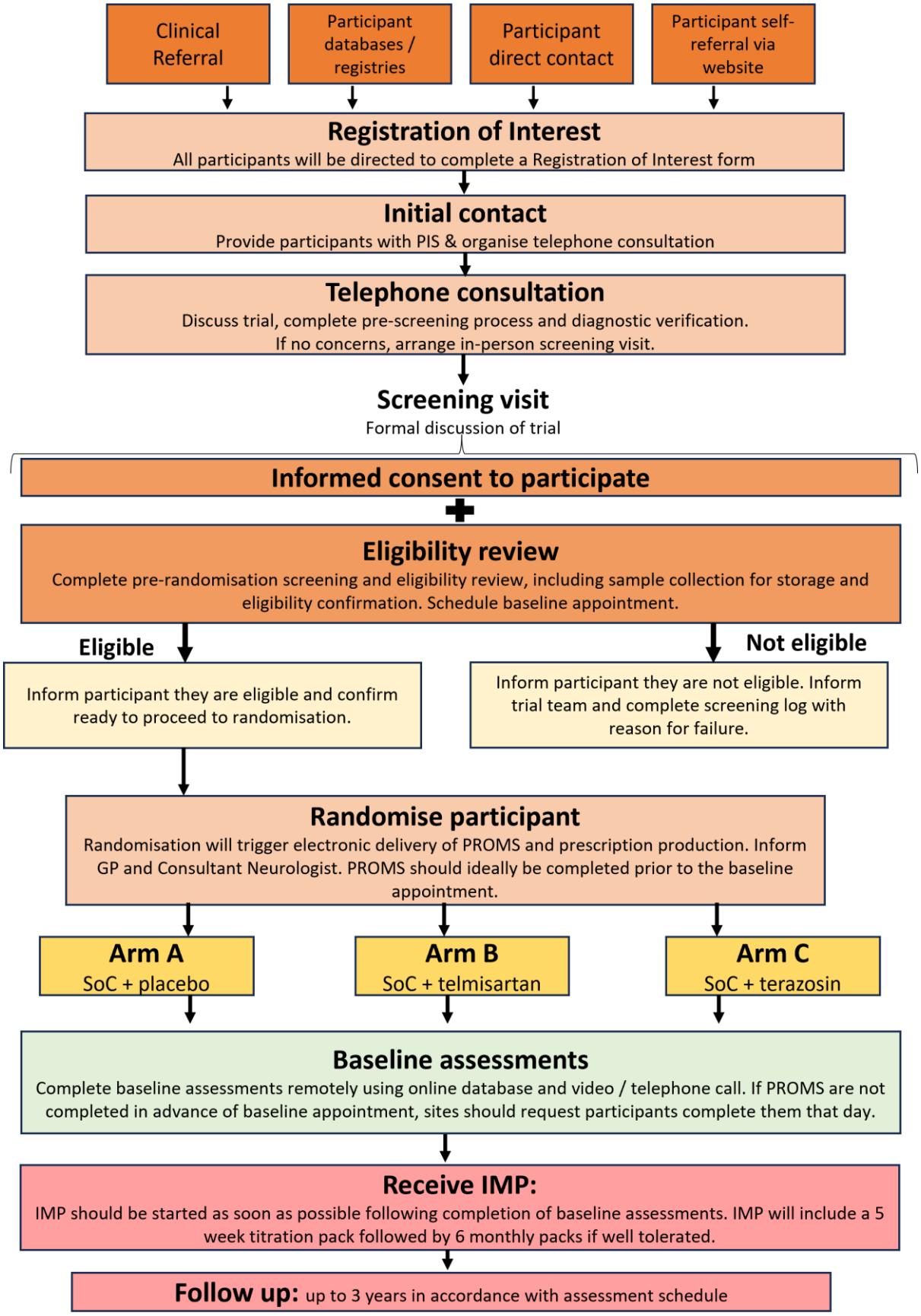
	open treatment arms, provided they meet any treatment-specific eligibility criteria.
Duration	The total trial timeframe for up to three initial treatment arms is estimated at 7 years: **Recruitment timeframe:** approximately 3-4 years from start of recruitment **Treatment timeframe:** 3 years total for each participant **Stage 1 interim analysis:** approximately 2.2 years after recruitment to treatment arm launches **Stage 2 interim analysis:** approximately 3.3 years after recruitment to treatment arm launches **Stage 3 initial efficacy analysis:** approximately 4.5 years after recruitment to treatment arm launches **Stage 4 final efficacy analysis:** approximately 5.7 years after recruitment to treatment arm launches The analyses will take place for each arm when they meet their required recruitment milestone and therefore timeframes are only an approximate estimation. As a platform trial, the study is designed to be an ongoing process for which new potential compounds can continue to be introduced and assessed without the need for dismantling or reconstructing trial infrastructure. This will enable the trial to continue recruitment and introduction of additional compounds past the initial timeframe of up to 7 years for assessing and reporting trial outcomes.
Funders	The trial has been funded by a consortium of organisations including: ● The Efficacy and Mechanism Evaluation (EME) Programme, an MRC and NIHR partnership ● Cure Parkinson's ● The Michael J Fox Foundation ● Parkinson's UK ● John Black Charitable Foundation ● Gatsby Charitable Foundation ● Van Andel Institute
Chief Investigator(s)	Professor Thomas Foltynie, University College London Professor Camille Carroll, Newcastle University

Figure 1: Trial Entry, Randomisation and Treatment



TRIAL ASSESSMENT SCHEDULE

Table 1: Trial Assessment Schedule

Activity	**Screening**	**Randomisation**	**Week 0 (Baseline)**	**Weeks 1-5 (Titration)**	**Week 13 (month 3)**	**Week 26 (month 6)**	**Week 39 (month 9)**	**Week 52 (month 12)**	**Week 65 (month 15)**	**Week 78 (month 18)**	**Week 104 (month 24)**	**Week 130 (month 30)**	**Week 156 End of study visit (month 36)**	**Week 165 Safety follow-up visit (month 38)**	**Early Termination**	**Unscheduled Visit**
Window		Ideally within 3 weeks of screening visit *(maximum of 4 weeks)*	within 4 weeks of screening visit *(maximum of 6 weeks)*	Ideally within 48 hours of completing baseline	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks [♦]	+/- 2 weeks		
Location	In-person	Telephone call+	Remote ~ or in-person	Telephone call (weekly)	Remote ~ or in-person	Remote ~ or in-person	Telephone Call	Remote ~ or in-person	Telephone Call	Remote ~ or in-person	Remote ~ or in-person	Remote ~ or in-person	Remote~ or in-person	Remote ~ or in-person	As required	As required
General activities:																
Informed consent	x															
Review of inclusion and exclusion criteria	x	x														
Demographic data (including lifestyle questions)	x															
Medical history (including previous medication exposures) [A]	x															

Activity	Screening	Randomisation	Week 0 (Baseline)	Weeks 1-5 (Titration)	Week 13 (month 3)	Week 26 (month 6)	Week 39 (month 9)	Week 52 (month 12)	Week 65 (month 15)	Week 78 (month 18)	Week 104 (month 24)	Week 130 (month 30)	Week 156 End of study visit (month 36)	Week 165 Safety follow-up visit (month 38)	Early Termination	Unscheduled Visit
Blood Pressure (Sitting, Lying and Standing) [#]	x		x										x	x	(x)	(x)
Vital signs (Pulse and Temperature)	x												x	x	(x)	(x)
Weight & Height [B]	x												x	x	(x)	(x)
Physical Examination	x															(x)
Neurological examination [C]	x															(x)
Drug accountability/ reconciliation [D]					x	x		x		x	x	x	x		(x)	(x)
Concomitant medication check [E]	x		x	x	x	x	x	x	x	x	x	x	x	x	(x)	(x)
Review/reporting of AEs/SAEs			x	x	x	x	x	x	x	x	x	x	x	x	(x)	(x)
Randomisation		x														
Prescription issued [F]		x		x*		x		x		x	x	x				
Screening & safety tests ¬																

Activity	Screening	Randomisation	Week 0 (Baseline)	Weeks 1-5 (Titration)	Week 13 (month 3)	Week 26 (month 6)	Week 39 (month 9)	Week 52 (month 12)	Week 65 (month 15)	Week 78 (month 18)	Week 104 (month 24)	Week 130 (month 30)	Week 156 End of study visit (month 36)	Week 165 Safety follow-up visit (month 38)	Early Termination	Unscheduled Visit
Electrocardiogram, 12 Lead ECG	x															(x)
Haematology & Differential Panel Whole Blood Sample [G]^	x															(x)
Biochemistry Panel [H]^	x															(x)
Liver function panel [I]^	x															(x)
Serum Sample [J]^	x															
HbA1c^	x															(x)
Urine pregnancy test [K]	x		x												(x)	(x)
FSH [L]	x															
Sample collection																
Blood panel (research bloods) [M]	x												X [♦]		(x)	
Clinician reported measures”																
Hoehn and Yahr Scale [N]	x		x		x	x		x		x	x	x	x	x	(x)	
MoCA [O]	x		x			x		x			x		x		(x)	

Activity	Screening	Randomisation	Week 0 (Baseline)	Weeks 1-5 (Titration)	Week 13 (month 3)	Week 26 (month 6)	Week 39 (month 9)	Week 52 (month 12)	Week 65 (month 15)	Week 78 (month 18)	Week 104 (month 24)	Week 130 (month 30)	Week 156 End of study visit (month 36)	Week 165 Safety follow-up visit (month 38)	Early Termination	Unscheduled Visit
MDS-UPDRS Parts Ia, III, & IV remote [P]	x [I]		x		x	x		x		x	x	x	x	x	(x)	
C-SSRS [Q]	x												x		(x)	
CGI-S			x													
CGI-C								x			x		x			
Participant reported measures°																
PHQ-9 [R]	x		x		x	x		x		x	x	x	x		(x)	
MDS-UPDRS Parts Ib & II [T]	x		x		x	x		x		x	x	x	x	x	(x)	
Falls questionnaire			x		x	x		x		x	x	x	x		(x)	
PDQ-8			x		x	x		x		x	x	x	x		(x)	
Participant expectations questionnaire			x										x		(x)	
EQ-5D-5L			x		x	x		x		x	x	x	x		(x)	
Resource use questionnaire (modified CSRI and iVICQ) [S]			x			x		x		x	x	x	x			
ICECAP-O			x		x	x		x		x	x	x	x		(x)	

Activity	Screening	Randomisation	Week 0 (Baseline)	Weeks 1-5 (Titration)	Week 13 (month 3)	Week 26 (month 6)	Week 39 (month 9)	Week 52 (month 12)	Week 65 (month 15)	Week 78 (month 18)	Week 104 (month 24)	Week 130 (month 30)	Week 156 End of study visit (month 36)	Week 165 Safety follow-up visit (month 38)	Early Termination	Unscheduled Visit
Drug Diary Card - Optional				x		x		x	x	x	x	x	x		(x)	
SPFQ– Optional ≠			x							x			x		(x)	
Partner measures (optional – depending on consent)																
Informed consent for partner	x															
PQoL-Carers			x			x		x		x	x	x	x		(x)	
EQ-5D-5L			x		x	x		x		x	x	x	x		(x)	

For sub-study specific schedule of assessments, please refer to the sub-study protocol appendices.

Notes / Annotations:
+: Sites should call participants to confirm eligibility outcome and advise of next steps including proceeding to randomisation, completing PROMS, confirmation of baseline appointment going ahead and expected receipt of IMP. PROMS should be encouraged to be completed prior to the baseline appointment. IMP should not be started until baseline assessments are complete.
(x): Activities listed for early termination and unscheduled visits are optional and should be completed in the clinician's judgement based on the reason for the visit.
~: Remote visit should ideally be conducted as a video call to complete assessments, but if needed the visit can be conducted via a telephone call with abbreviated assessment and will be encouraged to have an in person visit at 52 weeks, 104 weeks and 156 weeks.
A: Previous medication exposure should include: any of the currently recruiting IMPs within 6 months prior to screening visit or previous intolerance of any of the IMPs, current use of sartans (AT1 angiotensin receptor antagonists), aliskiren, ACE inhibitors or potassium sparing diuretics or known hypersensitivity or intolerance to sartans (AT1RAs), current use of lithium or use within the previous 6 months, current use of alpha blockers other than tamsulosin (alfuzosin, silodosin, prazosin, terazosin, and doxazosin), including natural supplements with this action (e.g. yohimbine).
#: Blood pressure monitors will be supplied to participants at the screening visit, to record their blood pressure in their own home if required. Instructions on when and how to take their blood pressure will be provided. A sitting blood pressure should be recorded first. Blood pressure should then be recorded after three minutes lying down, one minute after standing, and three minutes after standing. Blood pressure during follow-up is not a requirement and should only be taken if clinically indicated, for example, if

the participant has experienced symptoms of low blood pressure (e.g. light headedness or dizziness on standing). Should participants experience symptoms of low blood pressure between study visits, they should contact the study team for advice.
B: including BMI
C: including cranial nerve examination and limb examination (e.g., power, reflexes, sensation, coordination)
D: Confirmed on trial database during study visit, with use of optional drug diary card as aide-memoire (if completed by participant) and a physical pill count.
E: This includes a Parkinson's medication check and concomitant medication check. This is used to calculate Levodopa Equivalent Daily Dose (LEDD). The LEDD calculator https://www.parkinsonsmeasurement.org/toolBox/levodopaEquivalentDose.htmhttps://www.parkinsonsmeasurement.org/toolBox/levodopaEquivalentDose.htm
F: Prescription issued and sent to central pharmacy to dispense and post treatment directly to participant's home
¬: Screening and safety tests to be completed locally.
G: Full Blood count (haemoglobin, haematocrit, red blood cell count, white blood cell count, platelets, neutrophils, eosinophils, basophils, lymphocytes and monocytes). Coagulation factor to be completed for participants who consent to the Biosamples sub-study (See Biosamples Sub-Study Protocol Appendix for full details)
H: Urea, electrolytes, creatinine and cholesterol
I: Bilirubin, Albumin, Alkaline phosphatase and either ALT or AST
J: if WOCP includes Beta hCG testing if required
^: Investigator will be asked to sign whether any tests outside the Lab reference range are clinically significant or not clinically significant. Guidance for sample collection and transport can be found in the Sample Collection and Handling Manual
K: for women of child-bearing potential, a urine HCG pregnancy test should be carried out at screening. A pregnancy test is also required before starting IMP at the baseline visit (week 0) if the screening visit pregnancy test was more than 14 days ago. If the result of the urine HCG pregnancy test is positive or there is any doubt over the results of the urine HCG pregnancy test, then a serum HCG pregnancy test should be completed. In the case of suspected pregnancy in a female participant of child-bearing potential post first IMP dose, a urine pregnancy test (and serum HCG pregnancy test if positive) should be performed. If pregnancy post first IMP dose is confirmed, unblinding procedures should be initiated, or otherwise discussed with the chief investigator(s).
L: Follicle stimulating hormone (FSH) assessment required for post-menopausal women aged <60 years old to confirm FSH level > 35 mIU/mL and therefore pregnancy tests not required.
M: Depending on the facilities available on site, blood samples can be centrifuged, aliquoted and shipped directly to the storage site, or frozen for local storage and shipment in bulk.
♦ The end of study visit (Week 156) can be conducted either remotely or in-person. However, if the visit is conducted remotely, an in-person visit will need to be scheduled, where possible, to complete the research blood sample collection. To facilitate this, the research blood sample at week 156 can be collected +/- 4 weeks of the end of study visit date.
": Clinician-reported measures will be administered in-person at the screening visit where required to confirm eligibility. They can be completed in person by home-visit or remotely via video call or telephone call for subsequent follow-up visits where the participant is not attending for an in-person visit. Participant location, modality of completion, level of assistance required, and staff administration will be captured for all outcome measures.
N: Collected at screening to identify disease stage for stratification. Pull test should not be performed at remote visits. If for some reason the Hoehn and Yahr stage score cannot be directly assessed, please provide an estimate.
O: At screening, this is administered to confirm eligibility. Participant will be excluded if they score less than 21 as this indicates significant cognitive impairment

P: At screening, this is administered in-person to provide data for analysis comparing differences between in-person and remotely delivered MDS-UPDRS scores. The MDS-UPDRS Parts Ia and III should be completed online via video or telephone call for visits taking place remotely. If the visit is taking place in-person (in clinic or at home) the MDS-UPDRS parts Ia and III should be completed face to face. MDS-UPDRS Part III Q3.3 (Rigidity) and Q3.12 (Postural Stability) only completed at screening visit.
[l]: Administered by certified raters. At screening, this will be administered in-person if raters are based at participant's site, otherwise it will be administered remotely by raters via video call. Sites should attempt to use the same rater for individual participants as much as possible throughout their participation in the study.
Q: At screening, this is administered to confirm eligibility. Participant will be excluded if they answer "yes" to Questions 4 or 5 on the suicidal ideation domain as this indicates current suicidality
°All participant-reported outcome measures (PROMS) can be completed online using a link that is personalised to the participant. At the in-person screening visit, PROMS can be completed by the participant either online using their own device (smart phone, tablet etc.) or a site provided device (computer, tablet etc.) or can be completed on paper and entered into the database by site staff. Following the screening visit, participant-reported measures should be completed by participants remotely, prior to the visit taking place, where possible.
R: At screening, this is administered to confirm eligibility. Participant will be excluded if they score more than 14 as this indicates clinically significant depression
*first 6 monthly prescription issued at week 3 following confirmation of dose tolerability at this time point.
S: Resource use questionnaire includes modified Client Service Receipt Inventory (CSRI) and modified iMTA Valuation of Informal Care Questionnaire (iVICQ)
T: Use of interpreters is not allowed. for completion of the primary outcome measure. Therefore, when completed remotely, MDS-UPRS Parts Ib and II must be completed in English. If the participant is unable to complete the MDS-UPDRS Parts Ib and II in English, they can complete a paper version (in-person at the study site) using an approved (available) MDS-UPDRS translation for a language they are fluent in. If the participant is not fluent in any of the approved (available) languages, they will be considered ineligible.
≠: Study Participant Feedback Questionnaire (SPFQ) Different sections of the questionnaire will be administered at each timepoint to reflect the participant's experience at that point in the trial.

LAY SUMMARY

Parkinson's disease (PD) is the fastest growing neurological condition in the world. It is expected to affect 172,000 people in the UK by 2030 and currently costs the UK around £3.6 billion per year. Current treatments may partially improve symptoms, but over time they are less effective and can cause severe side effects. PD can increase physical disability, falls, and problems with speech, swallowing, mood, thinking and memory. There is an urgent need to find treatments that can slow or stop PD symptoms from getting worse.

Many treatments exist which may be able to slow the progression of PD. However, the current approach of testing treatments one at a time can take a long time. Our multi-arm, multi-stage (MAMS) trial will speed up this process. MAMS trials test a number of different treatments at the same time in separate treatment arms. The treatments are each compared against a placebo arm (dummy drug with no active treatment). Each treatment will have early reviews, called 'interim analyses', to check whether it is safe and seems to be working. If a treatment appears to be working then we will keep it in the trial until the final review, which tests if it really is effective. Treatments that do not appear to be working will be stopped and replaced with a new one. This approach needs fewer participants to get answers about treatments, and is cost-effective and faster compared to running multiple individual trials.

To choose the treatments we want to test, we carefully considered evidence for safety and effectiveness. The shortlist of treatments to test includes telmisartan, terazosin, and ursodeoxycholic acid (UDCA). The trial will start with two treatment arms and one placebo arm, with a third treatment arm added after one year. We can identify new treatments to add to the trial each year.

We will randomly allocate participants to a trial arm. The treatment and placebo tablets will look the same, so participants and research staff won't know which arm participants are in. All participants will continue to receive their normal treatment throughout the study, in addition to their trial tablets. Each participant will complete assessments at 13 weeks, 26 weeks and every 26 weeks after for 3 years to measure any change in their PD symptoms. These assessments can all take place from home, using online surveys and telephone / video calls if preferred. Blood tests will let us explore responses to treatments in different participant subgroups. There will be additional telephone calls during the first 5 weeks phase and at 39 weeks and 65 weeks to check how participants are finding the study medication and the study processes. These phone calls are also an opportunity to receive feedback and questions from participants.

People with PD are an integral part of our research team and have driven key decisions including choosing the way we judge whether a treatment is effective, how long the trial is, and how people take part. After the participant's first visit to a trial centre, all assessments can take place online if preferred. Treatments will be sent straight to a participant's home from a central pharmacy. Participants will be regularly updated with trial progress, including which treatments pass the early reviews.

We aim to recruit up to 400 participants to each arm from a wide network of 40 UK sites. Dedicated research staff will support participant recruitment and trial delivery in less experienced sites. Recruitment criteria are broad to ensure that:

- our trial population represents people with PD in the UK (including different ethnicities, locations, and ages)
- we identify treatments relevant for most types of PD

We will create a sustainable trial infrastructure to support the addition of future treatment arms via protocol amendments to enable the trial to continue. This will provide an ongoing opportunity for people with PD to take part in research and place the UK as the lead in the global search for better PD treatments.

CONTENTS

ABBREVIATIONS

ABBREVIATION	EXPANSION
ACE	Angiotensin-converting enzyme
AE	Adverse event
AR	Adverse reaction
AT1RAs	AT1 angiotensin receptor antagonists
bid	Bis in die (twice a day)
BNF	British National Formulary
BP	Blood pressure
CALY	Capability-adjusted life-year
CAP	Community advisory panel
CEAC	Cost-effectiveness acceptability curve
CEP	Cost-effectiveness plane
CGI-C	Clinical Global Impressions scale - Measure of clinical change
CGI-S	Clinical Global Impressions scale - Severity of illness
CI	Chief Investigator
CI	Confidence interval
CLRN	Comprehensive Local Research Network
CNS	Central Nervous System
COM	Clinical Operations Manager
CPM	Clinical Project Manager
CRF	Case Report Form
CRN	Clinical Research Network
CROM	Clinical reported outcome measure

ABBREVIATION	EXPANSION
CSRI	Client Service Receipt Inventory
C-SSRS	Columbia Suicide Severity Rating Scale
CTA	Clinical Trials Authorisation
CTCAE	Common Terminology Criteria for Adverse Events
CTIMP	Clinical trial of an investigational medicinal product
CTU	Clinical Trials Unit *(See MRC CTU at UCL)*
CUA	Cost-utility analysis
DBP	Diastolic blood pressure
DM	Data Manager
DMC	Data Monitoring Committee
DMT	Disease modifying therapy
DNA	Deoxyribonucleic acid
DPA	(UK) Data Protection Act
DSUR	Developmental Safety Update Report
eCRF	Electronic Case Report Form
eDC	Electronic data capture
EDI	Equality, Diversity and Inclusion
EHR	Electronic Health Records
EJS ACT-PD	Edmond J Safra Accelerating Clinical Trials in Parkinson's disease
EQ-5D-5L	EuroQol generic health-related quality of life questionnaire (5 domains, 5 levels)
FBC	Full blood count
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice

ABBREVIATION	EXPANSION
GP	General Practitioner
HBA1c	Haemoglobin A1c
HE	Health economics
HEAP	Health economic analysis plan
HES	Hospital Episode Statistics
HCG	Human chorionic gonadotropin
HRA	Health Research Authority
HRQoL	Health Related Quality of Life
ICECAP-O	ICEpop CAPability measure for Older people
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
ILCT	International linked clinical trials
IMP	Investigational medicinal product
iMTA	institute for Medical Technology Assessment
IRAS	Integrated Research Application System
IRB	Institutional Review Boards
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	Intention-to-treat
iVICQ	iMTA Valuation of Informal Care Questionnaire
IVW	Inverse variance weighting
LEDD	levodopa-equivalent daily dose
MAMS	Multi-arm, multi-stage

ABBREVIATION	EXPANSION
mCTA	Model clinical trial agreement
MDS-UPDRS	Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale
mg	Milligram
MHRA	Medicines and Healthcare products Regulatory Agency
MoCA	Montreal Cognitive Assessment
MRC	Medical Research Council
MRC CTU at UCL	Medical Research Council Clinical Trials Unit at University College London (also generally abbreviated to “CTU”)
MREC	Multi-centre Research Ethics Committee
MRI	Magnetic resonance imaging
mmHg	Millimetres of mercury
NCI	National Cancer Institute
NE	Notable Event
NHS	National Health Service
NHSD	NHS Digital
NHSCR	National Health Service Central Register
NIHR	National Institute for Health and Care Research
NIMP	Non-investigational-medicinal product
NRES	National Research Ethics Service
od	Once daily
OM	Outcome measure
ONS	Office for National Statistics
PD	Parkinson’s disease

ABBREVIATION	EXPANSION
PDQ-8	Parkinson's Disease Questionnaire- 8 item
PGK1	Phosphoglycerate Kinase 1
PHQ-9	Patient Health Questionnaire-9 item
PI	Principal Investigator
PIS	Participant Information Sheet
PK	Pharmacokinetics
PPI	Patient and public involvement
PPIE	Patient and public involvement and engagement
PQoL-Carers	Carers quality-of-life questionnaire for parkinsonism
PROM	Patient reported outcome measure
PSSRU	Personal Social Services Research Unit
PwP	People with Parkinson's
QA	Quality assurance
QC	Quality control
QALY	Quality-adjusted life-year
Qd	Quaque die (every day)
QMAG	Quality Management Advisory Group
QoL	Quality of life
QP	Qualified Person
R&D	Research and Development
RCT	Randomised controlled trial
REC	Research Ethics Committee
RGC	Research Governance Committee

ABBREVIATION	EXPANSION
RoI	Registration of interest
RRDN	Regional research delivery network
RRP	Recruitment and retention panel
RSI	Reference safety information
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAR	Serious adverse reaction
SBP	Systolic blood pressure
SD	Standard deviation
SmPC	Summary of Product Characteristics
SOC	Standard of Care
SOP	Standard operating procedure
SPC	Summary of Product Characteristics
SPFQ	Study Participant Feedback Questionnaire
SSG	Scientific Strategy Group
Sub-I	Sub Investigator
SUSAR	Suspected unexpected serious adverse reaction
SWAT	Study within a trial
TBD	To be defined
TD	Trial design
TLC	Three letter code
TM	Trial Manager
TMF	Trial Master File
TMG	Trial Management Group

ABBREVIATION	EXPANSION
TMT	Trial Management Team
TS	Treatment selection
TSC	Trial Steering Committee
UAR	Unexpected adverse reaction
UKCRN	UK Clinical Research Network (now the NIHR CRN)
WG	Working Group
WOCP	Women of child-bearing potential

GLOSSARY

Hoehn & Yahr stage: A simple method of staging PD that can be applied to participants in either the ON or OFF medication state. For the purposes of the trial inclusion criteria, staging will be applied according to their ON medication state:
Stage 1 - unilateral involvement only.
Stage 1.5 - unilateral and axial involvement.
Stage 2 - bilateral involvement without impairment of balance.
Stage 2.5 – mild bilateral involvement with recovery on retropulsion (pull) test. (Note: only choose this option during in-person assessments; pull test is not done remotely)
Stage 3 – mild to moderate bilateral involvement, some postural instability but physically independent.
Stage 4 - severe disability, still able to walk and to stand unassisted.
Stage 5 - wheelchair bound or bedridden unless aided.

"ON" medication state: This refers to the patient state when dopamine replacement therapies are having their best or maximal effect. Typically, this occurs 60-90 minutes following a dose of levodopa.

Inverse variance weighting (IVW): a combination of measures which gives more importance to the most precise items within the measure.

Motor symptoms: symptoms that affect movement and balance, e.g., tremor, stiffness, slowness of movement.

Non-motor symptoms: symptoms that do not affect movement or balance e.g., cognitive impairment, depression, anxiety, sleep problems etc.

Women of child-bearing potential (WOCP): For the purpose of EJS ACT-PD, a woman is considered of childbearing potential (WOCP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.
A postmenopausal state is defined as no menses for 12 months without an alternative medical cause and being aged ≥60 years old.

Post-menopausal:

- Women who have had amenorrhea for ≥12 consecutive months (without another cause) and are aged ≥60 years old. Women who have irregular menstrual periods and a documented serum FSH level > 35 mIU/mL.

Over-encapsulation: Inserting a tablet into an opaque capsule shell with backfill excipient to conceal the tablet products for blinding purposes.

Size 00 capsules: The size of the capsules used to over-encapsulate the trial tablets. Size 00 is 23.4mm in length (approximately the same as £1 coin) and 8.56mm in diameter, volume of 0.9ml.

Treating clinician/s: Principal Investigator, Sub-Investigator or another appropriately trained clinician named on the delegation log.

Blinded Rater: Team member who is named on the delegation log and adequately trained in all rater-administered assessments but does not need to be clinically qualified.

1. BACKGROUND

1.1 PARKINSON'S DISEASE

Parkinson's disease (PD) is a neurodegenerative disorder characterised by progressive disability involving both motor and non-motor symptoms[1]. It affects over 10 million people worldwide[2], and as the fastest growing neurological condition in the world[3] its prevalence is increasing.

PD is heterogeneous in its presentation and progression. Typical motor symptoms include slowness of movement (bradykinesia), rigidity, and tremor. Non-motor symptoms include cognitive decline, mental health conditions, sleep disturbances, and autonomic dysfunction[4-5]. PD can affect all ages, but incidence increases with age. Symptoms progress relentlessly, resulting in escalating care needs and an economic impact of £20,000 per annum per Parkinson's household[6].

1.2 CURRENT TREATMENT

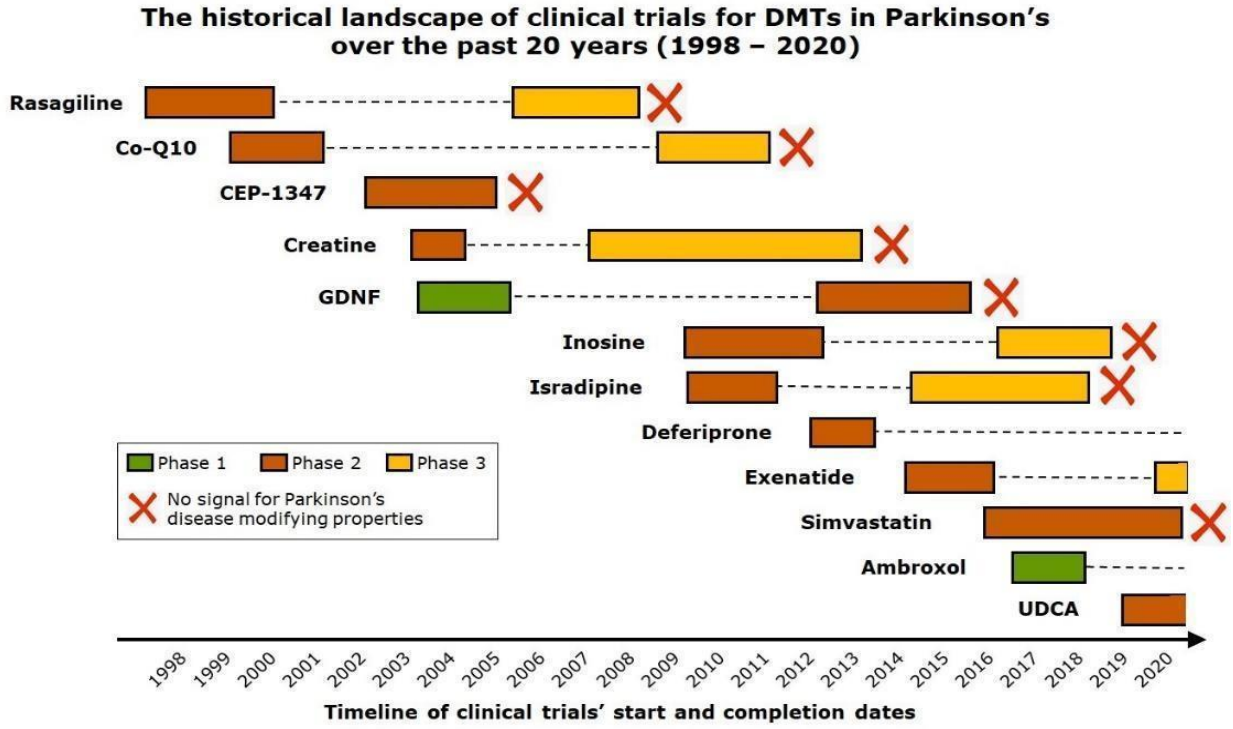
Symptomatic treatments for PD are available and mainly focus on dopamine replacement strategies. These can provide transient improvement in the core motor features of PD, namely tremor, limb rigidity and bradykinesia. However, these conventional treatments are only able to mask symptoms and, over time, become less effective with increasing side effects.

There are no current treatments proven to have any impact on the progressive nature of the disease. As symptoms progress, people with Parkinson's (PwP) may develop dopa-refractory gait and balance problems (leading to falls and risk of fractures), speech and swallowing problems (leading to difficulty in communication and aspiration pneumonia), cognitive impairment, visual hallucinations and dementia and mounting NHS and social care needs. These later disabilities are difficult to treat effectively and ultimately result in premature death. Identification of treatments that can slow or stop disease progression represents a major unmet need, to both improve patient quality of life and reduce burden on the health and social care systems.

1.3 CLINICAL TRIALS IN PD

A key aim for current PD research is identifying a disease modifying therapy (DMT) which is successful in delaying or halting disease progression. However, the process of setting up and running a clinical trial to assess whether a drug might slow down the rate of disease progression is hugely time and resource consuming. This is especially since they are typically set up and run independently for each clinical trial phase, requiring several repeated cycles of funding, trial permissions, site set-up and recruitment simply to assess a single candidate treatment. Currently, it can take more than 10 years for one treatment to go through this process, with large delays between phase 2 and 3 trials and most new interventions failing to provide improvements in outcomes[7] (see **figure 2**). This has resulted in several costly and disappointing results in PD research over the past 20 years.

Figure 2: The landscape of the major clinical trials for DMTs in Parkinson's over the past 20 years



Ongoing initiatives such as the International Linked Clinical Trials Programmes (ILCT)[8,9] and the Parkinson's 'Hope list'[10] have identified several exciting potential DMTs for PD, which are waiting to be assessed. The current clinical trials process creates a bottleneck for testing new treatments, slowing down our ability to identify those that are effective. Thus, to improve this process and match the urgent pace required, it seems sensible to simultaneously evaluate a greater number of promising new interventions, acknowledging that many may 'fail'.

1.4 Multi-arm, Multi-stage (MAMS)

Multi-arm multi-stage (MAMS) trials represent an innovative approach to complex clinical trial design. MAMS Platform trials can simultaneously recruit to multiple active treatment arms to be assessed against one shared placebo arm. Interim analyses are used at pre-specified timeframes to assess whether a drug/intervention is tolerable and engaging its target or reaching a preliminary measure of activity i.e., assessing its lack of activity. If deemed lacking in activity, recruitment to that treatment arm can be stopped. The ability to add new intervention arms ensures that more treatments can be tested and failed treatment arms can be replaced.[11] Treatments with encouraging data will continue to recruit and be evaluated at a Phase 3 stage. This adaptive approach therefore dispenses with the repeated cycle of dismantling and rebuilding the trial infrastructure, while allowing removal and addition of trial arms and adjustment of trial design simply through the process of substantial amendment (see **figure 3** for a hypothetical outline of a MAMS design).

Figure 3: A hypothetical MAMS

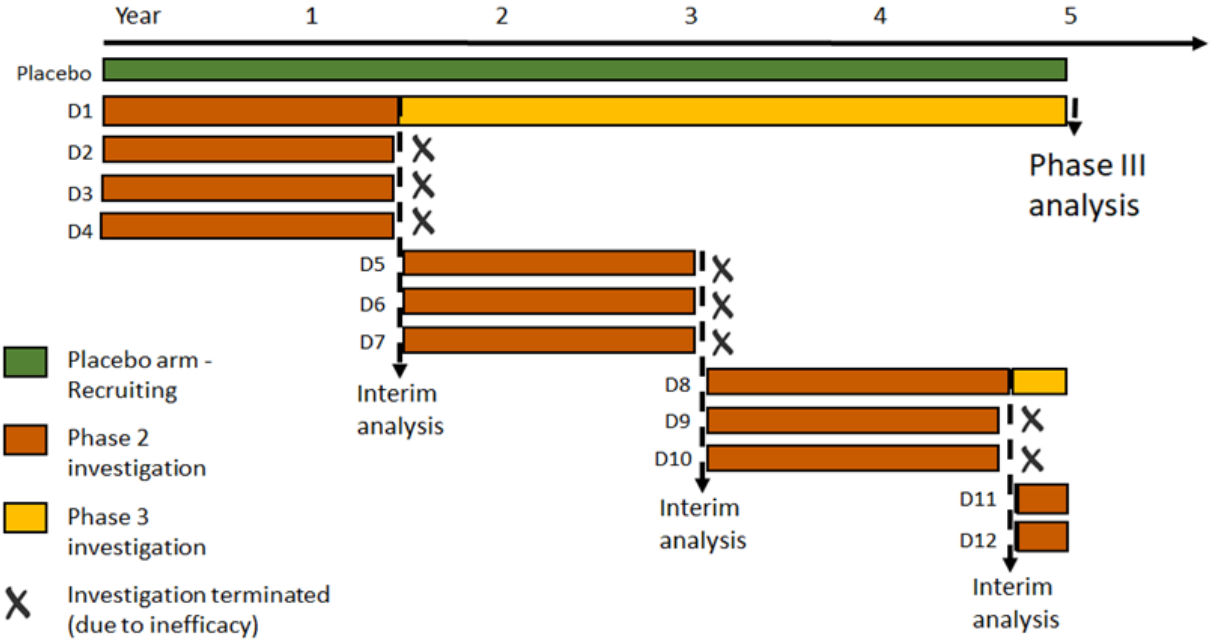


Figure 3 indicates what a hypothetical MAMS trial could look like. In this example, the trial launches with four different treatment arms (D1 – D4) and one shared placebo arm. At their first point of interim analysis to assess for activity, D1 passes and continues recruitment until primary (phase 3) analysis, whilst arms D2 – D4 fail and are terminated. At this point three new treatment arms are opened in their place (D5 – D7). At the next interim analysis, arms D5 – D7 fail to show signs of activity, are terminated, and replaced with arms D8-D10. with arm D8 continuing to primary analysis. As arms are terminated, new arms can continue to be opened in their place within the existing infrastructure. MAMS is a proven approach which has been pioneered in the oncology field with the identification of numerous agents that are now routinely incorporated into standard of care e.g., the STAMPEDE trial, as well as promptly identifying futile interventions.[12] The COVID-19 pandemic also triggered the development of the RECOVERY trial, based on MAMS principles, which enabled the rapid identification of multiple effective and ineffective drugs to improve outcomes from COVID-19 infection.[13]

1.5 The EJS ACT-PD Consortium

The Edmond J Safra Accelerating Clinical Trials in Parkinson's Disease (EJS ACT-PD) initiative[14] was formed in 2021. Co-led by University College London and University of Plymouth, the main aim of the initiative was to produce a protocol for a MAMS platform trial that is focused on the clinical evaluation of potential DMTs in PD. The EJS ACT-PD consortium included >90 key stakeholders from across the UK comprising PwP and carers, neurologists, geriatricians, clinical trialists, statisticians, funders, methodologists, epidemiologists, health economists, trials pharmacists and a range of experience from clinical and academic research experts in disease modifying drug development and trial design.

Six working groups were set up, each addressing a particular component of platform design and delivery: trial design, outcome measures, therapy selection, infrastructure, funding and sustainability and patient and public involvement and engagement (PPIE). The patient perspective was central to the process with patient/carer members embedded in each working group and thus involved in all decisions based on their collective discussions. A communications subgroup comprised of working

group members has aligned project messages, enabled early engagement with sites and potential participants, and produced a participant-focused recruitment and retention strategy. A Community Advisory Panel (CAP) of patient and public members also provided a diverse range of perspectives and insights, to assist with the trial's equality, diversity and inclusion (EDI) strategy. An additional level of oversight, as well as an international perspective, was provided by a panel of international advisors.

1.6 The EJS ACT-PD MAMS Platform Trial

The EJS ACT-PD Consortium has produced a protocol for the first MAMS trial for PD: Edmond J Safra, Accelerating Clinical Trials in Parkinson's Disease (EJS ACT-PD) – a Multi-arm Multi-stage Platform Trial for potential disease modifying approaches.

The trial will be led by Co-Chief Investigators Professors Tom Foltynie and Camille Carroll, based at UCL and Newcastle University, respectively. The daily management of the trial will be coordinated by a Trial Management Team (TMT) based at the Medical Research Council Clinical Trials Unit (MRC CTU) at UCL and overseen by the appointed TMG.

The EJS ACT-PD initiative (responsible for trial design, not trial delivery) has been funded to continue until December 2029 with a focus on developing sub-studies for integration into the EJS ACT-PD MAMS Platform Trial and ensuring the trial's ongoing sustainability past the first 3 treatment arms. The EJS ACT-PD initiative will be funded and managed independently of the trial but will work in close collaboration with the TMT at the MRC CTU.

1.6.1 Participant Population

The trial will recruit an inclusive and representative population, capturing the demographic, disease stage and multi-morbidity diversity associated with real-world PD. A proactive strategy for targeting under-served groups will include: the creation of culturally representative animated videos with translated subtitles/voiceovers; attendance and presentations at community events dedicated to Parkinson's awareness; and interaction with local Parkinson's support groups.

Broad inclusion criteria aim to facilitate the recruitment of the majority of PwP on stable PD medication that wish to take part. The trial will not aim to test treatments that might only be relevant for a subgroup of PwP. Exclusion criteria will be kept to a minimum except for logistical reasons (e.g., unable to comply with study requirements) and safety reasons (e.g., symptomatic orthostatic hypotension). On the basis of an initial 3 concurrent recruiting arms (2 active treatments and 1 placebo), with the addition of a 3rd active treatment arm within approximately the first 12 months, and allowing for approximately 30% withdrawal, an overall sample size of 1,600 participants (400 participants per arm) is required. We have undertaken a national site scoping survey with responses from over 95 sites across the UK which demonstrated that this sample size is achievable over a 3-4 year recruitment window.

The large and diverse participant population will allow confirmation that any successful intervention is indeed relevant to the broad population of people with PD and not restricted to the subpopulation of younger, Caucasian, higher educated people with PD who typically are over-represented in clinical trials.

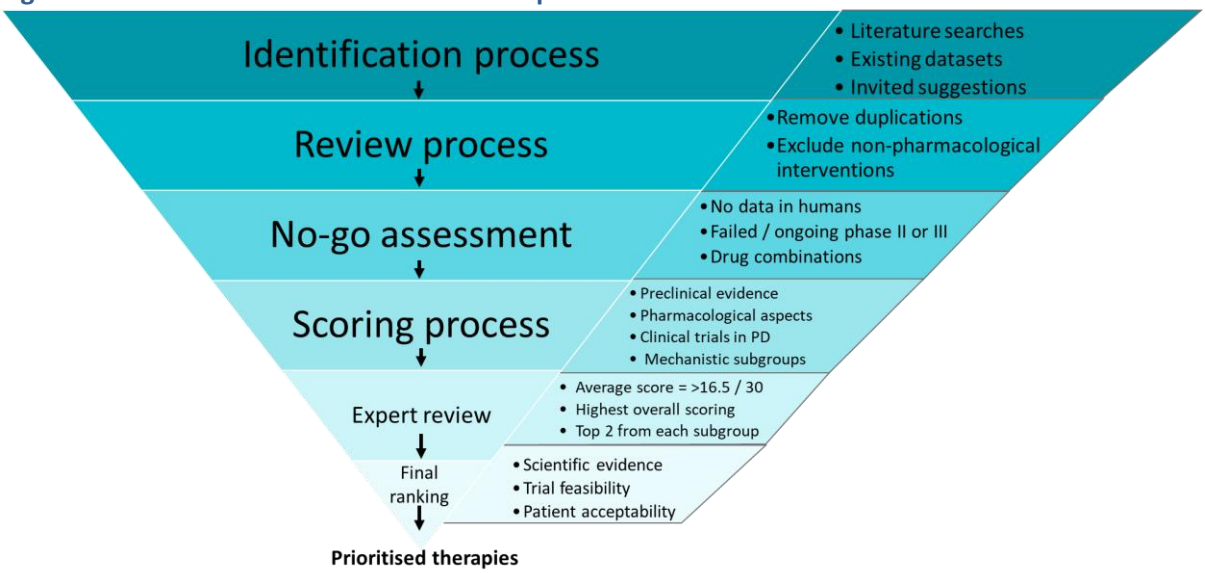
The collection of biosamples will allow confirmation of target engagement of the putative mechanism of action of the selected agents and provide further objective confirmation of efficacy. This platform will incorporate innovative exploratory outcomes such as digital

measures, imaging and milestone-based endpoints (subject to further funding). Participants' routinely collected healthcare data will also be sought and will include mortality and/or Hospital Episode Statistics to further capture the potential impact of interventions. Participant consent will allow future primary and social care datasets to be linked to long-term health impacts of the trial treatments.

1.6.2 TRIAL TREATMENTS

The platform will evaluate repurposed agents in the first instance. A systematic review of 293 potential candidates underwent a rigorous selection process culminating in a shortlist of 5 compounds, from which telmisartan and terazosin were prioritised as the first 2 treatment arms with additional arms expected to launch approximately every 12 months. An outline of the treatment selection process can be found in **figure 4**:

Figure 4: Outline of the treatment selection process



Telmisartan is an angiotensin-II type 1 receptor blocker (ARB) which plays a role in inflammation and apoptosis. It has extensive preclinical[15] and epidemiological data[16-18] and appears to reduce the risk of developing Parkinson's. It demonstrates neuroprotective properties in both neurotoxin and alpha-synuclein-based Parkinson's models[19-25].

Terazosin is an α1-adrenergic receptor antagonist which has pre-clinical evidence to suggest neuroprotective effects in reducing dopaminergic cell death[26,27]. Terazosin also has extensive epidemiological data demonstrating that users are less likely to be diagnosed with PD and have fewer PD-related complications (falls, dementia, gait problems)[27-30]. Clinical trial data also show lower -UPDRS Part III scores after 3 months when taking terazosin compared to placebo[31].

Further drug-specific information for active treatment drugs can be found in **appendix 2**.

1.6.3 Trial Design

The trial will launch with two active treatment arms (telmisartan & terazosin) and one shared placebo. Additional arms are expected to be launched to recruitment approximately every 12 months.

The trial will include two interim assessments for activity at pre-scheduled timepoints. The stage 1 analysis for each arm will take place when 133 participants reach 52 weeks post first dose of study medication and stage 2 when 200 participants reach 78 weeks post first dose of study medication. An early efficacy analysis for each arm will take place when 266 participants reach 104 weeks post first dose of study medication and the final efficacy analysis will be completed when 266 participants reach 156 weeks post first dose of study medication. This number of participants would achieve power of >0.95 to detect a 30% reduction in rate of progression of the outcome measure. A final 165-week assessment will be undertaken for safety and to evaluate effects after drug washout.

1.6.4 Outcome Measures

The primary outcome will be the combined patient reported score of MDS-UPDRS Part I (non-motor aspects of experiences of daily living) and MDS-UPDRS Part II (motor aspects of experiences of daily living), 156 weeks after randomisation allocation. The combination of these 2 scale subsections has construct validity and has been used for the power calculations for the trial. This outcome measure was selected following careful consideration and modelling utilising the Critical Path for Parkinson's dataset, undertaken by the Outcome Measures Working Group, including PwP and care partner members, endorsed by PPIE contributors. This measure can be captured remotely and is consistent with regulatory advice to prioritise patient reported outcomes

Secondary outcomes will include validated measures of motor deficit (MDS-UPDRS Part III), motor complications of symptomatic PD treatment (MDS-UPDRS Part IV), cognition (MoCA), severity of illness and clinical change (CGI-S and CGI-C), depression (PHQ-9) and health economic data (CSRI & EQ-5D-5L). All participants will be provided with a home blood pressure monitor at their in-person screening visit and instructed on self-measurement of pulse and blood pressure, should this be necessary due to their developing symptoms suggestive of low blood pressure, which will then lead to protocolised and individualised management advice.

1.7 Objectives

The MAMS approach allows us to test multiple treatments in parallel, add new promising treatments within the same trial infrastructure, and to remove and replace ineffective treatment arms at earlier timepoints. This type of trial infrastructure will increase the number of promising treatments that undergo evaluation as potential disease modifying interventions for PD. By so doing, this will increase the likelihood of finding agents that slow down the progression of the disease. The platform trial design will allow continued recruitment and follow up of participants in treatment arms passing early thresholds of activity, to allow their formal phase 3 evaluation of efficacy.
By improving the efficiency of trial design, the platform will provide more interim and phase 3 trial data over a shorter overall period and at a lower overall financial cost.

1.7.1 Primary objective(s)

The primary objective of the EJS ACT-PD Trial is to determine whether the active trial treatments result in a ≥30% reduction in rate of disease progression between the active treatment and placebo arms as measured by the MDS-UPDRS Parts I and II combined.

1.7.2 SECONDARY OBJECTIVE(S)

Secondary objectives of the EJS ACT-PD Trial are to determine:

- The safety and tolerability of the active treatments for people with PD when taken for up to 3 years
- The effects of the treatments on quality of life and patient reported efficacy outcomes in people with PD
- The effects of the treatments on objective assessments of the motor severity of PD
- The effects of the treatments on cognitive function in people with PD
- The effects of the treatments on Global Severity of PD
- The effects of the treatments on quality of life of partners of people with PD
- The cost effectiveness of the treatments for people with PD compared to current standard of care
- The success of our recruitment and retention strategies on recruiting a participant sample that is representative of the population of people with Parkinson's in the UK via various evaluation options (to be further defined via a future EDI sub-study)

1.7.3 TERTIARY OBJECTIVE(S)

Tertiary objectives include:

- To contribute to a large biobank resource to support the future analysis of progression biomarkers in PD
- To create a platform for future collaborations to improve trial design, for example innovative outcome measures and methodologies

2. Selection of Sites/Clinicians

The trial Sponsor has overall responsibility for site and investigator selection.

2.1 Site/Investigator Inclusion Criteria

A 'Site Capability Survey' was created by the EJS ACT-PD Initiative and disseminated to NHS sites across the UK. This survey collected responses from over 95 potential delivery sites, including information on their neurology and PD research experience, research facilities (including aspects important to PwP), clinical trials pharmacy access and drug delivery experience. The results of the survey informed the EJS ACT-PD Trial 'Tiered Site System' by which sites will be categorised into 1 of 3 tiers based on their level of experience and resources. The criteria for each tier have been agreed by the EJS ACT-PD Trial's 'Trial Management Group' (TMG). Sites with the most experience and facilities will be categorised as 'tier 3' sites, sites with moderate experience will be categorised as 'tier 2' and sites with the least experience will be categorised as 'tier 1'.

Selected sites will have the opportunity to receive core trial funding to cover a dedicated trial site staff member who will be responsible for delivering the trial at their site and recruiting and retaining participants (including from under-served communities) and supporting trial delivery and recruitment for tier 2 and tier 1 sites within their regional research delivery network (RRDN) as needed. The aim is to have at least one core-funded staff member within each RRDN and devolved nation.

The criteria for each site tier can be found below in **figure 5**.

Figure 5: An outline of the 'Tiered Site System' criteria for site inclusion

Requirements:	Tier 1:	Tier 2:	Tier 3:
Access to appropriately trained Principal Investigator (PI)	✓	✓	✓
Ability to deliver on-site / in-person study visits	✓	✓	✓
Ability to deliver remote study visits	✓	✓	✓
Ability to review AEs & carry out safety assessments including blood sample handling	✓	✓	✓
PD trial delivery experience	X*	Moderate	Expert
PD rater experience	X*	Moderate	Expert
Dedicated research delivery space	X	✓	✓
Access to specialist facilities	X	(✓)[I]	(✓)[I]

* tier 3 core-funded trial staff would support the delivery of rating in less experienced sites

[I] only required if site wishes to opt in to deliver optional sub-studies

A site evaluation form must be completed to confirm these criteria. The TMG at the MRC CTU will use the site evaluation information to determine the appropriate tier for each site.

2.1.1 SITE INCLUSION CRITERIA:

1. Sites must have access to the resources outlined in **section 2.1.2**.
2. Sites must be able to assign a Principal Investigator to manage the delivery of the trial.
3. Principal Investigators must be qualified neurologists, movement disorder specialists, or geriatricians who are experienced with the management of Parkinson's disease within their caseload.
4. Investigators and clinical trial sites must fulfil the minimum set of criteria listed for 'tier 1' sites as agreed by the EJS ACT-PD Trial Management Group (TMG).

Those centres that meet the criteria and are selected will be issued with the EJS ACT-PD Trial master file documentation for their Capacity and Capability (C&C) Approval and CTU accreditation documents. Once a site has been identified as being compliant with the inclusion criteria (and not excluded) and categorised into a tier, the trial team will provide the site with a copy of the protocol (when approved). The CTU trial team will liaise with sites regarding the required documentation and training for the site to be issued with confirmation of greenlight.

Sites will be encouraged to assign a sub-investigator and/or associate PI trainee via the Associate PI Scheme. Appropriate service support and research costs have been developed with input from experienced trial site staff who are members of the EJS ACT-PD consortium, to ensure that the EJS ACT-PD Trial is appropriately resourced to successfully deliver the trial to time and budget.

Site teams must be willing and able to take steps to avoid unintentional unblinding through Electronic Health Records (EHR) system.

2.1.2 PI'S QUALIFICATIONS & AGREEMENTS

1. The Principal Investigator should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial at their site and should provide evidence of such qualifications through an up-to-date curriculum vitae and/or other relevant documentation requested by the Sponsor, the REC /HRA and/or the regulatory authority(ies).

2. The Principal Investigator must be a qualified neurologist, movement disorder specialist, or geriatrician and have experience with the management of Parkinson's disease within their caseload.

3. The Principal Investigator should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current Investigator Brochure/SmPC, in the product information and in other information sources provided by the Sponsor.

4. The Principal Investigator should be aware of, and should comply with, the principles of GCP and the applicable regulatory requirements. A record of GCP training should be accessible for all investigators.

5. The Principal Investigator/site should permit monitoring and auditing by the Sponsor and Industry (such as IMP supplier), and inspection by the appropriate regulatory authority(ies).

6. The Principal Investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site.

7. If the Principal Investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigators/institution should ensure this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.

8. The Principal Investigator should maintain a delegation log of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.

9. The Principal Investigator should sign an investigator statement, which verifies that the site is willing and able to comply with the requirements of the trial.

2.1.3 Adequate Resources

1. The Principal Investigator should be able to demonstrate a potential for recruiting the required number of suitable participants within the agreed recruitment period.

2. The Principal Investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.

3. The Principal Investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.

4. The Principal Investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

5. The site should have sufficient data management resources to allow prompt data entry (as specified in the Data Management Plan). Sites that have previously participated in CTU-coordinated trials should have a proven track record of good data return.

6. The site must have appropriate internet and telephone access to input data into the trial database, complete the online Site Delegation Log, store trial related e-documents and administer remote assessments via video or telephone call.

7. Sites must have the capability to take and handle blood samples in line with the EJS ACT-PD Trial's protocol and lab manual.

2.1.4 Site Assessment

Each selected clinical trial site must complete the EJS ACT-PD Trial Accreditation documents, which include the Investigator Statement, Signature and Delegation of Responsibilities Log, and staff contact details. The Principal Investigator Statement verifies that the site is willing, and able to comply with the requirements of the trial. This will be signed by the Principal Investigator at the site. In addition, and in compliance with the principles of GCP, all site staff participating in the trial must complete the Signature and Delegation of Responsibilities Log and forward this to the CTU. The CTU must be notified of any changes to trial personnel and/or their responsibilities. An up-to-date copy of this log must be stored in the Investigator Site File (ISF) and the electronic Trial Master File (eTMF) at CTU.

2.2 Site/Investigator exclusion criteria:

1. Sites that are unable to assign a suitably qualified Principal Investigator.
2. Sites that do not meet the Tier 1 criteria as outlined in **section 2.1** and **Figure 5.**

2.3 Approval and Activation

The Clinical Trial Authorisation (CTA) for the trial requires that the Medicines and Healthcare Products Regulatory Agency (MHRA) be supplied with the names and addresses of all participating site principal investigators. Trial staff at the CTU will perform this task; full contact details will be provided for all investigators prior to their entering participants.

Site training will be performed prior to the activation of sites and will include all processes for the trial, including but not limited to, protocol training, rater-administered assessments, PD awareness, database and data management, handling of investigational medicinal product, adverse event reporting, laboratory sample handling, and frequency and expectations for any monitoring visits. A log of attendees will be kept in the eTMF as a record of participants present at all types of training events.

Before a site can open to recruitment, formal Sponsor Site Green light will be completed to document that the site has met all the requirements and completed any necessary assessments to participate in the trial. Written confirmation of site activation will be sent to the PI and relevant members of the site research team via email. The site will be added to the EJS ACT-PD trial database with the relevant permissions granted for site staff. The EJS ACT-PD central pharmacy will be notified when a site is activated, including details of the site's ID and PI contact details (and being updated should investigator details change during the trial).

1. The site should conduct the trial in compliance with the protocol as agreed by the Sponsor and, if required, by the regulatory authority(ies), and which was given favourable opinion by the REC and/or IRB.
2. The PI or delegate should document and explain any deviation from the approved protocol, and communicate this with the trial team at the CTU.

A list of activated sites may be obtained from the Trial Manager at the CTU and will be made available on the trial website www.ejsactpd.mrcctu.ucl.ac.uk.

2.4 Site Management

The EJS ACT-PD Trial Management Team (TMT) at the MRC CTU at UCL will manage the trial's recruiting sites. The MRC CTU will manage the Quality control monitoring by performing regular analyses of potential risks that may threaten the safety, success or scientific integrity of the trial. On-site monitoring will be performed as necessary, to ensure each site is meeting the necessary standards required for all aspects of participant recruitment, data collection, safety monitoring and sample management.

3. SELECTION OF PARTICIPANTS

There will be **no exceptions** to eligibility requirements at the time of randomisation. Questions about eligibility criteria should be addressed prior to attempting to randomise the participant.

The eligibility criteria are the standards used to ensure that only medically appropriate potential participants are considered for this study. Patients not meeting the criteria should not join the study. For the safety of the participants, as well as to ensure that the results of this study can be useful for making treatment decisions regarding other patients with similar diseases, it is important that no exceptions be made to these criteria for admission to the study.

Participants will be considered eligible for randomisation in this trial if they fulfil all the inclusion criteria and none of the exclusion criteria as defined below, including the drug specific exclusion criteria (**Section 3.2.1**). If drug specific exclusion criteria are met for an arm, participants may be considered for randomisation across other arms.

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3.1. PARTICIPANT INCLUSION CRITERIA

1. Diagnosis by neurologist, movement disorders specialist or appropriately experienced clinician of clinically established or clinically probable PD in the clinician's opinion. In the presence of any diagnostic doubt, the Movement Disorder Society diagnostic criteria[32] will be applied.
2. Diagnosed with Parkinson's disease at age 30 years or older, no upper age limit.
3. Currently on Parkinson's medication (levodopa-containing preparations or dopamine agonists, used either as single agents or in combination) for at least 2 months prior to screening visit.
4. Female participants who are women of child-bearing potential (WOCP) must have confirmation of a negative pregnancy test at screening visit. See **Table 1** and **Section 6.6.4** for details on pregnancy testing.
5. Female participants who are WOCP and male participants and their partners who are WOCP must be taking highly effective contraceptive treatment(s). See **Section 6.6.4** for details on pregnancy and **Appendix 1** for details on highly effective contraception.
6. Documented informed consent.
7. Eligible for at least one of the active treatment arms (See **Section 3.2.1** for treatment specific exclusions).
8. Randomisation should ideally take place within 3 weeks of the screening visit but no later than 4 weeks after the screening visit.
9. If a participant is being re-randomised into the trial, additional timing of entry requirements must also be met:
    - For participants being re-randomised after completing 156 weeks' follow-up and the arm was not closed due to lack of activity, a 26-week washout period from last dose of IMP must be completed before their screening visit. If the primary analysis indicates that the IMP was ineffective then this washout period can be reduced to 6 weeks.
    - For participants being re-randomised following treatment arm termination due to lack of activity, a 6-week washout period from their last dose of IMP must be completed prior to screening assessment.

    See **section 4.4** *for further details on the re-randomisation process.*

3.2. PARTICIPANT EXCLUSION CRITERIA

1. Diagnosis or suspicion of other cause for parkinsonism such as atypical parkinsonism, dystonic tremor, essential tremor, drug-induced parkinsonism.
2. Known carriers of recessive PD gene mutations PRKN, PINK1 or DJ1 (based on previous medical tests / notes).
3. Clinical diagnosis of dementia or MoCA <21 at screening visit.
4. Currently in another ongoing interventional trial or exposure to any IMP within an experimental interventional trial within 6 months prior to screening visit (exception for EJS ACT-PD participants that are being re-randomised due to treatment arm termination following lack of activity as only a 6-week wash out period is required. See **Section 3.2.2** and **Section 4.4** for further details).
5. Unable or unwilling to comply with study requirements.
   For example, unable to complete the MDS-UPDRS in one of the approved available translated languages.
6. Diagnosis of clinically significant depression that is not appropriately treated or >14 on PHQ-9 at screening visit.
7. Current suicidal ideation within one year prior to the screening visit as evidenced by answering "yes" to Questions 4 or 5 on the suicidal ideation portion of the Columbia-Suicide Severity Rating Scale (C-SSRS).
8. Participants who have had deep brain stimulation (DBS) or on a waiting list for brain surgery including deep brain stimulation and / or currently taking or on a waiting list for advanced therapies for Parkinson's disease (such as any infusion therapy).
9. Monotherapy with monoamine oxidase-B inhibitor (MAO-BI).
10. Previous exposure to any of the currently recruiting IMPs within 6 months prior to screening visit or previous intolerance of any of the IMPs.
11. Participant has any concurrent medical condition, abnormal laboratory tests, progressive neurological disorder or uncontrolled, clinically significant systemic disease that, in the opinion of the Investigator, could cause study participation to be detrimental to the participant (e.g., end stage renal failure, severe heart failure, unstable angina, uncontrolled hypertension or uncontrolled orthostatic hypotension, severe liver disease, uncontrolled diabetes, or severe anaemia).
12. Pregnant or breastfeeding or intending to become pregnant during the study or within 70 days after the final dose of study drug.
13. Confirmed diagnosis of cancer and is requiring active management of that cancer and/or in the view of the local team, the diagnosis and/ or its treatment may compromise their ability to remain participating in the trial for 156 weeks or tolerate any of the active treatments.
14. Participants with hepatobiliary disorders or abnormal liver function tests at the screening visit consisting of one of the following (see **section 3.5.3** for re-screening opportunities):
    - ALT or AST >2x the upper limit of normal
    - Total serum bilirubin >1.5x ULN (except for participants with Gilbert's disease, for whom the upper limit of serum bilirubin is 51.3 µmol/l)
15. Participants with a history of alcohol/drug abuse/dependence within the 3 years prior to screening visit.
16. Participants with either of the following:
    - Sitting systolic blood pressure (SBP) less than 100 mmHg or sitting diastolic blood pressure (DBP) less than 50 mmHg, irrespective of symptoms
    - Orthostatic hypotension manifesting as any of the following:

- Decrease in BP > 20 mmHg systolic or > 10 mmHg diastolic on supine to standing, associated with clinical symptoms
- Decrease in BP >30mmHg systolic and/or BP >15 mmHg diastolic on supine to standing regardless of symptoms
- If the lowest BP on standing is less than 100 mmHg or lowest diastolic on standing is less than 50 mmHg

If, in the assessing clinician's opinion, the postural BP drop is attributable to transient/reversible factors (e.g. related to use of antihypertensives, dehydration, elevated room temperature, postprandial state), one repeated orthostatic BP assessment is allowed once those factors are addressed; additional re-screening will be allowed if the participant has their hypotension/orthostatic hypotension treated.

Information on repeating screening tests due to abnormal results and re-completing the screening visit can be found in **section 3.5**.

If a treatment arm is stopped early following interim analysis, or a new treatment arm is introduced to the trial, the overall and treatment specific inclusion / exclusion criteria will be re-assessed and updated as needed. Any changes will be submitted via substantial amendment.

3.2.1. TREATMENT-SPECIFIC EXCLUSION CRITERIA

In addition to the core inclusion and exclusion criteria above, there are arm-specific eligibility criteria for each arm to determine to which arms a participant can be randomised.

As this is a blinded study, caution as determined by the clinical team and their clinical judgment must be used when using any of the medications or treatments listed in **Section 5.12.3** and **Table 7.** A clinician can decide after careful consideration, if there is a cautionary medication or treatment, the participant can still be allowed in the trial; details will be provided on the database.

3.2.1.1. Telmisartan-specific exclusion criteria

1. Participants currently taking sartans (AT1 angiotensin receptor antagonists), aliskiren, ACE inhibitors or potassium sparing diuretics.
2. Participants with a known hypersensitivity or intolerance to sartans (AT1RAs)
3. Participants with a history of angioedema.(*Angioedema is a potentially life threatening condition causing swelling of the skin and subcutaneous tissues often including the lips or tongue)*
4. Participants with known aortic or mitral stenosis that the investigator judges to make telmisartan use potentially unsafe.
5. Participants with known renal artery stenosis.
6. Participants with hyperkalaemia (serum potassium (K+) level of ≥ 5.5 mmol/l). If hyperkalaemia is identified, one re-screening will be allowed, either within 4 weeks or after identification and treatment of precipitants.
7. Participants currently taking lithium or taken within the previous 6 months.

3.2.1.2. Terazosin-specific exclusion criteria

1. Participants currently using alpha blockers other than tamsulosin (alfuzosin, silodosin, prazosin, terazosin, and doxazosin), including natural supplements with this action (e.g. yohimbine).
2. Participants with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption.
3. Participants with a known sensitivity to quinazolines e.g. alfuzosin, silodosin, prazosin, terazosin, and doxazosin, erlotinib, gefitinib, afatinib, lapatinib, and vandetanib.

4. Participants using Strong CYP3A4 Inhibitors ~~regularly~~ ~~currently or have had more than or equal to 2 prescriptions in the past 12 months~~ either currently taking or planned courses for ongoing clinical indication (e.g., ritonavir, Paxlovid, itraconazole, ketoconazole (unless topical), clarithromycin).

3.2.2. RE-RANDOMISATION FOLLOWING WITHDRAWAL

Participants who withdraw from the trial following randomisation will not be eligible to re-enrol in the trial.

Participants whose study participation ceases due to a treatment arm being discontinued following interim analysis will be eligible for re-randomisation to a new treatment arm, subject to continuing to meet eligibility criteria and completing a washout period of 6 weeks prior to screening assessment. If a treatment is deemed lacking activity, then it will not be expected to have any impact on clinical trial results and therefore a 6-week washout will suffice. See **section 4.4** for more information on re-randomisation.

3.3. NUMBER OF PARTICIPANTS

The total target number of participants is 400 per arm. We have allowed for a withdrawal rate of up to 25% over the planned trial duration (3 years' treatment). The novel trial design and the aim to recruit a diverse, potentially research-naive population, means that there is less evidence in the literature on which to base our expected withdrawal rates. We will therefore closely monitor withdrawal throughout the trial duration. If withdrawal rates are higher than expected we will co-create and implement supportive recruitment and retention strategies, which may be generic or site-specific.

The MDS-UPDRS Part I & II combined as a primary outcome measure, over a 3 year study duration with a 30% reduction in rate of progression compared to participants on placebo would require a sample size of 266 participants per arm to complete 36 months post first dose of study medication to achieve power of >0.95.

The first two analysis stages (stage 1 and stage 2) are interim tests for activity based on the inverse variance weighting (IVW) of all MDS-UPDRS Parts I, II and remote III and employ large one-sided alpha. These analyses will look for signs of activity / engagement to determine whether to continue recruitment and follow-up. The sample size required for the stage 1 analysis is 133 participants per arm having received 52 weeks post first dose of study medication. The sample size required for stage 2 is 200 participants per arm having received 78 weeks post first dose of study medication.

If an arm proceeds past stage 2 it will progress to the primary analysis to determine treatment efficacy compared to placebo. The stage 3 analysis is an early efficacy analysis which requires 266 participants per arm having received 104 weeks post first dose of study medication. If efficacy cannot be determined at stage 3, the treatment will continue to the stage 4 analysis which requires 266 participants in each arm having received 156 weeks post first dose of study medication.

The stage analyses will be completed separately for each arm based on meeting pre-defined recruitment milestones and so will not be dependent on all arms reaching the recruitment target at the same time. The number of participants required for each analysis will be inclusive of the participants from the stage prior, given that the arm passes the stage 1 and 2 lack of activity analyses.

3.4. Co-enrolment Guidelines

Co-enrolment in previous or future trials is considered in **Section 4.3**.

3.5. Screening & Randomisation Procedures

3.5.1. Pre-Screening Procedures & Registration of Interest

Potential participants will be identified via a variety of pathways including:

1. Clinician or GP referral.
2. Direct contact between potential participants and sites.
3. PwP who have registered with charities (e.g., Cure Parkinson's and Parkinson's UK) and academic or clinical mailing lists (e.g., University College London Movement Disorders Centre) to receive research communications.
4. PwP who have consented to contact for future research or registered with research registries to receive research communications.
5. Online self-referral via the registration of interest survey.
6. Participants in arms that are terminated due to lack of activity can be re-randomised, provided they meet the general and arm-specific eligibility criteria and complete a 6-week washout period.

Potential participants must complete a Registration of Interest (RoI) form, which will include brief, high-level eligibility questions and will be accompanied by the participant information sheet (PIS) and a lay version of the eligibility criteria. This will empower potential participants to self-screen their own eligibility and reduce time resource for participants who are not eligible. Site delivery staff will be available to help support potential participants with completion of the RoI form, if needed. Following completion of the RoI form, potential participants will be contacted to discuss the trial to determine the participant's interest and potential eligibility (pre-screening) and to confirm the in-person screening visit if appropriate. Sites may utilise different approaches to encourage efficiencies. This will not include any trial-specific procedures.

3.5.2. Consent

All trial procedures, including sub-study procedures, should only be performed once written informed consent has been obtained. Separate PIS and consent forms will be provided for the sub-studies (please refer to the sub-study specific appendices for further details).

The PIS will be made available to the participant at the time of completing the RoI form and should be provided at least 72 hours prior to the in-person screening visit to ensure participants have time to read, reflect and consider participation. Study teams will call participants for an initial trial discussion and to confirm the date of the in-person screening visit. Study teams should confirm in this phone call that the participant has access to the PIS and book the in-person screening appointment for a minimum of 72 hours after the RoI form was completed. If the participant has not yet read the PIS, the study team should send them a copy of this and confirm the in-person screening appointment for a minimum of 72 hours after the PIS was sent. The PIS will also be accessible to download via the trial website.

Written informed consent to participate in the EJS ACT-PD Trial and be randomised must be obtained from participants after explanation of the aims, methods, benefits and potential hazards of the trial, the participant has the opportunity to ask questions and receive satisfactory answers and BEFORE any trial-specific procedures are performed or any samples are taken for the trial. The consent form will also confirm that the participant is happy with:

a) the sharing of their contact details with the central pharmacy for prescription dispensing and delivery purposes
b) their routine health care records e.g. HES and mortality via NHSD and/or ONS to be retrieved using name, postcode and NHS number and linked to their study data
c) their blood samples being collected and stored for trial purposes
d) sharing of their trial data with other researchers as required.
e) The involvement of their partner in the trial

It must be made completely and unambiguously clear that the participant is free to refuse to participate in all or any aspects of the trial, at any time and for any reason, without incurring any penalty or affecting their standard clinical treatment.

The consent signing will occur at the face-to-face screening visit. If participants cannot physically sign the consent form themselves (e.g., due to PD symptoms such as severe tremor) then they can give consent orally in the presence of at least one witness for an advocate to sign on their behalf and have this recorded in writing.

Signed consent forms must be kept by the investigator in an Investigator Site File and a copy given to the participant (via email or a physical printed copy). The full consent process must be documented in the participant's medical notes and required elements in the trial database including: the date the PIS was provided or downloaded by the participant; when initial eligibility and telephone consultation was conducted; when the consent form was signed and when eligibility prior to randomisation was confirmed by the PI or appropriate delegate. Monitoring of the completed informed consent forms by the TMT at the CTU will be utilised through the course of the trial. Once consented, a participant identification number (participant ID) and three letter code (TLC) will be assigned to be used in the trials eDC system. The three letter code is a unique code associated with the trial ID to act as a secondary identifier. The eligibility assessments will be then carried out to evaluate participant eligibility during the screening visit.

3.5.3. Abnormal Screening Results

If any of the screening tests are classified as ineligible, then the following processes should be followed:

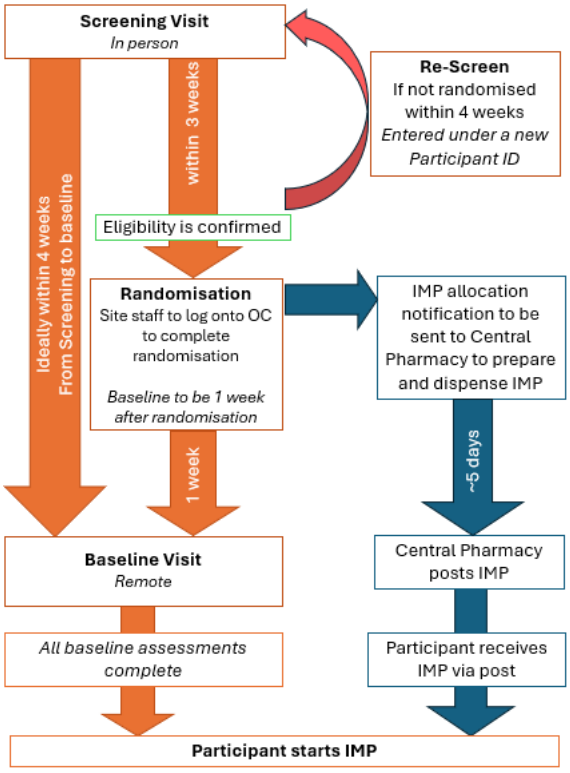
- Abnormal blood tests:
  - If there is no obvious reason for the abnormal result the blood test may be repeated once; if the participant is considered eligible based on the repeat result they can proceed to randomisation, if completed within 4 weeks of the initial screening visit. If there is no obvious reason for the abnormal result and the repeated result is still abnormal, the participant should be referred for review with their normal clinical care team. The participant will be eligible for re-screening following relevant clinical management.
- Abnormal blood pressure readings:
  - If the abnormal blood pressure reading may be attributable to transient/reversible factors (e.g. dehydration, elevated room temperature, postprandial state), then the reading should be repeated once those factors are addressed within a maximum of 4 weeks of the initial screening visit. If there is no obvious reason for the abnormal result or the repeated result is still abnormal, the participant should be referred for review with their normal clinical care team. The participant will be eligible for re-screening following blood pressure management.

If the participant consents to join the study, a letter will be sent to the general practitioner (GP) and Parkinson's treating clinician informing them of the trial and the participant's involvement. This process is summarised in **figure 1.**

3.5.4. SCREENING AND RANDOMISATION TIMING OF ENTRY

At the screening visit, the randomisation and the baseline visits should be scheduled with the participant. **Figure 6** illustrates the suggested timing of these activities.

Figure 6: Suggested timing of screening, randomisation and baseline visit



Randomisation should ideally take place within 3 weeks of the screening visit. Randomisation must be completed no later than 4 weeks after the screening visit. If a participant has not been randomised within 4 weeks of the screening visit, they will need to be re-screened using a newly provided participant identification number (participant ID).

The baseline visit should be scheduled at least 1 week after the randomisation date to allow time for the preparation and posting of IMP by the central pharmacy. The baseline visit should ideally take place within 4 weeks of the screening visit and no later than 6 weeks after the screening visit.

3.5.5. PROCEEDING TO RANDOMISATION AND BASELINE

Sites should contact the participant to inform them of whether they are eligible to proceed with participation.

If a participant is eligible, the site should:

- complete the randomisation process in the trial database
- confirm the scheduled baseline visit with the participant to complete the clinician-reported outcome measures (either via video or telephone call)
- provide the participant with further instructions for their baseline assessments

- provide the participant with guidance on delivery and taking trial treatment and other trial procedures.

Once randomisation in the trial database is complete, a prescription for the participant's allocated arm will be produced so that the central pharmacy can prepare and post the medication directly to the participant. Trial treatment should not be started until after the baseline assessments have been completed. Once the participant has completed their baseline assessments, trial treatment should be started. If trial treatment has not been received by the baseline assessment date, trial treatment should be started as soon as it is received. Receipt of IMP and the date the participant started study medication should be confirmed by site staff and documented in the trial database in the week 1 titration phone call with the participant. If IMP is not started within 1 week of being received (as confirmed in the week 1 titration phone call with the participant), then the site team must record this delay and contact the EJS ACT-PD Trial Management Team to determine how to proceed.

If a participant is ineligible following screening or the participant does not want to proceed, they should not be randomised. The reason for not proceeding should be recorded in the trial database as well as being documented within the participant's medical record. Participants who withdraw before being randomised, or were deemed ineligible can attend a new screening visit at a later date where appropriate, provided the reason for ineligibility is adequately addressed. If a participant attends a new screening visit, they should be recorded in the trial database using a newly provided participant identification number (participant ID). Their new participant ID should be linked to their previous ID within the database. This also applies if a participant is being re-randomised (please refer to **section 4.4**).

For details on the recruitment and consent of Partners, please refer to **Section 10.2.**

4. RANDOMISATION

Please refer to **section 3.5** for Screening & Randomisation Procedures and **Section 9.1** and for Method of Randomisation.

4.1. RANDOMISATION PRACTICALITIES

Participants will be randomised at each centre via the eDC system once the eligibility criteria have been entered and confirmed. Randomisation will use minimisation, stratified by biological sex, age, tier of site, and Hoehn & Yahr stage.

For participants eligible for both active treatment arms, the ratio between the three arms will be 1:1:1

- Arm A : SoC plus Placebo
- Arm B : SoC plus Telmisartan
- Arm C : SoC plus Terazosin

For participants eligible for only one active treatment arm, the ratio between that arm and the placebo arm will be 1:1. Overall balance will be monitored throughout the trial.
If participants are ineligible for a specific active treatment arm, they can be assessed for eligibility and randomised to other arms for which they are eligible. Any proposed arm-specific exclusions will be carefully reviewed to determine their likelihood to bias disease progression as determined by the primary outcome. This will determine whether:

1. Introduced bias can be accounted for in the trial analysis
2. An arm-specific placebo "sub-cohort" must be established

All trial arms (both active (B, C) and placebo) will be visually matched and dispensed at the same frequency (tablets / day) to maintain blinding.

4.2. RANDOMISATION CODES & UNBLINDING

Randomisation codes and unblinding are considered in **Section 5.9.**

4.3. CO-ENROLMENT GUIDELINES AND REPORTING

Concurrent participation in another clinical trial of an investigational medicinal product (IMP), medical device or other experimental intervention such as a physiotherapy trial, is not allowed. A minimum 26-week washout period is required following participation in another interventional trial before completing screening for the EJS ACT-PD Trial. Participants on trial treatment may join observational studies at any point during their participation, but EJS ACT-PD Trial data must continue to be collected and entered into the trial's database as per the trial's Assessment Schedule.

Questions regarding co-enrolment should be directed to the MRC CTU TMT at mrcctu.ejsactpd@ucl.ac.uk.

4.4. RE-RANDOMISATION INTO THE TRIAL

Participants whose trial participation ceases following treatment arm closure due to lack of activity at stage 1 or stage 2 analysis are able to attend a new screening visit and be considered for re-randomisation to a new trial arm. There must be a 6-week washout from last trial treatment dose

prior to screening visit. Participants will need to complete a new RoI form to notify the trial of their interest to return to the trial and be re-randomised. Participants re-entering the trial will be considered a new participant and will need to re-complete all screening tests and eligibility processes described in **section 3.5**.

Participants who complete their 156 weeks of treatment on an arm that has not been closed due to lack of activity are able to be re-randomised following a 26-week washout period. At this point, they will be considered a new participant and will need to complete all of the screening and eligibility process described in **section 3.5**, including recompleting the RoI form. Participants can attend their new screening visit 26 weeks after their last dose of IMP. If the primary analysis for a treatment is completed and found to be negative, then the washout period for participants who have completed 156 weeks of this treatment can be reduced to 6 weeks.

Participants who re-enter the trial will be provided with a new screening ID which will be linked to their original screening ID within the trial database. This will enable re-randomisation rates to be monitored.

Participants who withdraw from the trial will not be able to be re-randomised.

5. TREATMENT OF PARTICIPANTS

Initially two different mechanistic classes of potential neuroprotective drug are planned to be tested against a control (placebo) in participants with PD in the first iteration of the platform trial. The third and fourth treatment drugs, each targeting a different mechanism, have been identified and are planned to open for recruitment at approximately 12 and 24 months respectively, following the trial's launch to recruitment. Amendments to this protocol will be submitted to support the addition of these arms. We expect further treatment arms to be added in future amendments. All participants will continue to receive their normal Standard of Care (SoC) through routine prescribing practice. Instructions on how and when to take the trial treatment will be provided to participants following randomisation. All participants and trial delivery staff will be blinded to the treatment allocation.

5.1. INTRODUCTION

Following a rigorous selection process, telmisartan and terazosin have been selected as the first two drugs to be evaluated in the trial. Please refer to the drug specific appendices for further details regarding the selected active treatments.

The EJS ACT-PD Trial will use randomised double-blind, placebo-controlled comparisons. Participants with a diagnosis of PD and confirmed eligibility will be randomly assigned equally (e.g., in the ratio of 1:1:1) to each of the actively recruiting treatment arms or placebo for which they are eligible:

- Arm A: Standard of Care (SoC) plus placebo
- Arm B: SoC plus telmisartan
- Arm C: SoC plus terazosin

Please refer to **section 5.7** for dose interruptions and discontinuations for all IMPs. It is the responsibility of the treating clinician/s at the delivery site to ensure the treatment regimen is followed.

Amendments to this protocol will be made when additional treatment arms are added. The current IMPs in this trial are telmisartan, terazosin and placebo. All participants will continue with their SoC; SoC is not being investigated in this trial and is regarded as a non-IMP.

5.1.1. STANDARD OF CARE

NHS SoC is not being investigated as part of the EJS ACT-PD Trial. It is guided by NICE Technology Appraisal Guidance (TAG) documents. Examples of current SoC include, but are not limited to:

1. Participants receiving symptomatic oral or transcutaneous drug treatments for Parkinson's disease.
2. Participants receiving oral or transcutaneous drug treatments for the relief of side effects due to Parkinson's disease medication.
3. Participants receiving Rivastigmine patch for dopa-related psychosis to allow for higher (therapeutic) levodopa doses.
4. Participants receiving physiotherapy, occupational therapy or speech therapy according to existing NHS standard of care.
5. Participants following guidance around their diet and lifestyle (e.g., exercise)

5.2. PRODUCTS

Blinded IMPs, including placebo, will be supplied to a central pharmacy for the EJS ACT-PD Trial. The IMPs will be packaged and labelled in accordance with local regulations and Good Manufacturing Practice, stating that the drug is for clinical trial use only and should be kept out of the reach and sight of children. The IMPs will be purchased, over-encapsulated as needed, packaged, labelled and distributed by Sharp Clinical Services (UK) to a central pharmacy who will store, dispense and distribute directly to participants. The prescriptions and supply management processes are detailed in the pharmacy file. Further information on the background and product details for each IMP, is in the individual drug specific appendix (**appendix 2**)**.**
The packaging and capsules will be visually matched for both active and placebo treatments via over-encapsulation to ensure blinding is maintained throughout the trial.

WGK Clinical Services Ltd is the central pharmacy and will be responsible for dispensing and posting the trial treatments to study participants via information received on electronic prescriptions. Participants will receive their trial treatments via post which will be signed for by the participant or member of their household. After the initial 5-week titration phase, participants will be supplied with sufficient trial treatment for a minimum of 6 months at each delivery. The first 6-month supply will be issued at week 3 of the titration phase following confirmation of tolerability, this should ensure approximately 3 weeks overage throughout the trial in the event of delayed study visits or postal issues.

5.3. ARM A

Arm A will be a single shared arm, consisting of SoC plus placebo, visually matched and taken at dose intervals to match the active arms.

Participants in Arm A will receive:

An over-encapsulated placebo capsule taken once daily to match the treatment arms.
This will be dispensed according to the same titration schedule as the treatment arms.

Table 2: Titration schedule 1, for Arm A (placebo)

Week:	1	2	3	4	5	Cont.
Dose:	1 capsule od	1 capsule od	1 capsule od	1 capsule od	1 capsule od	1 capsule od

During the titration phase (weeks 1 to 5) participants will be dispensed 5 bottles. There will be one bottle per week during the titration phase labelled 1, 2, 3 etc to correspond with the week.

Following completion of titration, participants in Arm A will receive:

- Placebo 1 tablet, over-encapsulated, 180 capsules per bottle, 1 bottle received every 6 months.

5.4. ARM B

Participants in Arm B will receive:
Over-encapsulated telmisartan 40mg per day for 36 months (plus their usual SoC).

Any brand / manufacturer of the IMP with a marketing authorisation in the UK can be used by the supplier for over-encapsulation and trial supply.

5.4.1 Regulatory Status

Approved by the FDA in 1998 and by the EMA in 2011 for hypertension.

5.4.2 Treatment Schedule

Telmisartan will be administered once daily (od). It will be titrated according to the following schedule:

Table 3: Titration schedule for telmisartan

Week:	1	2	3	4	5	Cont.
Dose:	20mg od	20mg od	20mg od	40mg od	40mg od	40mg od

During the titration phase (weeks 1 to 5) participants will be dispensed 5 bottles. There will be one bottle per week during the titration phase labelled 1, 2, 3 etc to correspond with the week.

Following completion of titration, participants in Arm B will receive:

- Telmisartan 40mg, over-encapsulated, 180 capsules per bottle, 1 bottle every 6 months.

5.5 Arm C

Participants in Arm C will receive:
Over-encapsulated terazosin 5mg per day for 36 months (plus their usual SoC).

Any brand / manufacturer of the IMP with a marketing authorisation in the UK can be used by the supplier for over-encapsulation and trial supply.

5.5.1 Regulatory Status

Approved in 1998 by the FDA and in 2016 by the EMA for hypertension.

5.5.2 Treatment Schedule

Terazosin will be administered once daily (od). It will be titrated according to the following schedule:

Table 4: Titration schedule for terazosin

Week:	1	2	3	4	5	Cont.
Dose:	1mg od	2mg od	2mg od	4mg od	5mg od	5mg od

During the titration phase (weeks 1 to 5) participants will be dispensed 5 bottles. There will be one bottle per week during the titration phase labelled 1, 2, 3 etc to correspond with the week.

Following completion of titration, participants in Arm C will receive:

- Terazosin 5mg, over-encapsulated, 180 capsules per bottle, 1 bottle every 6 months.

5.6 Dispensing and Storage

IMP for the EJS ACT-PD Trial will be shipped directly from the Sharp Clinical Services (UK) Ltd for storage at the central pharmacy until dispensed. A named trial pharmacist at the central pharmacy will be required to maintain complete records of all IMP dispensed.

Procedures for drug labelling, accountability, storage and destruction will be detailed in the trial's Site IMP Management Guidance document and must be in compliance with applicable local regulations, GCP and the protocol. All IMP will be dispensed to coincide with the dispensing schedule documented in the trial's Site IMP Management Guidance document.

Following participant randomisation, an electronic prescription will be produced and approved by a delegated staff member at the participant's site. The electronic prescription will be provided to the central pharmacy. The central pharmacy will dispense and post the IMP to the participant's home address. Postage will require a signature from either the participant or a member of their household. The central pharmacy will confirm IMP receipt based upon receipt of the postage signature and site staff will confirm receipt via drug compliance checks at each study visit.

5.7 Dose Modifications, Interruptions & Discontinuations

No dose reductions can be performed at any point during the trial.

During Titration Phase

During the titration process, from receiving IMP to 5 weeks, trial site staff should contact participants via telephone call on a weekly basis and any adverse events will be recorded. A summary of these telephone calls should be recorded in the participant's notes and trial database, including if the call was not answered. If trial site staff are unable to get hold of the participant for the entire 5 week titration phase then they should not approve the prescription for the first 6 months of treatment until able to confirm whether the participant has been able to tolerate the trial medication.

If a participant feels they are unable to tolerate their dose of IMP due to adverse events emerging following a dose escalation, they will be given clinical advice and / or prescription, as per usual clinical care for the treatment of the adverse event. If they are unable to tolerate increases in the IMP according to the titration schedule despite optimal clinical advice, they will be given the option to temporarily pause IMP while clinical advice / standard of care is further optimised. Following pausing of IMP for 4 weeks or more, a participant will need to re-start IMP titration for the arm in which they were originally randomised. If the participant is unable to tolerate dose titration on a second occasion, they will discontinue study medication and be invited to remain in follow-up. All dose interruptions or discontinuations will be captured in the participant's clinical care notes and the trial database.

Table 5A. Action required following pause of treatment – During Titration Phase

Duration of treatment pause (During titration phase)	Action
Less than 4 weeks	Continue at previous dose following clinical care for adverse event.
4 weeks or more	Restart 5-week titration

Post Titration Phase

After the 5-week titration process, doses of IMP can be paused or stopped due to safety reasons, clinician choice, or participant choice. If a participant pauses / does not take their IMP for a maximum of 2 consecutive weeks, they can return to their previous IMP dose and continue. However, if a participant pauses / does not take their IMP for more than 2 consecutive weeks, but then is able to resume IMP (in the treating clinician's judgement), they will be given a 5-week dose titration kit to allow them to safely do so. If the participant pauses IMP for 4 weeks or more, this will be recorded as a treatment discontinuation and restarting IMP will be considered on a case-by-case basis as discussed by the PI and TMG.

Table 5B. Action required following pause of treatment – Post Titration Phase

Duration of treatment pause (Post titration phase	Action
Up to and including 2 consecutive weeks	Restart IMP
More than 2 consecutive weeks and less than 4 weeks	Restart IMP following 5-week titration
4 weeks or more	Treatment discontinuation. IMP restarting to be considered on a case-by-case basis.

If a participant develops an intercurrent illness during the 156 weeks' follow up, they may again be advised to pause IMP. During this time the participant will be given clinical advice / prescription in line with usual clinical care. If the participant pauses IMP, the above table should be referred to restarting IMP.

5.7.1 EXPECTED TOXICITIES AND SIDE EFFECTS

5.7.1.1 Orthostatic hypotension

Orthostatic hypotension can be identified by taking a blood pressure reading after 3 minutes of rest whilst lying down and then repeating the blood pressure reading after 1 and 3 minutes of standing. Orthostatic hypotension is diagnosed in this way by identifying the excessive decrease in blood pressure occurring on standing, which may or may not be symptomatic.

Orthostatic hypotension may be symptomatic or asymptomatic. Orthostatic hypotension, defined as a decrease in BP > 20 mmHg systolic or > 10 mmHg diastolic on supine to standing (up to 3 mins), is considered an AE if **symptomatic** or **requires active management** including con-medication changes and non-pharmacological interventions (other than hydration and dietary advice).

Any participant developing clinically significant new or worsening OH at any point after randomisation will be given clinical advice to manage the symptoms, tailored according to the clinician's judgement.

To facilitate remote monitoring of blood pressure in the event of symptomatic OH, each participant will be given and taught to use a home blood pressure measuring device. Participants will receive instructions and guidance on how to identify and address low blood pressure whilst taking part in the study. Participants will be advised to contact their site delivery team if they have any concerns and to only take their blood pressure when requested by the study team. Participants' partners / family members / carers can assist with taking their blood pressure if needed.

5.7.1.2 Hypotension

Hypotension may be symptomatic or asymptomatic. Hypotension, defined as SBP < 100 mmHg or DBP < 50 mmHg (in any position – lying, sitting or standing), is considered an AE if **symptomatic** or **requires active management** including con-medication changes and non-pharmacological interventions (other than hydration and dietary advice).

5.7.1.3 Other toxicities

It is possible to have an allergic reaction to these medications, with symptoms such as:

- A skin rash or itching
- Swelling of lips, throat or face
- Large hives
- Trouble breathing or wheeziness

If participants experience symptoms of allergic reaction linked to the initiation or change in dose of IMP, they should be advised to stop taking the medication immediately and seek medical assistance without delay.

5.7.2 Stopping Drug Early

Discontinuation criteria are considered in **section 5.10.**

5.7.3 Accountability & Unused Drugs

Participants will be asked to confirm compliance with IMP in weekly phone calls with their site delivery team during the 5-week titration process and at each study visit following titration completion, with the date of IMP initiation being confirmed and recorded in week 1. Participants will be provided with an optional drug diary card to assist with noting medication intake. The research team will review and summarise the participant's drug compliance via the trial database and a pill count during the study visit. Reasons for any dose interruption or discontinuation including missed doses will be recorded in the trial's database. All the packaging and unused capsules, after the completion of a pill count, should be returned by participants to their local pharmacy and can be destroyed as per standard local procedures by pharmacy.

The central pharmacy will record the following information:

1. Each batch of IMP dispensed to each participant
2. Confirmation of IMP postage to participants
3. Receipt of IMP when it reaches participants

A nominated trial pharmacist at the central pharmacy will be responsible for accountability of trial treatment supplies. Accountability must include tracking all IMP received at the central pharmacy, dispensed to participants and destroyed as unused or expired on-site. The trial pharmacist will sign a document to confirm that central pharmacy systems and standard operating procedures (SOPs) are in place to cover IMP ordering, receipt, storage and dispensing, and that their systems will enable accurate traceability of all trial drugs. The SOPs will be submitted and a documented review performed by the TMT as part of the vendor assessment.

A Site IMP Management Guidance document will be provided to the central pharmacy prior to activation by the TMT at the MRC CTU.

5.7.4 Compliance & Adherence

Participants will be made aware of the importance of compliance with the trial protocol at screening, randomisation, and subsequent follow-up visits. Participants will be provided with access to an optional drug diary card to assist them to record whether they have taken their trial treatment as per their prescription, or experienced any side-effects after randomisation. Participants will be informed that missed doses should not be made up if not taken on the relevant day but should be noted to enable them to inform the site team at their visits.

Compliance will be discussed at each follow-up visit to determine since the last study visit, how many days of their prescribed dose (depending on treatment arm and tolerance) have been taken. If the optional diary card has been completed, this can be used to assist the conversation. The research team will review and summarise the participant's drug compliance via the trial database and a pill count during the study visit. Reasons for non-compliance will be sought and addressed where appropriate. Reasons for any dose delay or missed or additional doses will also be recorded in medical notes and the EJS ACT-PD Trial database. If site delivery teams have any concerns regarding treatment compliance, they should discuss this with the participant.

5.8 Handling cases of Trial Treatment Overdose

Any dose in excess of that specified according to the protocol will constitute an overdose. Measures will be taken to minimise accidental overdose of trial treatment by providing adequate education to trial participants. Participants will be asked to inform site staff as soon as possible following treatment overdose; site staff should report all cases of treatment overdose to the TMT within 24hrs of being informed. After accidental or deliberate overdose of trial treatment, if no AE occurred then trial treatment does not need to be paused and can continue as normal (one tablet per day) unless deemed unsafe by the treating clinician. If the overdose resulted in an AE, the treating clinician should treat the participant accordingly, which may include pausing trial treatment, and if medically required, unblinding the treating clinicians/participants to their trial treatment, (please see **section 5.9**). If no unblinding occurred following an accidental overdose of trial treatment, then trial treatment can continue as normal or be re-introduced (if paused) in accordance with **Table 5** with consultation with the EJS ACT-PD Trial Management Team (without unblinding them to treatment allocation).

Any participant taking a deliberate overdose of trial treatment should discontinue trial treatment for the remaining duration of the trial and no further supply of trial treatment will be given. The participant, if willing, should remain in trial follow-up and complete trial visits for safety and efficacy as per the schedule of activities. The participant will be asked to return any unused IMP to their local site, so that site staff can complete a pill count to ensure the participant has no remaining IMP.

5.9 Unblinding

Unblinding participants' trial treatment is discouraged during the trial as blinding is considered critical to its integrity. The treatment allocation must not be broken except in medical emergencies when the appropriate management of the participant necessitates knowledge of the treatment allocation. In many cases, particularly when the emergency is clearly not investigational product related, the problem may be properly managed by assuming that the participant is receiving an active treatment without the need for unblinding.

All participants will be unblinded at the end of the trial when data are mature, database lock and primary analysis has been completed or earlier, at the recommendation of the IDMC.

5.9.1. UNBLINDING ARISING FROM EHR

As the trial is double-blinded, neither participants nor delivery staff will be aware of which treatment a participant has been randomised to. Participants' treatment allocations will be stored only in the randomisation server, separate to the EJS ACT-PD Trial database, and will not be stored in any other form of Electronic Health Record (EHR). This will remove the risk of accidental unblinding due to participant or staff EHR access.

5.9.2. EMERGENCY UNBLINDING

All participants will be given a participant card which includes emergency contact details for unblinding purposes, including out of hours if necessary for trial-related emergencies only.

Unblinding of allocation to trial treatment can be performed if required only in a medical emergency, where knowledge of the participant's treatment allocation would change immediate clinical management. This can be requested by any treating doctor and performed in medical emergencies via the trial website. The doctor requiring the unblinding may contact or notify the participant's site prior to unblinding to discuss the circumstances if this will not result in a delay to treatment; site contact details (including out-of-hours contact) can be found on the participant's card. The card also contains the location of the EJS ACT-PD Trial website where the unblinding can be performed. If it has not been possible to contact the participant's local site, the trial emergency numbers (also found on the participant card and on the trial website) can be used to contact the delegated members of the EJS ACT-PD Trial who will escalate the situation as necessary. However, if it is not possible to contact a member of the trial team via the trial emergency number, the procedure for rapid break of blinding is in place so that unblinding can be performed to not delay treatment.

To unblind, an online form which can be found via the EJS ACT-PD website (www.mrcctu.ejsactpd.ucl.ac.uk), must be completed and submitted. The form will require the requesting treating doctor's full name, GMC number and NHS email address where they will receive the unblinded information. This form can be completed by the requesting doctor treating the medical emergency or by the delegated EJS ACT-PD Trial staff team member. The EJS ACT-PD Trial team (centrally and at site) will only receive notification that the participant has been unblinded and details of the individual who has carried out the unblinding. They will not receive details of the treatment allocation. The trial's unblinded statistician will receive a notification that the participant was unblinded, including their trial ID number and the details of their treatment allocation.

If unblinding occurs, then the site investigator(s) must document this, with the reason for unblinding, and report it to the EJS ACT-PD Trial team within 24 hours of the occurrence via the relevant eCRFs on the Trial's database **without unblinding the Trial Team or site team to the allocation**. Treatment allocation information must be kept confidential and should be disseminated only to those individuals who must be informed for medical management of the participant.

The Trial Statistician at the MRC CTU at UCL will be notified of all emergency unblindings.

5.9.3. UNBLINDING BY THE CTU

MRC CTU at UCL staff who are not involved in the day-to-day running of the trial and the unblinded trial statisticians will be responsible for unblinding possible suspected unexpected serious adverse reactions (SUSARs) for notification to the regulatory authorities. For further details, please refer to **section 7** of this protocol.

5.9.4. UNBLINDING FOLLOWING TRIAL CLOSURE

Once statistical data lock has occurred for a treatment arm and no further changes will be made to the data, the primary analysis will occur. All participants allocated to that treatment arm will be unblinded following completion of the primary analysis. The Principal Investigator at each site will be notified in writing of the treatment allocations of all participants randomised by the site to that treatment arm. It will be the responsibility of the Principal Investigator or delegate to inform participants of their treatment allocation, where considered appropriate. If available, participants should be informed of the overall trial results when informed of their treatment allocation, to give context and aid interpretation.

Participants allocated to the placebo arm will not be informed that they are on the placebo arm until the trial reaches statistical data lock for all treatment arms active at their time of randomisation.

5.9.5. UNBLINDING FOLLOWING ARM CLOSURE

If a treatment arm does not pass the stage 1 or stage 2 analysis, it will be closed and participants on this arm will be withdrawn from trial treatment, the trial and follow-up. The arms will only end following completion of the stage analysis. All participants on this arm will be informed of their treatment allocation when advised of the results of the stage analysis.

Participants taking placebo will only be unblinded following early closure of a treatment arm, if all visually / dose matched active treatment arms end at this timepoint, due to the consequent unblinding (i.e., they are no longer acting as matched controls for an active treatment arm). In this scenario the TMG, TMT and any other relevant oversight committees will consider the potential for unblinding.

5.10 PROTOCOL TREATMENT DISCONTINUATION

In consenting to the trial, participants are consenting to EJS ACT-PD Trial treatment in accordance with the trial protocol. However, a participant may stop treatment early, or have their trial treatment stopped early by clinical investigators, for any of the following reasons:

- Unacceptable toxicity or adverse event (see **section 5.7** for discontinuation)
- Intercurrent illness that prevents further treatment
- Any change in the participant's condition that justifies the discontinuation of treatment in the clinician's opinion
- Change in clinical diagnosis during participation and therefore no longer diagnosed with PD
- Pregnancy
- Intent to become pregnant / conceive
- Withdrawal of consent for treatment by the participant
- Trial arm discontinuation as part of the MAMS design

This section refers to stopping trial treatment early and permanently, e.g., due to the reasons above. For management of pausing trial treatment due to toxicities see **section 5.7**.

As the participant's participation in the trial is entirely voluntary, they may choose to discontinue the trial treatment at any time without penalty or loss of benefits to which they are otherwise entitled. Although the participant is not required to give a reason for discontinuing their trial treatment, a reasonable effort should be made to establish this reason while fully respecting the participant's rights. Early cessation of trial treatment should be recorded on the relevant trial Case Report Form(s) and flagged within the trial database, along with any accompanying information as appropriate.

When a participant joins the EJS ACT-PD Trial, they are providing consent for trial follow-up and data collection as well as trial treatment. If a participant discontinues their trial treatment, they should not be presumed to have withdrawn consent for follow up and data collection too (refer to **Section 6.8** for an overview of the options for withdrawing consent). Consequently, they should always be followed up in accordance with the assessment schedule, providing they are willing. Participants should be encouraged to not leave the whole trial because their data is important for the analysis even if they have stopped trial treatment.

The default position for participants who stop trial treatment early should be that they continue with follow-up visits, either in-person or remotely, as per the trial assessment schedule and their electronic health records / routine data is still accessed for analysis purposes. If a participant is considering stopping all trial follow up early, refer to **Section 6.8**.

5.11 Treatment Data Collection

Please refer to **section 6** or **Table 1** for assessment schedules required.

Trial treatment must be recorded on the appropriate eCRF in the EJS ACT-PD Trial database. In addition, reasons for any interruptions or discontinuations of trial treatment must be documented in the appropriate eCRF. Please refer to **section 5.7.4** on compliance and adherence.

5.12 Non-Trial Treatment

5.12.1 Medications Permitted

Investigators may prescribe concomitant medications or treatments deemed necessary to provide symptomatic treatment except for those medications identified as not permitted in **section 5.12.2**. Care should be taken with medication identified as 'use with caution' in **section 5.12.3.**

Participants can also continue their SoC as determined by the participant's Parkinson's treating clinician (please refer to **section 5.1.1**).

5.12.2 Medications Not Permitted

If participants are taking any of the medications listed in **Table 6**, then they may still be eligible to participate in the trial in another active treatment arm (i.e. they will only be excluded from the treatment arm where there is a known concern related to their medication see **Table 6**). The inclusion / exclusion criteria and medications not permitted will be updated as needed via substantial amendment when new treatment arms are introduced into the trial.

Participants must not be prescribed any of the active IMPs during the trial. This also includes medications that are combined or include the IMPs as an ingredient. At randomisation (for eligibility) participants must not have been exposed to any of the actively recruiting IMPs in the 6 months prior to randomisation.

In view of the double-blind nature of the trial, none of the medications listed in **Table 6** or the general exclusion criteria may be prescribed to any active participants after randomisation in view of safety concerns associated with at least one of the possible active treatments, regardless of which treatment arms the participant is eligible for. If any of these medications is deemed essential for the effective clinical care of a participant, they must discontinue IMP but can remain in the trial for follow-up as per this protocol. Once the participant has stopped taking the contraindicated medication, they can resume trial treatment according to the investigator's discretion and if within the appropriate timelines for restarting trial treatment as outlined in **Section 5.7.**

Table 6: Medications not permitted

	Not permitted within these treatment arms:
Aliskiren, ACE inhibitors or potassium sparing diuretics e.g., sprironolactone, amiloride or frumil	Telmisartan
Lithium	Telmisartan
Sartans	Telmisartan
Strong CYP3A4 Inhibitors (e.g., ritonavir, Paxlovid, itraconazole, ketoconazole, clarithromycin)	Terazosin
Alpha blockers (other than tamsulosin)	Terazosin

5.12.3 Medications and Treatments to be Used With Caution

The drugs/procedures listed in **Table 7** have been found to interact unfavourably with the EJS ACT-PD Trial IMPs (please refer to the current approved SmPC for a full list of contraindicated drugs). As this is a blinded study, caution as determined by the clinical team and their clinical judgement must be used when using the following medication/treatments:

Table 7: Medications and procedures to be used with caution

	Caution due to:	**Advice:**
Risk involved with cataract surgery (risk of intra-operative floppy iris syndrome). Participants will be advised to inform their ophthalmic surgeon that they are participating in a trial that might include terazosin if they are due for cataract surgery.	Terazosin	Participant should temporarily discontinue trial treatment. Trial treatment to be resumed according to the investigator's discretion and within the appropriate timelines for restarting trial treatment as outlined in **Section 5.7.**
Use of tamsulosin or PDE5 inhibitors (sildenafil, tadalafil, vardenafil) can cause excessive hypotensive effects.	Telmisartan and terazosin.	Participant should avoid taking trial treatment for a minimum of 4 hours after taking this medication.
Regular and long term use of NSAIDs (at least 1 daily dose of NSAIDs for more than 1 week). Low dose Aspirin is not a concern with Telmisartan.	Telmisartan	Can impair renal function and increase hyperkalaemia; ensure adequately hydrated and consider monitoring renal function while continuing to take trial IMP.

Thiazide or loop diuretics	Telmisartan	May result in volume depletion; ensure adequately hydrated while continuing to take trial IMP.
Digoxin	Telmisartan	May increase digoxin level; monitor digoxin levels when initiating, adjusting and discontinuing telmisartan

If it is necessary for the participant to receive one of these treatments or take one of these cautionary medications for a short period of time, then advice should be followed as described in **Table 7**.

5.12.4 Treatment After Trial Event

After completion of their 156 weeks' trial participation, all participants will be aware that no further IMP will be prescribed or dispensed by the trial team. All further treatments/prescriptions will be at the discretion of their responsible physician. In the event that any of the formal efficacy analyses demonstrate a clear advantage of using any of the IMPs, the relevant safety and efficacy data will be made public with the intention of following the necessary pathways for the IMP to become licensed as SoC for people with Parkinson's.

5.13 Co-enrolment Guidelines

Co-enrolment in previous or future trials is considered in **Section 4.3**.

6. ASSESSMENTS & FOLLOW-UP

6.1. TRIAL ASSESSMENT SCHEDULE

For the Trial Assessment Schedule please refer to **Table 1** at the start of this protocol.

All trial assessments will be conducted in the patient's usual ("ON") dopaminergic medication state. The time since last levodopa / dopaminergic medication will be recorded in the database for the MDS-UPDRS part III.

6.1.1. DATA COLLECTION

Investigations in this trial will use the results of data collected and processed from rater-administered and patient-reported outcome measures. Other investigations will use local assessments at site (such as blood tests and outcome assessments) as per the assessment schedule (**Table 1**).

These data will be collected by the EJS ACT-PD Trial database, which will be an electronic data capture (eDC) system used by the MRC Clinical Trials Unit at UCL. Paper source data worksheets will also be available and their use is recommended to sites (see **Section 8.4** for further details on Source Data and Worksheets). eDC at sites must only be completed by personnel who have completed the MRC CTU eDC training and have been delegated to do so by the Principal Investigator, as recorded on the Signature and Delegation of Responsibilities Log.

Participants completing assessments via eDC in the trial database, will receive personalised links when assessment completion is required. The link will enable them access only to the assessments they are required to complete and will be linked within the system to their participant record (via their participant ID and TLC). The trial teams at sites will have access to view the assessment records of participants at their sites, so that they can send reminders or query data as needed. Additionally, if participants need assistance when completing the patient-reported assessments, they can contact the site trial team at their local site for help with this, or can attend for an in-person visit to complete paper versions. The local site can report any database issues or request help from the TMT.

The trial team at MRC CTU will have access to pseudonymised (via their participant ID and TLC) participant assessment records for all trial participants to maintain oversight of trial delivery and data collection.

If trial staff at participating sites or participants complete any data collection manually (e.g., on physical paper copies), it is the site's responsibility to transfer the data into the trial database using the relevant eCRF.

It is the responsibility of staff at participating sites to obliterate all personal identifiable data on any hospital reports, letters, etc., prior to sending to or sharing with the MRC CTU for monitoring purposes. The only personal identifiers that such records should include are the participant ID and TLC.

Data required for long-term follow-up of participants' health status will also be collected for up to 20 years after the participant's treatment arm ends. Participants will provide consent for their personal information to be shared with national register mechanisms e.g., Office of National Statistics, NHS

Digital, so that they can access the participants' medical records to obtain the relevant data for these analyses. This will also include consent for these organisations to share the linked pseudonymised data with UCL.

6.1.2. TREATING CLINICIAN, BLINDED RATER AND CORE-FUNDED STAFF

Sites are required to identify delegated staff members to act as a treating clinician(s) and blinded raters for the EJS ACT-PD Trial due to the experience and training required, with appropriate arrangements for cover in case of staff absence. The treating clinician cannot also be the blinded rater.

The nominated treating clinician may be the site's PI, Sub-I or an additional staff member who is appropriately trained and qualified to treat PwP. The treating clinician(s) are responsible for assessing eligibility (including reviewing their medical history), obtaining informed consent, monitoring and assessing AEs (e.g., attribution of severity and causality) and reviewing concomitant medications.

The blinded raters will complete the necessary training to act as trial 'raters' including the MDS-UPDRS online training programme, the EJS ACT-PD Trial remote delivery training and the online MoCA certification, all of which will be included in the EJS ACT-PD training process. Blinded raters will be responsible for administering rater-reported assessment of the primary outcome, MDS-UPDRS Parts Ia either in person or via video call for all participants consented at their site and if required, at other sites within their RRDN region. Ideally, the blinded rater should also administer MDS-UPDRS Parts III and IV, MoCA, C-SSRS, CGI-S and CGI-C however these can be conducted by a suitably trained delegated rater at site if required.

The blinded rater should not be involved in reviewing AEs and should not be the first point of contact for the participants. Treating clinicians will provide advice regarding management of PD related symptoms or adverse events.

Several trial-funded site staff members will be based at selected participating sites. The role of the trial-funded site staff will include recruitment and delivery of the trial at their site, alongside the PI, Sub-I and (if separate) the treating clinician, ensure recruitment of under-served groups and support tier 1 and 2 sites within their RRDN region.

The trial-funded site staff may serve as the 'treating clinician' or 'blinded rater' at their sites.

6.2 CLINICAL ASSESSMENTS

6.2.1 PHYSICAL AND NEUROLOGICAL EXAMINATION AND DEMOGRAPHY

Full physical and neurological examination will be performed at the screening visit as part of the eligibility assessment and will include both height and weight.

Core demographic information will be collected at screening and inputted into the EJS ACT-PD Trial database. This information will facilitate monitoring of recruitment inclusivity and will include documentation of participants' date of birth, ethnicity and biological sex. Their approximate home location (maintaining confidentiality) will be recorded to enable calculation of Index of Multiple Deprivation and Rural Urban Classification. Additional lifestyle data will be collected during the screening visit, including the participant's first language, smoking history, caffeine intake, exercise and years of education.

6.2.2 VITAL SIGNS

Vital signs (pulse and temperature) will be evaluated according to the assessment schedule in **Table 1**. Any additional monitoring with assessment of vital signs is at the discretion of the Investigator as per standard clinical practice or as clinically indicated.

6.2.3 MEDICAL HISTORY

Participants' medical history will be assessed via discussion with the participant and review of the participant's medical notes to ensure they meet the eligibility criteria. Participants' medical history and co-morbidities, date of diagnosis of PD and any family history of PD will be recorded by the site team via eDC in the trial database. Medical history is used to record any medical event that has occurred or is persisting prior to randomisation.

6.2.4 CONCOMITANT MEDICATION

At each visit, a review of concomitant medication must be performed to document all prescribed and over-the-counter medications (any relevant natural supplements e.g., yohimbine), their dose and frequency. This will allow calculation of a participant's levodopa equivalent daily dose (LEDD) according to standard formula[33] , and to ensure any contraindicated medications are not being taken. Please refer to **section 5.12** for further details regarding non trial medication.

6.2.5 TREATMENT COMPLIANCE ASSESSMENT

Participants will be made aware of the importance of compliance with the trial protocol at screening, randomisation and subsequent follow-up visits. An optional drug diary card will be available for participants to use to record their trial treatment compliance. Please refer to **Section 5.7.4** for compliance and adherence management.

6.2.6 VIDEO AND TELEPHONE ASSESSMENTS

The screening visit must be conducted in-person.

After the screening visit, participants have the option to proceed with all remaining trial visits remotely if they wish, although in-person visits can be selected if preferred and are encouraged for the assessments at 52, 104 and 156 weeks. Remote visits with site staff can be conducted via video call. Rater-administered assessments should be completed with participants via video call using an online platform (e.g., Zoom, Microsoft Teams, Google Meet) where possible. In extenuating circumstances, certain abbreviated rater-administered assessments can be completed via telephone call as detailed in site training.

Participants unable to participate in video calls will be encouraged to have an in person visit at 52, 104 and 156 weeks. Additionally, where participants do not have access to the internet or have the necessary IT skills, all visits can be conducted in person and where local arrangements allow, study visits can be conducted as home visits.

Participants can opt to attend annual visits (at weeks 52, 104 and 156) in-person if they prefer. However, if week 156 is conducted remotely, an in-person visit should be schedule to complete the blood sample collection for the research bloods. To facilitate the blood sample collection, the in-person visit can take place within +/- 4 weeks of the end of study visit (week 156). Full details of sample collection processes can be found in the Sample Handling and Collection Manual.

Study visits during the 5-week titration phase, and at 39 weeks and 65 weeks timepoints will consist of a telephone call from a delegated staff member from the participant's trial site. These visits will

provide an opportunity for trial staff to receive feedback from participants with regards to their trial experience so far, and for participants to ask questions or raise queries between study assessments.

At all visits, adverse events, concomitant medications and treatment compliance will be assessed.

6.3 Procedures for Assessing Efficacy

All the following assessments should be conducted by a delegated assessing clinician, as per the study visit schedule. All assessments will be completed in the ON medication state. Where possible, the same blinded rater should administer all rater assessments for each participant's duration in the trial.

6.3.1 Movement Disorder Society Revised Unified Parkinson's Disease Rating Scale (MDS-UPDRS)

The MDS-UPDRS is the standard validated tool for the assessment of people with PD (Goetz et al., 2008), often regarded as the gold standard outcome measure in PD trials.[34] It is divided into four sections: non-motor experiences of daily living including mood and mental state (parts Ia and Ib), motor experiences of daily living (part II), an examination of the motor features of PD (part III), and motor complications arising from the use of dopamine replacement (part IV). Of those, parts Ib and II are patient-reported, whereas parts Ia, III and IV are clinician-administered.

For participants who are not fluent in English, the patient-reported parts will be available in paper format for specified approved languages for completion in-person.

The in-person elements of part III (item 3.3 for assessing rigidity, and item 3.12 for assessing postural stability) will only be administered at screening as part of this trial. All other elements of part III will be administered at all subsequent study visits as per the schedule of assessments., whether conducted in-person or remotely. Full working instructions on remote delivery will be included as part of the trial training package. Sites should use the same rater for individual participants as much as possible throughout their participation in the study to reduce variability.

6.4 Procedures for assessing clinical reported outcomes

6.4.1 Montreal Cognitive Assessment (MoCA)

The MoCA test is a widely used screening assessment for detecting cognitive impairment. The MoCA test is a one-page 30-point test administered in 30 minutes. It has been validated for PD and is the recommended minimum cognitive screening measure in clinical trials of PD where cognitive performance is not the primary outcome measure.[35] The recommended cut-off when screening for dementia is 24/25, individuals with a MoCA score < 21 at screening will be excluded as this indicates moderate cognitive impairment.[36]

6.4.2 Levodopa-equivalent daily dose (LEDD)

To facilitate comparisons between participants taking different regimes of conventional PD medications, a set of conversion factors have been used to convert each of the commonly used PD medications to a "Levodopa equivalent daily dose (LEDD)". The LEDD of each of their medications can then be summed for inter-participant / inter-group comparisons. The LEDD calculator can be accessed at the following link:
https://www.parkinsonsmeasurement.org/toolBox/levodopaEquivalentDose.htm"https://www.parkinsonsmeasurement.org/toolBox/levodopaEquivalentDose.htm

6.4.3 Clinical Global Impression (Severity of Illness and Clinical Change)

The CGI is a clinician-rated instrument to determine the progress and treatment response of patients and provide a global vision on the participant's situation. Two of its components are the CGI severity (CGI-S) and change (CGI-C) scales[37]. Both the CGI-C and the CGI-S consist of just one question each, to be answered in a 7-point categorical scale (level of improvement/worsening and severity of illness, respectively).

6.5 Procedures for assessing patient-reported outcomes and Quality of life

6.5.1 Patient Health Questionnaire (PHQ-9)

The 9-item Patient Health Questionnaire (PHQ-9) scores each of the 9 criteria for depression included in the Fourth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) from 0 to 3 according to frequency.[38] It has previously been used to assess depression in disease-modifying PD trials.[39] The cut-off point for identifying moderately-severe depressive symptoms is >14;[40] as such individuals with a PHQ-9 score >14 at screening will be excluded.

6.5.2 Parkinson's Disease Questionnaire (PDQ-8)

The PDQ-8[41] is the short version of the PDQ-39[42], a PD-specific health status questionnaire used both clinically and within research, to reduce participant burden. The PDQ-8 contains 8 items representing each of the 8 different domains in the PDQ-39: mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication and bodily discomfort. Regarding psychometric properties, the PDQ-8 has shown satisfactory internal consistency, item–total correlation, test–retest reliability, and convergent validity, as well as responsiveness to interventions and sensitivity to change.[43,44]

The PDQ-8 can also be used indirectly to provide utility scores via mapping for use in health economic analysis. This will form part of a secondary health economic analysis, where QALYs are calculated over the follow-up time period using utility scores mapped from the PDQ-8 responses.

6.5.3 Modified Hoehn & Yahr Stage

The modified Hoehn and Yahr staging system is simple method of staging PD that can be applied to people with PD in either the "ON" or "OFF" drug state. For the purposes of the trial inclusion criteria, staging will be applied according to participants' "ON" drug state. See Glossary for a description of the stages.

6.5.4 ICEpop CAPability measure for Older people (ICECAP-O)

The ICEpop CAPability (ICECAP) measures provide an assessment of what is important to patients in terms of being able to enjoy life. This suite of measures was designed to assess well-being for use in evaluating social care interventions, and has been found to be sensitive to change in PD. The ICECAP-O for older people covers five dimensions: attachment, security, role, enjoyment, and control.[45] A tariff can be applied to the responses to calculate capability scores from which capability-adjusted life-years (CALYs) can be calculated as the area under the curve, in a similar way to how QALYs are calculated from utility scores.

6.5.5 Carer's Quality-of-Life Questionnaire for Parkinsonism (PQoL Carers)

The 26-item Parkinsonism Carers Quality of Life (PQoL Carers) is a self-completed questionnaire enquiring about various aspects of the wellbeing of people caring for people with parkinsonism (e.g.,

social activities, relationship to the patient, stress, mood), from which a summary index is calculated.[46] The PQoL Carers has been validated in carers of people with Parkinsonism, and has high internal consistency as well as good convergent, concurrent, and discriminant validity, the latter being especially helpful in a disease-modifying trial, and has been shown to have good psychometric properties in Rasch analysis.[46] People with Parkinson's and their care partners were involved in the review and decision-making process of which care partner measure was most suitable and acceptable to include.

6.5.6 EQ-5D-5L

The EQ-5D-5L is a simple questionnaire regarding perceived health on the day of completion within 5 domains (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), each answered according to 5 response levels (no problems, some problems, moderate problems, severe problems, extreme problems) and a visual analogue scale capturing overall health[47,48]. The EQ-5D-5L allows calculation of utility scores, which are used to calculate quality-adjusted life-years (QALYs), and thus enable standardised health economic analyses to be performed. As a means for calculating QALYs, it is useful for providing evidence to decision makers such as NICE that rely on this type of information in the form of a cost-utility analysis for approval of new therapies and resource allocation decisions.

6.5.7 Resource Use Questionnaire

The resource use questionnaire developed for this study incorporates the modified Client Service Receipt Inventory (CSRI) and the modified institute for Medical Technology Assessment (iMTA) Valuation of Informal Care Questionnaire (iVICQ), which together cover self-completed health care, social care and paid/unpaid carer resource use as well as out-of-pocket costs, and use of care home and respite services, relevant to Parkinson's.[49,50] The questionnaire is administered every 6 months starting from baseline, asking each time about care received over the preceding 6 months.

6.5.8 Study Participant Feedback Questionnaire (SPFQ)

The Study Participant Feedback Questionnaire (SPFQ) has been based on TransCelerate-SPFQ and adapted to make the questionnaire trial specific. The questionnaire is optional for participants to complete at three timepoints (Baseline (week 0), week 78 and week 156) and aims to obtain feedback from participants about their trial experience.

6.6 Procedures for Assessing Exploratory Measures

6.6.1 Falls Questionnaire

The falls questionnaire is an amended version of the 'Oxford Parkinson's Disease Centre' falls questionnaire which defines and captures PD-related falls, can quantify fall frequency, and can be easily completed by participants online.

6.6.2 Participant Expectations Questionnaire

The participant expectations questionnaire is a brief questionnaire which aims to assess expectancy and treatment arm preference of participants to determine whether expectations of benefit have any therapeutic impact.

6.7 Procedures for Assessing Safety

All the following assessments should be conducted and/or reviewed by the treating clinician. Following randomisation, any significant worsening noted during study visits and any other potential safety assessment required or not required by protocol should be recorded as a non-serious or serious AE, as appropriate, and reported accordingly on EJS ACT-PD Trial Adverse Event eCRF **(see section 7)**.

6.7.1 Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is administered as a brief clinical interview to detect suicidal ideation and suicidal behaviour. Four constructs are measured: severity of ideation ("severity subscale", rated on a 5-point ordinal scale), intensity of ideation ("intensity subscale", with 5 items, each rated on a 5-point ordinal scale), behaviour subscale (5-category nominal scale), and lethality subscale (6-point ordinal scale).[51]

The C-SSRS will be administered at the screening and end of study (or early termination) visits.

If any concerns are identified, usual care and clinical pathways should be followed.

6.7.2 Blood tests

Participants will be required to have the assessments listed in **Table 1** prior to randomisation in order to assess and ensure participant safety.

Additional blood tests can also be carried out during the trial period as clinically indicated.

6.7.3 Blood pressure

All participants will be provided with a home blood pressure monitor and instructed on how to perform self-measurement of blood pressure. Participants will be advised to report new or worsening symptoms suggestive of orthostatic hypotension, such as light headedness or dizziness on standing, to the site study team, who will provide instruction and guidance regarding blood pressure measurement and management. In the event of concerning symptoms or blood-pressure readings at home, an unscheduled visit can be arranged for in-clinic assessments to be undertaken and appropriate management to be implemented.

The site team should treat participants found to have concerning blood pressure readings according to usual standard of care. Individuals with recurrent or persistent significant orthostatic hypotension despite usual standard of care interventions (for example salt tablets, TED stockings, fludrocortisone, midodrine), which in the opinion of the principal investigator is compromising participant well-being or safety, should be withdrawn from trial treatment but with continuation of follow-up according to protocol.

Any additional monitoring with assessment of blood pressure is at the discretion of the Investigator as per standard clinical practice or as clinically indicated. As blood pressure readings are not being used to inform trial outcomes the devices do not require re-calibration during the 36 months of participation.

6.7.4 Pregnancy

Participants or their WOCP partners must agree to use appropriate contraceptive treatment(s) (listed in **Appendix 1**) throughout the trial treatment period and for 70 days after the end of the trial treatment (e.g. which is five elimination half-lives after final treatment).

For WOCP participants, a urine HCG pregnancy test is required at screening and repeated at baseline if more than 14 days have elapsed between these visits. A serum HCG pregnancy test should be carried out if the result is positive or there is any doubt over the results of the urine HCG pregnancy test.

If a pregnancy occurs in a trial participant or a male participant's partner, it is a reportable event. Please refer to **section 7.2** for how it must be reported. A further information sheet must be provided and informed consent form completed to obtain consent to collect information and outcome of the pregnancy.

Any pregnant participant must stop trial treatment in the event of pregnancy. If the participant is willing, they should continue with usual follow up procedures. Additionally, unblinding procedures **(section 5.9)** should be initiated (unless the participant wishes to terminate the pregnancy for other reasons) as it may implicate how pregnancy is managed.

Please note, authorised products guidance for telmisartan and terazosin is available in the SmPC. A pregnancy risk assessment has been completed as part of this protocol development to evaluate the risk of pregnancy and consider appropriate mitigation strategies.

6.7.5 ELECTROCARDIOGRAM

An electrocardiogram (ECG) will be performed at the in-person screening visit to identify any cardiac abnormalities. The ECG results should be reviewed by the treating clinician and a decision made within their clinical judgement as to whether the results indicate abnormalities which require clinical intervention before the participant can participate in the trial. If a participant fails this ECG eligibility requirement at screening, this should be recorded in the EJS ACT-PD Trial database.

6.8 OTHER ASSESSMENTS

6.8.1 EQUALITY, DIVERSITY & INCLUSION (EDI)

Equality, diversity, and inclusion (EDI) data collection will occur at screening. EDI data will be collected and reported to further the understanding of the demographic breakdown of PwP in the UK who have participated in the trial. This data can also be used in future research and analyses to explore potential demographic differences in (for example) disease progression, treatment side effects and treatment efficacy.

The EDI data will include:

- Gender identity
- Sexual orientation
- Ethnicity
- Caring responsibilities
- Socio-economic status
- First 3 characters of postcode to identify geographic location

If participants do not want to provide any of the EDI information, all questions will include a 'prefer not to say' option.

6.8.2 BIOSAMPLES

Research blood samples will be collected from all participants for bio archiving, these should be collected as per **section 10.1**.

6.9 EARLY CESSATION OF FOLLOW-UP

When a participant joins the EJS ACT-PD Trial, they are providing consent for trial treatment, follow-up, and data collection as well as the collection of biosamples and optional participation in relevant sub-studies. As detailed in **Section 5.10**, if a participant chooses to discontinue their trial treatment, they should always be encouraged to continue with follow-up as per the trial assessment schedule. It should be made clear to the participant that continuing to provide follow-up data is important for the success of the trial. However, if the participant does not wish to remain on trial follow-up, their decision must be respected. If a participant wishes to discontinue participation in some aspects of the trial, it should not be presumed they wish to discontinue all of them. Instead, site staff should have a discussion with the participant exploring the situation and what options may suit the participant. Reasons for early cessation of follow-up include at least the following:

- Withdrawal from further treatment (as addressed in **Section 5.10**)
- Withdrawal from further trial follow-up visits
- Withdrawal from further sample collections
- Withdrawal from trial sub-studies
- Withdrawal from further routine health record use
- Withdrawal of Partner's participation in trial
- Pregnancy (see **Section 6.8.1**)
- Loss to follow up (Lost Contact for Now) (see **Section 6.8.2**)
- Death

As participation in the trial is entirely voluntary, participants may choose to discontinue trial follow-up at any time without penalty or loss of benefits to which they are otherwise entitled.
If a participant decides to discontinue some or all aspects of the trial, the EJS ACT-PD Trial team should be informed of this, and a discussion should be held between the site and the trial team. This discussion is to determine the participant's situation and, if proceeding with discontinuation, what is the participant's chosen level of discontinuation.

Should a participant receive an alternative diagnosis for their suspected Parkinson's disease symptoms, which means they no longer clinically established or clinically probable PD, then they should discontinue trial treatment but can remain in trial follow-up. The change in diagnosis should be recorded in the trial database.

Should a participant undergo Deep Brain Stimulation (DBS) surgery or start infusion therapy during their participation, they can continue trial treatment and remain in trial follow-up..

Early cessation of trial follow-up should be recorded in the participant notes and reported on the relevant eCRF via eDC in the EJS ACT-PD trial database, along with any accompanying information as appropriate. Although the participant is not required to give a reason for discontinuing trial follow-up, a reasonable effort should be made to establish this reason while fully respecting the participant's rights.

Previously collected data on participants who stop follow-up early will be kept and included in analysis, in line with the GDPR exemption which states that the 'right to erasure' of data does not apply where data processing is necessary for the performance of a task in the public interest in the area of public health, with the appropriate safeguards in place.

Participants who stop trial follow-up early will not be replaced.

Participants who have withdrawn from the trial may change their minds and re-consent to participate in trial follow-up. However, participants who have withdrawn from trial treatment but remain in follow-up cannot re-consent to trial treatment, unless following a temporary pause which still allows for re-titration (see **table 5A** and **table 5B**). If participants do withdraw their consent for trial follow up as well as treatment, the trial will still access their routine healthcare data for trial analysis purposes unless this consent is also withdrawn.

Following withdrawal, participants' care may return to their normal clinical care provider (such as their Parkinson's specialist or GP). Trial data collected during the participant's participation in the trial will be kept for research and analysis purposes.

6.9.1 Pregnancy

Should a participant become pregnant during their participation, they should discontinue trial treatment but continue with trial follow-up. Should a participant's partner become pregnant during trial participation, the pregnant individual should be asked to consent to the pregnancy consent form for pregnancy follow-up. See **Section 6.6.4** and **Section 7.2** for further details.

6.9.2 Lost to Follow-up (Lost contact for now)

Every effort should be made to follow up participants who have been randomised. Participants should, if possible, remain under the care of a Parkinson's specialist physician for the duration of the trial. If the care of a participant is returned to the GP, it is still the responsibility of the investigator to ensure that the follow-up data required by the protocol are collected and reported for those participants who have consented for follow-up.

Participants who have not formally withdrawn from the trial, but are unable to be contacted or located, despite the best efforts of the research team (e.g., several contact attempts using all available contact details), can be considered 'lost contact for now' after 1 year has passed since the last contact with the trial team.

6.10 Participant Transfers

If a participant moves from the area, every effort should be made for the participant to be seen at another participating trial site. All database entry should be update prior to the participant transfer, including resolution of any queries and signing of visits by the PI. Copies of the participant consent form(s) and any other relevant documentation related to the participation in the trial should be provided to the new site and the participant will need to sign a new consent form. Once this has been done, the new site will take over responsibility for the participant; until this has been done, responsibility for the participant lies with the original site.

6.11 COMPLETION OF PROTOCOL FOLLOW UP

A participant will continue follow-up (regardless of treatment) for 3 years or until their treatment arm is ceased following stage 1 or stage 2 analysis completion, whichever occurs first.

Participants who are on an arm that terminates at stage 1 or stage 2 analysis and therefore does not continue to efficacy analyses from stage 3 onwards, are able to be re-screened and considered for re-randomisation to an arm that has continued to stage 2 onwards or is a new treatment arm which is still recruiting for stage 1 analysis. This can only be after a 6 week wash out period after final dose of the trial treatment for arms deemed ineffective. At this point, they will be considered a new screening participant and repeat the process described in **section 3.5**.

Further linkage for long-term analysis for these participants may occur through the trial's routinely collected data (not requiring further follow-up) should they have agreed to this in the consent form.

7 SAFETY REPORTING

The principles of GCP require that both investigators and Sponsors follow specific procedures when notifying and reporting adverse events or reactions in clinical trials. These procedures are described in this section of the protocol. **Section 7.1** lists definitions, **Section 7.3** gives details of the investigator responsibilities and **Section 7.4** provides information on CTU responsibilities.

7.1 DEFINITIONS

The definitions of the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), as amended, based on the principles of GCP apply to this trial protocol. These definitions are given in **Table 8**.

Table 8: Definitions

TERM	DEFINITION
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial participant to whom a medicinal product has been administered including occurrences that are not necessarily caused by or related to that product.
Adverse Reaction (AR)	Any untoward and unintended response to an investigational medicinal product related to any dose administered.
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature or severity of which is not consistent with the information about the medicinal product in question set out in the Summary of Product Characteristics (SPC) or Investigator Brochure (IB) for that product.
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR)	Respectively any adverse event, adverse reaction or unexpected adverse reaction that: ▪ Results in death ▪ Is life-threatening* ▪ Requires hospitalisation or prolongation of existing hospitalisation** ▪ Results in persistent or significant disability or incapacity ▪ Consists of a congenital anomaly or birth defect ▪ Is another important medical condition***

*The term life-threatening in the definition of a serious event refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it were more severe, for example, a silent myocardial infarction.

**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation.

*** Medical judgement should be exercised in deciding whether an AE or AR is serious in other situations. The following should also be considered serious: important AEs or ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the

other outcomes listed in the definition above; for example, a secondary malignancy, an allergic bronchospasm requiring intensive emergency treatment, seizures or blood dyscrasias that do not result in hospitalisation or development of drug dependency.

7.1.1 MEDICINAL PRODUCTS

An investigational medicinal product (IMP) is defined as a medicinal product which is being tested or used as a reference, including a placebo, in a clinical trial (Clinical Trial Regulation (536/2014).

Adverse reactions include any untoward or unintended response to drugs. Reactions to an IMP or comparator should be reported appropriately.

The IMPs for this trial at the time of this version of the protocol:

- Placebo
- Telmisartan (20mg and 40mg formulations)
- Terazosin (1mg, 2mg and 5mg formulations)

7.1.2 ADVERSE EVENTS

Adverse Events include:

- An exacerbation of a pre-existing illness
- An increase in frequency or intensity of a pre-existing episodic event or condition
- A condition (even though it may have been present prior to the start of the trial) detected after trial drug administration
- Continuous persistent disease or a symptom present at baseline that worsens following administration of the study treatment

Adverse Events do not include:

- Medical or surgical procedures; the condition that leads to the procedure is the adverse event
- Pre-existing disease or a condition present before treatment that does not worsen
- Hospitalisations where no untoward or unintended response has occurred, e.g., elective cosmetic surgery

The severity of AEs and/or ARs (serious and non-serious) in this trial should be graded using the National Institutes of Health Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL)*.

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.

Grade 4 Life-threatening consequences; urgent intervention indicated.

Grade 5 Death related to AE.

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

7.2 Pregnancy (Notable Event)

Pregnancy is not an adverse event. However, if a pregnancy occurs in a trial participant or a partner of a trial participant, it is a notable event. Female trial participants must stop trial treatment (please refer to **section 5.10** and **6.8.1**).

Therefore, if a pregnancy occurs in a trial participant the EJS ACT-PD Trial team at MRC CTU at UCL must be notified within 24 hours of the site becoming aware of the event using the relevant eCRF in the trial database. If pregnancy occurs in a participant or the partner of a trial participant, consent should be obtained to collect any follow-up information on the pregnancy. All pregnancies, either in a participant or in the partner of a male participant, will be followed up to collect information until 30 days following the outcome of the pregnancy, end of treatment period or end of trial regardless of the outcome. The outcome of pregnancy will be reported using the relevant eCRF in the trial database.

In the event of an abnormal pregnancy outcome, this should be considered an SAE and the relevant processes followed as outlined in **section 7.3**.

7.3 Investigator Responsibilities

Participants should report any side-effects or symptoms that are concerning them. The site study team should provide advice on how they should be managed and any other action needed.

All AEs should be recorded in the participant's medical notes, however only the events detailed below should be reported through the trial database on an AE eCRF.

Grade 3 and 4 Adverse Events (AEs) are reportable from the time of randomisation until 8 weeks after discontinuation of trial treatment or end of study period (if participants discontinue trial treatment but remain in follow-up).

All grade AEs that lead to a modification in trial treatment (i.e. pause, re-titration or discontinuation) are reportable from the time of randomisation until 8 weeks after discontinuation of trial treatment or end of study period (if participants discontinue trial treatment but remain in follow-up).

Adverse Events of Special Interest: All grade AEs related to blood pressure changes that lead to a change in blood pressure management (including con-medication changes and non-pharmacological interventions (other than hydration and dietary advice)) are reportable from the time of randomisation until 8 weeks after discontinuation of trial treatment or end of study period (if participants discontinue trial treatment but remain in follow-up).

All grade Serious Adverse Events (SAEs) are reportable from the time of randomisation until 8 weeks after discontinuation of trial treatment or end of study period (if participants discontinue trial treatment but remain in follow-up) via the trial database. **SARs continue to be reportable until the treatment arm is closed.**

All **Notable Events** are reportable from the time of randomisation until their final follow-up visit (165 weeks or early termination visit).

7.3.1 INVESTIGATOR ASSESSMENT

Adverse events will be recorded and graded according to the CTCAE v5.0 as stated in **section 7.1.2**, using a recognised medical term or diagnosis that accurately reflects the event. Adverse events will be assessed by the local investigator for severity, relationship to the investigational product, possible aetiologies, and whether the event meets criteria of an SAE and therefore requires expedited notification to the CTU.

7.3.2 SERIOUSNESS

When an AE or AR occurs, the investigator responsible for the care of the participant must first assess whether or not the event is serious using the definition given in **Table 8**. If the event is serious (regardless of grade), then the AE eCRF (including the SAE section) must be completed in the trial database within 24 hours. The database will alert the MRC CTU to inform them that an SAE has been recorded. If the event is not an SAE but meets the notable event criteria (see **section 7.2**), the site team must complete and submit the relevant eCRF in the trial database within 24 hours via the same mechanism.

7.3.3 Causality

The investigator must assess the causality of all SAEs in relation to the trial therapy using the definitions in **Table 9**. There are five categories: unrelated, unlikely, possible, probable, and definitely related. If the causality assessment of a serious event is unrelated or unlikely to be related, the event is classified as an SAE. If the causality of a serious event is assessed as possible, probable or definitely related, then the event is classified as an SAR.

Table 9: Assigning Type of SAE Through Causality

RELATIONSHIP	DESCRIPTION	SAE TYPE
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	SAR
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	SAR
Possible	There is some evidence to suggest a causal relationship (for example, because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (for example, the participant's clinical condition, other concomitant treatments).	SAR

Unlikely	There is little evidence to suggest that there is a causal relationship (for example, the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (for example, the participant's clinical condition, other concomitant treatment).	Unrelated SAE
Unrelated	There is no evidence of any causal relationship	Unrelated SAE

If an SAE is considered to be related to trial treatment and drug is stopped, refer to **section 5.7.**

7.3.4 NOTIFICATION

The CTU should be notified of all SAEs within 24 hours of the investigator becoming aware of the event. Upon completing the SAE section of the AE eCRF, the trial database will alert the TMT.

Following trial arm closure or stopping of follow-up at 3 years, any subsequent events that may be attributed to treatment should be reported to the MHRA using the yellow card system.

7.3.4.1 NOTIFICATION PROCEDURE

1) The AE eCRF must be entered into the trial database by an investigator (named on the Signature List and Delegation of Responsibilities Log, who is responsible for the participant's care; this will be either the Principal Investigator or another medically qualified person with delegated authority for SAE reporting). Due care should be paid to the grading and causality of the event, as outlined above.

    a. In the absence of the responsible investigator, the form should be entered by a member of the site trial team. The responsible investigator should subsequently check the AE eCRF, make changes within the trial database, as appropriate, as soon as possible.

2) The minimum criteria required for reporting an SAE are the participant trial ID, name of investigator reporting, the event term, and why it is considered serious.

3) The SAE section of the AE eCRF must be submitted via eDC using the trial database. The database will alert the TMT that an SAE has been submitted.

4) Follow-up: participants must be followed up until clinical recovery is complete and laboratory results have returned to normal or baseline, or until the event has stabilised. Follow-up should continue after completion of protocol treatment if necessary. Any updates to the initial report should entered on the EJS ACT-PD Trial database as information becomes available.

    a. Extra, annotated information and/or copies of test results may be requested by the EJS ACT-PD team and/or provided separately securely via email (e.g. via Galaxkey). The participant must be identified by participant ID only. The participant's name should not be used on any correspondence and should be deleted from any test results.

5) Staff should follow their institution's procedure for local notification requirements.

7.4 CTU Responsibilities

Medically qualified staff at the CTU and/or the Chief Investigator (or a medically qualified delegate) will review all SAE reports received. The causality assessment given by the local investigator at the hospital cannot be overruled; in the case of disagreement, both opinions will be provided in any subsequent reports.

The CTU is undertaking the duties of trial Sponsor and is responsible for the reporting of SUSARs and other SARs to the regulatory authorities (MHRA), as appropriate. Fatal and life-threatening SUSARs must be reported to the competent authorities within 7 days of the CTU becoming aware of the event; other SUSARs must be reported within 15 days.

The CTU will also keep all investigators informed of any safety issues that arise during the course of the trial.

The CTU, as delegate of the Sponsor, will submit Annual Safety Reports in the form of a Developmental Safety Update Report (DSUR) to Competent Authorities (Regulatory Authority and Ethics Committee).

Any drug companies involved (Sharp Clinical Services (UK) Ltd) will also be notified of all reportable (serious and unexpected and drug-related/unknown relationship) events. CTU will also provide companies with a copy of the Annual Safety Report in the required format.

7.4.1 Expectedness

If there is at least a possible involvement of an IMP, the investigator may make an initial assessment of the expectedness of the event, however the Sponsor has the overall responsibility for determination of expectedness. An unexpected adverse reaction is one not previously reported in the current approved versions of the reference safety information (RSI) detailed in **Table 10**, or one that is more frequent or more severe than previously reported. The definition of an unexpected adverse reaction (UAR) is given in **Table 8**.

Table 10: RSI Location for IMP

IMP Name	RSI Document	Section/Table
Telmisartan 20mg	Telmisartan 20mg SmPC Teva Pharmaceuticals Europe B.V	Section 4.8
Telmisartan 40mg	Telmisartan 40 mg SmPC Teva Pharmaceuticals Europe B.V	Section 4.8
Terazosin 1mg	Terazosin (Hytrin) 1mg ADVANZ Pharma SmPC	Section 4.8
Terazosin 2mg	Terazosin (Hytrin) 2mg ADVANZ Pharma SmPC	Section 4.8
Terazosin 5mg	Terazosin 5mg Teva UK Limited SmPC	Section 4.8

8 Quality Assurance & Control

8.1 Risk Assessment

The Quality Assurance (QA) and Quality Control (QC) considerations have been based on a formal Risk Assessment, which acknowledges the risks associated with the conduct of the trial and how to address them with QA and QC processes. QA includes all the planned and systematic actions established to ensure the trial is performed and data generated, documented and/or recorded and reported in compliance with the principles of GCP and applicable regulatory requirements. QC includes the operational techniques and activities done within the QA system to verify that the requirements for quality of the trial-related activities are fulfilled. This Risk Assessment has been reviewed by the CTU's Research Governance Committee (RGC) and has led to the development of a Data Management Plan (DMP), Safety Management Plan, IMP Management Plan, Patient and Public Involvement (PPI) Plan and Monitoring Plan which will be separately reviewed by the Quality Management Advisory Group (QMAG).

8.2 Central Monitoring at CTU

CTU staff will review the electronic Case Report Forms (eCRF) data and the trial database for errors and missing data points and will raise queries and initiate monitoring visits as appropriate.

Other essential trial issues, events and outputs will be detailed in the Monitoring Plan that is based on the trial-specific Risk Assessment.

8.3 On-site or remote Monitoring

The frequency, type and intensity for routine monitoring and the requirements for triggered monitoring will be detailed in the Monitoring Plan.

On-site or remote monitoring may be used through the course of the trial. Site staff may be asked to send anonymised form sections to the CTU for remote verification or asked to complete forms to confirm compliance with protocol procedures.

The Monitoring Plan will also detail the procedures for review and sign-off.

8.3.1 Direct Access to Participant Records

Participating investigators should agree to allow trial-related monitoring, including audits, ethics committee review and regulatory inspections by providing direct access to source data and documents as required. Participants' consent for this must be obtained when signing the informed consent form to participate in the trial.

8.3.2 Confidentiality

The EJS ACT-PD Trial plans to follow the principles of the UK DPA regardless of the countries where the trial is being conducted.

8.4 Source Data

The investigator and institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial participants. Source data are contained in source documents and are defined by ICH GCP (E6) and amended, as all information in original records that are used for the reconstruction and evaluation of the clinical trial. Source documents are the first place where the source data are recorded. These can include hospital records, clinical and office charts, laboratory notes, X-rays, and pharmacy dispensing records.

Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail). Each data element should only have one source and is the place where data is first recorded.

For this trial, various documents may be considered source data and may include paper notes, laboratory results, worksheets and electronic health records. For this trial, the eCRFs will not be the source document for any data elements with the following exceptions:

- Patient reported outcome measures (PROMs), as detailed in the Participant reported measures section of Table 1 Trial Assessment Schedule, which have been entered directly onto the database by the participant.
    - *If the PROM is completed on a paper version and entered on the trial database by the site team, the completed paper version would be considered the source document.*
- Clinician reported outcome measures (CROMs), as detailed in the Clinician reported measures section of Table 1 Trial Assessment Schedule, which have been entered directly onto the database by the clinician or rater.
    - *If the CROM is completed on a paper version and entered on the trial database by the site team, the completed paper version would be considered the source document.*
- Partner completed measures which have been entered directly onto the database by the partner. These eCRFs include:
    - Parkinsonism Carers Quality of Life (PQoL Carers)
    - EQ-5D-5L
    - *If the partner outcome measure is completed on a paper version and entered on the trial database by the site team, the completed paper version would be considered the source document.*
- Clinical reviewer form for event reviews
- Adverse event MedDRA coding
- Values that are derived by the EJS ACT-PD eDC system such as AE number.

EJS ACT-PD source data worksheets will be provided. Worksheets can be utilised and their use is recommended to sites.

A source data agreement will be put in place as part of the green light process with each site. This agreement will define the source documents and the data therein, together with location of these source documents and any applicable plans for transmission of source data between the site and the Sponsor or delegated institution.

8.5 Protocol Deviations

A protocol deviation is defined as any change, divergence, or departure from study design or procedures. Sites will be trained on identifying, grading and recording protocol deviations during the site initiation visit or training. On identification of a protocol deviation at site, the site study team

should grade and record the deviation onto the site-specific protocol deviations log. The investigator is ultimately responsible for reviewing and signing off the log. For critical protocol deviations the TMT should be informed by email within 1 working day of the investigator becoming aware of the protocol deviation. For major deviations the TMT should be informed within 2 weeks of the investigator becoming aware.

The CI(s) should review the deviation to assess whether participant safety or study integrity has been affected by the deviation and to what extent the deviation has affected the project. If the deviation is found to impact on safety or research integrity, the CI(s) will inform the sponsor within 72 hours. Minor protocol deviations will be shared with the TMT periodically via a site-specific protocol deviation log which contains all site deviations. A list of protocol deviations will be discussed within the TMG meetings and any relevant oversight committees to identify any repeated problems and provide a solution to reduce similar deviations.

9 Statistical Considerations

This trial will be a multi-arm multi-stage (MAMS) platform trial that will adapt and develop with the aim of adding more arms as it progresses. As such, there are currently two distinct stages to the trial and a statistical analysis plan (SAP) will be produced for the lack of activity analyses (stage 1 and stage 2) and the efficacy analyses (stage 3 and stage 4) and agreed by the Independent Data Monitoring Committee (IDMC) and Trial Steering Committee (TSC).

The statistical analysis will be based on all participants as randomised, irrespective of subsequent adherence with the allocated treatment (a 'treatment policy' estimand strategy for handling non-adherence to the randomised arm). A treatment adherence analysis (hypothetical on-treatment estimand) restricted to data from participants up until the point they discontinued randomised treatment (as specified) will also be conducted at each analysis as outlined in the SAP. A CONSORT diagram will be used to describe the flow of participants through the trial. Baseline characteristics will be summarised by randomised group. Continuous variables will be summarised using summary statistics (mean, standard deviation, median, minimum, and maximum) by treatment group, and categorical variables will be presented using frequency distributions by treatment group.

9.1 Method of Randomisation

Randomisation will be performed by the PI or delegated member of the clinical team at local sites using the EJS ACT-PD database. Each participant will be randomised using their unique participant ID that was allocated sequentially at screening. Eligibility and consent will be verified before each participant is randomised. Trial arm allocation into the active treatment arms or placebo (1:1:1) will use stratification. The stratification criteria will include:

- Biological sex
- Age
- Trial centre tier
- Hoehn & Yahr stage

Randomisation with stratification will ensure comparability across the trial arms on these characteristics. The stratification criteria were selected as the rate of PD progression is known to be impacted by patients age and biological sex, as well as by disease stage (assessed by Hoehn & Yahr), and stratification by site tier allows for differences in standard of care that may impact disease course or trial delivery.

Full details of the randomisation procedure are given in **Section 4** above.

The Trial Statistician will generate unique randomisation codes which are linked to treatment allocation and assigned at randomisation. The list of randomisation codes will be provided to the EJS ACT-PD Trial database and the Qualified Person (QP) at the central pharmacy who will ensure that trial treatment is labelled and dispensed appropriately, and that the trial team and participants remain blind to treatment.

The drug will be dispensed and delivered to participants following randomisation, after tolerability is confirmed during week 3 of the titration phase and every 6 months thereafter. A delegated member of the site team who is qualified to write prescriptions will complete a new prescription form on the trial's eDC system, which will then notify the QP at the central pharmacy of the bottle number of the

trial treatment to be dispensed. Enough trial treatment will be provided to the central pharmacy to ensure availability of adequately labelled bottles for pharmacy dispensing.

Following the stage 1 and 2 analyses, participants from any treatment group discontinued at the analysis stage for reasons of lack of activity will be given the opportunity to be 're-randomised', after a suitable washout period, providing they still meet the eligibility criteria (see **Section 4.4** for re-randomisation procedures). The randomisation method described above will still apply to those being re-randomised.

9.2 Outcome Measures

The trial analyses will be split into two phases: assessment for trial treatment lack of activity (stages 1 & 2), and assessment for trial treatment efficacy (stages 3 & 4). The lack of activity analyses will determine if there is enough activity of the trial treatment compared to the SoC plus placebo, to continue recruitment to and follow-up of the treatment arm.

Arms with treatments not deemed to lack activity at both the stage 1 and stage 2 analyses will proceed with recruitment and follow-up until the target is reached and the primary analysis is undertaken. The efficacy analyses will determine whether the treatment demonstrates sufficient effectiveness compared to SoC plus placebo.

The power of analyses will increase with the number of participants and the length of time participants are in the trial. The exact timeframe is therefore subject to the rate of recruitment. The recruitment milestones required to be achieved for the analyses to take place are based on conservative estimates following detailed recruitment modelling incorporating non-linear recruitment and dropouts. The recruitment milestones and statistical criteria required for each analysis are detailed in **Table 11** below:

Table 11: Statistical analysis criteria for stage and primary analyses

Analysis	Outcome measure	Reduction in slope (delta)	Power target (actual)	One sided alpha	Critical value	Analysis trigger: recruitment milestone (per arm)	Estimated years after trial start
Stage 1 (activity)	MDS-UPDRS I-II-III (IVW)	30%	>90% (92.2%)	50%	0	133 completed 52 weeks	2.2
Stage 2 (activity)	MDS-UPDRS I-II-III (IVW)	30%	>90% (98.1%)	30%	6.0%	200 completed 78 weeks	3.3
Stage 3 (efficacy)	MDS-UPDRS I & II	30%	*no target* (80.3%)	0.5%	22.4%	266 completed 104 weeks	4.5
Stage 4 (efficacy)	MDS-UPDRS I & II	30%	>90% (96.2%)	2%	16.0%	266 (66% of 400) completed 156 weeks	5.7

9.2.1 Interim Outcome Measure: MDS-UPDRS Parts I, II & III

The stage 1 and stage 2 analyses will use the MDS-UPDRS Parts I, II and remote elements of part III combined using inverse variance weighting (a combination which gives more importance to the most

precise items within the measure), to assess for evidence of activity of the trial treatments. Statistical modelling indicated that this combination of parts were the most sensitive to change at an interim timepoint, as well as being deemed feasible for trial delivery and acceptable to people with Parkinson's. To support the remote delivery of study visits, a modified version of the MDS-UPDRS Part III will be administered, removing the requirements for rigidity (item 3.3) and postural stability (item 3.12). Remote assessment of the MDS-UPDRS Part III has been shown to meet standards of usability and allow for successful completion,[52] whilst demonstrating good correlation with prior in-person research assessments.[53] A guide to in-home, remote assessment of the MDS-UPDRS Part III has been developed and validated for patient and carer use across multiple languages and cultures.[52]

The MDS-UPDRS (parts I, II, remote III, and IV) will be completed at baseline (week 0), week 13, week 26 and every 26 weeks thereafter.

9.2.2 Primary Outcome Measure: MDS-UPDRS Parts I & II combined

The primary outcome measure is the rate of change in the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Parts I and II Combined comparing each active treatment arm against placebo. When 266 participants from each arm have reached 156 weeks post first dose of study medication, the trial will have >95% power to detect a 30% reduction in the rate of change of this measure. This measure provides a relevant, patient-reported, acceptable, valid and deliverable endpoint for a large, long-term trial, and is based on PPIE preferences, has promise for capturing change and reflects relevant features of PD progression including non-motor symptoms.[54,55] Proportionate treatment effect sizes (reduction of the mean slope) of between 20-50% were initially considered, but a value of 30% that was deemed clinically meaningful, plausible and also appeared to offer promising levels of power under realistic sample sizes, was eventually targeted.

Arms with treatments not deemed to lack activity at both the stage 1 and stage 2 analyses will proceed with recruitment and follow-up until the target is reached and the primary analysis is undertaken.

For the efficacy analyses, a linear mixed model will be used to compare the rate of change between active and placebo treatment arms using all available sum-scores of UPDRS I and II across the 7 potential timepoints after baseline (see schedule of activity). The treatment effect will be assessed with a model parameter interacting treatment group with time. The model will include participant-level random effects for slope and intercept, which will be allowed to co-vary. Other fixed effects in the model will include those for the stratification variables of biological sex, site tier, age, and screening Hoehn & Yahr score, as well as time since diagnosis and adjustment for scores at baseline.

An initial efficacy analysis (stage 3) will take place for each arm when 266 participants have completed 104 weeks post first dose of study medication using a very small alpha criterion (probability of false positive) (see **Table 9** above). This is predicted to take place approximately 4.5 years from the first recruited participant. If this analysis shows efficacy, then the approval process could be started to introduce the treatment into standard of care. This would reduce the overall trial length for that treatment. If the initial analysis does not show efficacy, then the arm will continue to a final primary analysis which will take place when approximately 266 participants have completed 156 weeks post first dose of study medication (see **Table 9**).

9.2.3 Secondary Outcome Measures

The clinician and patient-reported secondary outcome measures will be:

1. Hoehn & Yahr Scale (H&Y)
2. Montreal Cognitive Assessment (MoCA)
3. Levodopa-equivalent daily dose (LEDD)
4. Part III of the MDS-UPDRS in the ON medication state (remote elements only)
5. Part IV of the MDS-UPDRS in the ON medication state
6. Clinical Global Impression Scale (CGI) – Severity of illness (CGI-S) and Measure of clinical change (CGI-C).

The participant-reported secondary outcome measures will be:

1. Patient Health Questionnaire – 9-item (PHQ-9)
2. Parkinson's Disease Questionnaire (PDQ-8)
3. Carers quality-of-life questionnaire for parkinsonism (PQoL Carers)

The health-related quality of life and resource use outcome measures will be:

1. ICECAP-O capability measure for older people
2. EQ-5D-5L – administered separately to participants and partners
3. Resource use questionnaire (modified CSRI + modified iVICQ)

The safety and tolerability outcome measures will be:

1. Suicidal ideation as assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS)
2. Adverse events/ Serious Adverse Event rates.
3. Treatment compliance.
4. Trial withdrawal and treatment discontinuation rates.

9.3 Sample Size

The EJS ACT-PD Trial will recruit approximately 400 participants per year, randomised equally (e.g., 1:1:1) across the active arms they are eligible for and the placebo arm. A withdrawal rate has been assumed, based on a Weibull distribution,[56] which leaves 75% recruited participants remaining by year 3 (participants will contribute data to the analysis up until withdrawal). The targeted treatment effect (informed by the literature and chosen with patient and clinical input) is a 30% reduction in the rate of increase in MDS-UPDRS Parts I and II combined.

The power calculations indicate that 400 participants are required to be randomised to each arm to guarantee the operating characteristics (see **Table 11** in **section 9.2**). Each analysis stage is triggered by a recruitment and follow up milestone. The first two analysis stages are interim tests for activity based on the inverse variance weighting (IVW) of all MDS-UPDRS Parts I, II and remote III and employ large one-sided alpha. This means that arms are designed to continue if there is an emerging sign of treatment activity. The third stage is an early look for efficacy based on the primary outcome of parts I and II and uses a very strict one-sided alpha of just 0.5% in order to stop early for efficacy. The final stage has a one-sided alpha of 2% to (conservatively) maintain pair-wise error against SoC at 2.5%.

An early efficacy analysis will take place when 266 participants reach 104 weeks post first dose of study medication and the final efficacy analysis will be completed when 266 participants reach 156

weeks post first dose of study medication. This number of participants would achieve power of >0.95 to detect a 30% reduction in rate of progression of the outcome measure.

Note, the sample size is smaller than powering for a baseline adjusted treatment difference at 3 years, because the analysis uses data from all visits to estimate treatment effect. When it comes to analysing the trial, this has the advantage that all observed data on each patient contributes to the treatment effect, regardless of whether they have completed follow-up.

Extended details of the power calculation:

As is common in MAMS trials of this type, where the different treatments have different postulated mechanisms of action, we control the pairwise error rate, not the familywise error rate.[57] Having reviewed the longitudinal MDS-UPDRS data from the Critical Path for Parkinson's consortium (CPP: https://c-path.org/program/critical-path-for-parkinsons/) it is reasonable to assume a linear increase in over time in our clinical cohort MDS-UPDRS Part I-III and combinations thereof. This assumption leads to a power calculation that is robust even if the trend in MDS-UPDRS over time is not strictly linear, provided the treatment effect remains approximately proportional.[58]

To estimate power we use the approach of Frost et al[58] where we calculate the covariance matrix for the fixed parameters of the linear mixed model (X design matrix) for a hypothetical 2 person trial, one each in the control arm and treatment arm respectively. Power for a 2n-sized trial can be calculated in the standard way, scaling up the size of the trial to 2n by dividing the standard error of the slope#treatment interaction parameter by √(n). For combining the outcome of more than one Part of the MDS-UPDRS we can similarly calculate the covariance matrix for a multivariate mixed model, with random effects and error variances each allowed to covary across Parts I-III. Any linear combination of interaction terms from across the Parts (such as inverse-variance weighting) can be considered as the covariance matrix will include covariances of parameters across Parts, leading to an appropriate standard error for that combination (treatment effect) to be used in power calculations.

The impact of dropout and staggered recruitment, where an analysis at a fixed point in calendar time will mean later recruited participants will have a reduced number of visits and hence outcome measurements, can be dealt with by the same approach. The sample can be grouped into separate cohorts according to how far in the trial they have reached (by that point for staggered recruitment, definitively for dropout) and the treatment effect standard error is calculated as above for each cohort. Power or sample size for the trial as a whole then requires a weighted combination of the test statistic for each cohort with weights based on relative size of the cohort according to the pattern mixture method of Dawson and Lagakos.[60]

The input variance parameters come from extensive meta-analysis of the CPP dataset, specifically using the observational studies only to reflect the expected heterogeneous profile of the EJS ACT-PD participants. If i indexes participants, j indexes observation time t_j in years from baseline $\{t_1,\ldots,t_8\}=\{0, 0.25, 0.5, 1, 1.5, 2, 2.5, 3\}$, and k indexes Parts I, II and III of the MDS-UPDRS then Y_{ijk} indexes the MDS-UPDRS score of participant i at time t_j for Part k.

The algebraic form of the multivariate model:

$$Y_{ijk} = \beta_{0k} + \beta_{1k}t_{ijk} + \beta_{2k}t_{ijk}T + \zeta_{ik} + \zeta_{ik}t_{ijk} + \epsilon_{ijk}$$

where T represents a binary indicator of whether the participant was on the treatment arm. ζ and ϵ

are the random effect and error terms, respectively. To perform the power calculation for a linear combination of the Parts, we must supply a 6x6 random effect covariance matrix (each row/column representing in order: the random intercept and then slope of Part I, then the same for Part II and then the same for Part III) and a 3x3 error variance matrix (each row/column defining in order Part I, Part II and Part III), and are assumed independent from each other.
From the CPP analysis our random effect covariance matrix G is

$$\begin{pmatrix} 11.09 & 0.33 & 6.97 & 0.55 & 3.66 & 0.70 \\ 0.33 & 0.79 & 0.54 & 0.58 & 0.37 & 0.39 \\ 6.97 & 0.54 & 13.70 & 0.43 & 9.90 & 0.10 \\ 0.55 & 0.58 & 0.43 & 1.32 & 0.32 & 1.14 \\ 3.66 & 0.37 & 9.90 & 0.32 & 31.53 & -1.94 \\ 0.70 & 0.39 & 0.10 & 1.14 & -1.94 & 3.76 \end{pmatrix}$$

And our error covariance matrix *R*

$$\begin{pmatrix} 8.94 & 2.21 & 1.81 \\ 2.21 & 10.56 & 4.79 \\ 1.81 & 4.79 & 39.03 \end{pmatrix}$$

If Z represents a design matrix for the random effects across all three Parts, and X represents the design matrix for the fixed terms across all three Parts, then the model covariance matrix is

$$\Sigma = R + ZGZ'$$

and the covariance of the estimated fixed parameters is

$$Var(\hat{\beta}) = (X'\Sigma^{-1}X)^{-1}$$

From the resulting 9x9 matrix, the 3rd, 6th and 9th term on the diagonal are the variances of the three treatment effects (slope#treatment interaction) which can be used along with the appropriate off-diagonal covariances to calculate the variance of linear combinations of Parts I-III

$$Var(aX + bY + cZ) = a^2Var(X) + b^2Var(Y) + c^2Var(Z) + 2abCov(X,Y) + 2acCov(X,Z) + 2bcCov(Y,Z)$$

where a, band c are chosen weights such as 1/var for IVW for the activity stages 1 and 2, or simply 1 for the efficacy stages 3 and 4.

Power to detect the treatment effect at significance level α is given by

$$1 - \Phi[\mu - \Phi^{-1}(1 - \alpha/2)]$$

where μ is the standardised treatment effect under the alternative hypothesis.

Note, that the actual slope of the control group β_{1k} is not directly relevant to our calculations. Although we define the treatment effect in terms of a 30% relative reduction in slope gradient, the relevant treatment effect parameter β_{2k} actually enters the power calculation stage as an absolute per-time unit difference and so the study is actually powered for these differences even if the mean control slope is modelled as, for examples zero (flat). These absolute per-time unit differences are 1.12, 1.38 and 1.61 for Parts I-III, respectively.

9.4 ESTIMANDS

Table 12: Description of Estimands

Component	Description	Notes
Patient population	Adults aged over 30 with a clinical diagnosis of PD, satisfying the inclusion criteria	Detailed inclusion criteria specified elsewhere.
Interventions	One capsule per day, containing either placebo, terazosin or telmisartan	Dose detailed elsewhere
Primary Endpoint	MDS-UPDRS total score across parts I and II, unweighted	At 156 week timepoint
Population level summary	Change in linear rate of increase MDS-UPDRS Parts I and II, over the course of follow-up	Estimated using the treatment X time interaction parameter in a linear mixed model.
Intercurrent events & strategy	Loss to follow-up. Primary: treatment policy strategy. Supplementary estimand: hypothetical on-treatment strategy.	We will attempt to complete the intended follow-up, even if participants withdraw from treatment. For the primary analysis, missing data will be imputed consistent with treatment status, to allow the mixed model analysis to target the treatment policy estimand. For the supplementary estimand, we will use a mixed model for all the available on-treatment data. We anticipate only a small number of deaths, and a very small number of these directly related to Parkinson's. Therefore these will be handled using a hypothetical (i.e. alive and in study) strategy.

We are aiming to identify the difference in the rate of change of MDS-UPDRS Part I & II combined, between a population representative sample of participants with Parkinson's disease on dopaminergic

replacement therapy followed up over 156 weeks, according to randomisation allocation, and adjusted for biological sex, site tier, age, and screening Hoehn & Yahr score, as well as time since diagnosis and adjustment for scores at baseline.

9.5 Interim Checking & Analyses

9.5.1 IDMC meetings

Six-monthly following opening of recruitment, with timings of meetings later in the follow-up adapted to coincide with the milestones for analysis set out in **Table 11**.

Guidance to the IDMC will make clear that interim analyses and stopping rules are intended to guide, not automate, formulation of advice to the TSC.

9.5.2 Stopping rules

The stopping rules are set out in **Table 11**.

The stopping rules will be addressed by fitting the primary analysis model to all the observed data (on or off treatment), without any imputation of missing on or off treatment values.

9.5.3 Participants to be included in the analysis

Interim stage analyses and primary analyses will include all participants in their randomised groups plus any pre-planned subgroup analyses.

This guidance will be modified if additional intervention arms are opened.

9.5.4 Additional analyses, not specified in Table 11

None.

9.6 Analysis Plan (Brief)

Analyses of all outcomes will be detailed in the Statistical Analysis Plan. Here we focus on the analysis methods for the primary outcome, and summarise the approaches for secondary outcomes.

The SAP will detail the statistical methods in all analyses used for description of demographic and baseline characteristics, assessing treatment compliance, evaluation of effectiveness of the treatments on primary and secondary outcomes, and evaluation of safety. This section summarises the main issues.

9.6.1 Stage 1 & stage 2 analyses

Analysis Stage 1 and 2 will use all available on-treatment data. This will bias the arms towards continuing, if anything.

Each pair of (telmisartan, placebo) and (terazosin, placebo) arms will be analysed separately at each stage.

Data-lock and subsequent analysis will be triggered by the recruitment and follow-up milestones set out in **Table 11**.

For both stage 1 and 2, the analysis will fit a tri-variate 'random-intercepts-and--slopes (with covariance)' model jointly to the three components of MDS-UPDRS, with random intercept, slope and residual error terms correlated across components. (This is consistent with that used for the power calculations, described above.) In the fixed part, each component will adjust separately for all randomisation strata and the corresponding baseline. For each component, the model will include a treatment effect and treatment-time effect.

The treatment-time estimates for each component will be combined in an inverse-variance weighted average, with corresponding standard error estimate (as detailed in the power calculations above), and these will be used to determine if the criteria for continuing (**Table 11**) are met.

Based on our analysis of previous trial data, it is anticipated that MDS-UPDRS will follow a normal distribution and that the assumptions for the linear mixed model will be met. However, assumptions will be assessed using plots of model residuals and if they are materially violated, non-parametric methods will be used for inference (e.g. bootstrap confidence intervals). In this context note type-1 error is protected even if residuals are non-normal because of the randomisation justification for inference from F-tests.

No sensitivity analyses are planned to inform decision making for the interim analyses.

Safety outcomes (AE, AR, SAE, SAR, SUSAR etc.) as described in **section 9.2** for each arm will be tabulated by randomised group at the Analysis Stage 1 and 2 as part of the decision made by the IDMC of whether a treatment will progress to Analysis Stage 3. However, as EJS ACT-PD is using repurposed established drugs, additional formal stopping rules based, for example, on SUSAR rates or toxicities are not proposed.

9.6.2 STAGE 3 & STAGE 4 ANALYSES

The same primary analysis model will be used at Stage 3 and Stage 4; however, to control the type 1 error the criteria for stopping for efficacy at Stage 3 is higher (see **Table 11**).

The primary outcome data is the total of MDS-UPDRS Parts I and II for each patient at each follow-up time.

All available data from all patients (regardless of treatment / compliance status) will be analysed by randomised group, consistent with the treatment policy estimand.

Analysis of each treatment arm and concurrent placebo will be done separately (not necessary to do this, but it is more transparent)

Consistent with the treatment policy estimand:

(i) Every effort will be made to collect outcome data regardless of treatment status (e.g. treatment withdrawal, suspension)

(i) Missing outcome data due to withdrawal and/or loss to follow-up in the placebo group will be assumed missing at random; no imputation is needed for this group under the mixed model analysis.

(iii) Data from the active groups collected after withdrawal from treatment will be included in the primary analysis

(iv) Where participants in the active groups discontinue treatment and subsequent follow-up data are missing, this will be imputed under the 'Copy Increments in Placebo' assumption.[61,62] Under this assumption, following a patient's treatment cessation, each patient's mean MDS-UPDRS score will increase from its current value in parallel to the placebo arm. This assumption encapsulates (a) maintaining treatment benefit accrued to the point of treatment cessation, and (b) no further benefit after treatment cessation. Note that this assumption, when implemented by multiple imputation, is information anchored - no information about the treatment effect is gained, or lost, relative to an analysis under the missing at random assumption.

Multiple imputation will use 100 imputations. The treatment effect will be estimated by fitting a linear mixed model - with treatment arm specific random intercepts and slopes (with covariance term) and residual error - to the primary outcome. The fixed part will adjust for all randomisation strata and the corresponding baseline. The model will include a baseline treatment effect and treatment-time effect. The treatment-time coefficient is the treatment effect of interest.

Based on our analysis of previous trial data, it is anticipated that MDS-UPDRS will follow a normal distribution and that the assumptions for the linear mixed model will be met. However, assumptions will be assessed using plots of model residuals. Note type-1 error is protected even if residuals are non-normal because of the randomisation justification for inference from F-tests.

Supplementary analysis:

The treatment policy estimand will be supplemented by the hypothetical on-treatment estimand, which will be estimated by fitting the same model under the missing at random assumption for all treatment arms.

Sensitivity analysis:
Sensitivity analysis for the treatment policy estimand will use delta-method MI in the active arms, where only 50% of the treatment benefit (in terms of reduction in rate of increase in UPDRS score) is maintained after treatment discontinuation.

Secondary analysis:

Section 9.2.3 lists the secondary outcomes.

Analysis of all secondary outcomes use all available data in each randomised group (including after treatment withdrawal) - consistent with the treatment policy estimand.

Longitudinally measured continuous outcomes will be analysed using a linear mixed model, with unstructured covariance matrix separate for each treatment group, full baseline X visit and treatment X visit interaction, adjusting for baseline and randomisation strata.

Longitudinally measured discrete and ordinal outcomes will be analysed using a generalised linear mixed model with common, covarying, random intercepts and slopes, full baseline X visit and treatment X visit interactions, adjusting for baseline and randomisation strata.

Secondary outcomes not measured longitudinally will be analysed using a (generalised) linear model of final outcome on baseline, treatment and randomisation strata.

Sensitivity analysis: not planned for secondary analyses.

9.6.3 HEALTH ECONOMIC ANALYSIS PLAN

9.6.3.1 OVERVIEW OF THE ECONOMIC EVALUATION

An economic evaluation will be conducted to calculate the mean incremental cost per quality-adjusted life-year (QALY) gained of offering a new intervention vs. placebo to PwP in the study, from the perspective of the NHS and personal social services, over the horizon of the follow-up time period. Analyses will be done pairwise, comparing each new intervention arm against data from participants recruited contemporaneously into the placebo arm.

9.6.3.2 UTILITY AND QUALITY OF LIFE DATA

QALYs will be calculated from utility scores using standard tariffs, from EQ-5D-5L responses collected from participants with Parkinson's at baseline (week 0), and 13, 26, 52, 78, 104, 130, and 156 weeks (or until follow-up ends), and at early termination visit if that takes place. Participants in the partner sub-study will provide EQ-5D-5L responses at the same timepoints, minus a week 13 visit. Total QALYs per participant will be regressed controlling for baseline utility and stratification variables.

9.6.3.3 RESOURCE USE DATA

Costs will be calculated by applying standard unit costs (NHS Reference costs for hospital attendances, Personal Social Services Research Unit, PSSRU, costs for primary and community care, and British National Formulary, BNF, for medication costs) to resource use items captured from participants via the resource use questionnaire at baseline (week 0), and 26, 52, 78, 104, 130 and 156weeks (or until follow-up ends), and from information captured in the intervention and concomitant medication CRFs. Costs will be summed to generate total cost per participant, and regressed controlling for baseline values and stratification variables, and descriptive statistics will report costs as overall costs and according to suitable categories. Placebo medication will be costed as zero.

9.6.3.4 WITHIN TRIAL ANALYSIS

Mean (standard deviation) costs and QALYs will be calculated by arm according to randomised group, adjusting for baseline values and stratification variables, using bootstrapped seemingly unrelated regression to account for the joint nature of costs and QALYs and for their typically skewed distributions. The summary result of the incremental cost-effectiveness ratio (ICER) as the median bootstrapped result with 95%CI will be reported alongside the mean (95%CI) incremental costs and incremental QALYs for each pairwise comparison.

Bootstrapped results will be plotted on a cost-effectiveness plane (CEP), and transformed into the cost-effectiveness acceptability curve (CEAC) using a range of suitable cost-effectiveness thresholds, including the standard NICE threshold of £20,000-30,000/QALY gained, to show the likelihood of a new treatment pathway being acceptably cost-effective compared to the control arm.

Predictors of missingness will be explored, and approaches to impute missing data will be considered, including multiple imputation using chained equations if appropriate.

9.6.3.5 MODEL BASED ANALYSIS

The incremental cost per QALY gained will also be estimated for the lifetime of the participant using a cohort model-based approach, if appropriate. If a decision analytic model is created, probabilistic sensitivity analysis will be performed, and the results similarly plotted on a CEP and CEAC.

9.6.3.6 SECONDARY ANALYSIS

Both within-trial and lifetime analyses will include a secondary wider cost perspective that will include out-of-pocket costs, private care costs, use of care home and respite care services, and paid/unpaid or informal care.

Further secondary analyses will also include QALYs calculated via mapping from PDQ-8 responses, and using CALYs calculated from responses to the ICECAP-O, and including carer QALYs calculated from care partner EQ-5D-5L responses.

Multi-arm analyses will also be performed where appropriate, potentially using network meta-analysis, reporting net monetary benefit at a range of cost-effectiveness thresholds.

10 ANCILLARY STUDIES

10.1 RESEARCH BLOOD SAMPLES

A repository of biological samples from participants will be created using research blood samples from all consented participants. The purpose of the research blood samples is so that biomarker and mechanistic discovery-driven studies can be conducted. These studies may take place during the trial or as part of future projects, both as part of the EJS ACT-PD study and by other researchers/ organisations (which may be international). The studies may include discovery endpoints, such as: to determine early surrogates of efficacy; to identify predictors of or associations with progression; to provide evidence of study drug activity; or to increase knowledge and understanding of disease biology and drug safety.

The research blood samples to be collected will include 26ml (2x 10ml, 1x6ml) of blood at screening and 156 weeks. Research blood samples will be processed locally at sites and stored in a -80 freezer. These processed samples will be sent periodically in batches to the Francis Crick Institute (FCI) in London. Analyses using the samples, or data derived from the samples, may be performed by the FCI, or by external laboratories depending on requirements. Full details on research blood sample collection and handling can be found in the Sample Collection and Handling Manual.

All participants providing research blood samples will consent to storage and analyses to be conducted on their samples. Any requests to share or access samples during the trial will be approved following decisions / applications made to the EJS ACT-PD Trial Management Group. Following trial completion, any remaining samples will continue to be stored for use in future projects at the FCI and will be overseen by FCI management procedures. All requests to share or access samples following trial completion will be approved following decisions / applications made to an EJS CT-PD sample access committee.

Participants who originally consent to providing research blood samples collected for the biorepository can withdraw their consent for future sample collection, sample sharing, and use at any time, without penalty or loss of benefits to which they are otherwise entitled. If a participant does decide to withdraw this consent, the EJS ACT-PD team should be informed of this, and a discussion should be held between the site and the trial team. The withdrawal of consent will only apply to future collection, sharing, and use, not retrospectively, due to the difficulty in tracking down and removing samples and relevant data.

Further details on collection, transport and storage will be provided in the Sample Collection and Handling Manual.

10.1.1 BIOREPOSITORY GOVERNANCE

The EJS ACT-PD biorepository will be governed by the trial TMG until the end of trial, as defined in **section 11.5.3**. After the end of the trial, the governance and ownership of the biorepository will be as outlined in a collaboration agreement between the relevant trial parties and the FCI. The biorepository will be open to the general research community after trial completion or sooner if agreed by the TMG. Proposals for use during the trial will be reviewed by the TMG and prioritised given the finite nature of the specimens. Following trial completion, proposals will be reviewed by an EJS ACT-PD sample access committee. At the conclusion of the review process, three outcomes for specimen use requests are possible:

1. Approval. However, even after a specimen use committee approval, the release of biospecimens may be withheld for pragmatic considerations including requiring a fully executed data sharing agreement and evidence of appropriate ethical and regulatory approvals.
2. Re-evaluation. This intermediate category is for well-written applications but for which a) there is unclear significance with respect to the priorities set forth, or b) there are other potentially addressable issues raised by the committee. Applicants will be provided the opportunity to respond to concerns raised by the committee. The application may be re-submitted or, at the recommendation of a committee member, re-addressed by the committee at future review the committee will make a final decision after one or, at most two, re-submissions.
3. Disapproval. The proposal for use is rejected (feedback will be provided).
4. Unless exempted by the TMG, funding must be provided by the requesting investigator for preparation and shipping of samples and, if relevant, for extraction of corresponding clinical data.

Failure to provide funding within an agreed-upon time frame may result in revocation of the approval.

Sharing of the results obtained from the measures conducted under approved biospecimen use requests will be required within an agreed-upon time frame. Failure to conduct the proposed studies within an agreed-upon time frame will lead to the requirement to return the samples and revocation of the approval.

10.2 PARTNER SUB-STUDY

Partners or spouses of participants will also be invited to participate in the trial, where the participant with Parkinson's has provided consent for their partner's involvement. The Partner PIS will be made available to the participant via the RoI and should be discussed with the participant during the pre-screening telephone call. Partners should be invited to join the participant at their initial screening visit should they be interested in participating in the trial, following appropriate consent (i.e. verbally during the pre-screening telephone call) that they may be approached being obtained from the participant.

10.2.1 OBJECTIVES

The purpose of the Partner sub-study is to evaluate the impact that providing care for a person with Parkinson's has on the partner's or spouse's quality of life and if this changes during the course of the trial. The difference in impact of Parkinson's disease and health-related quality of life between active treatment and placebo arms will be measured by:

- Carer's quality-of-life questionnaire for parkinsonism (PQoL Carers).
- Carer health-related quality of life as assessed by the EuroQol five-dimension scale questionnaire (EQ-5D-5L).

10.2.2 PARTNER INCLUSION CRITERIA

1. Be a spouse or partner of a participant with Parkinson's who is taking part in the EJS ACT-PD trial.
2. Participant with Parkinson's has consented to their partner's participant in the Partner Sub-Study.
3. Be 18 years or older at the time of providing consent.
4. Documented informed consent.

10.2.3 Recruitment of Partners

Partners will be provided with the 'partner information sheet' and asked to sign the 'partner informed consent form'. Partners should discuss their participation with the participant with Parkinson's and the site study team. They can consent at the screening appointment, if they attend with the person with Parkinson's, or they can complete the consent form at home and return it to the site. Partners will receive a participant ID number separate to that of the participant with Parkinson's disease, but which will allow linkage between the participant with Parkinson's disease and partner. All partner measures will be self-completed and can be completed remotely without any required administration from the study team.

Once consented, a partner identification number (partner ID) will be assigned to be used in the trial's eDC system.

10.2.4 Assessments and Follow-up of Partners

Partners will complete questionnaires at baseline and then every 26 weeks until week 156. These can be completed remotely. See **Table 1: Trial Assessment Schedule**.

10.2.4.1 Data Collection and Assessments

Partners completing assessments via eDC in the trial database, will receive personalised links when assessment completion is required. The link will enable them access only to the assessments they are required to complete and will be linked within the system to their record (via their partner ID). The trial teams at sites will have access to view the assessment records of the partners at their sites, so that they can send reminders or query data as needed. Additionally, if the partner needs assistance when completing the partner-reported assessments, they can contact the site trial team at their local site for help with this and paper versions can be made available. The local site can report any database issues or request help from the TMT.

The trial team at MRC CTU will have access to pseudonymised (via their partner ID) participant and partner assessment records for all trial participants and partners to maintain oversight of trial delivery and data collection.

If trial staff at participating sites or partners complete any data collection manually (e.g., on physical paper copies), it is the site's responsibility to transfer the data into the trial database using the relevant eCRF.

CARER'S QUALITY-OF-LIFE QUESTIONNAIRE FOR PARKINSONISM (PQOL CARERS)

The 26-item Parkinsonism Carers Quality of Life (PQoL Carers) is a self-completed questionnaire enquiring about various aspects of the wellbeing of people caring for people with parkinsonism (e.g., social activities, relationship to the patient, stress, mood), from which a summary index is calculated.[45] The PQoL Carers has been validated in carers of people with parkinsonism, and has high internal consistency as well as good convergent, concurrent, and discriminant validity, the latter being especially helpful in a disease-modifying trial, and has been shown to have good psychometric properties in Rasch analysis.[45] People with Parkinson's and their care partners were involved in the review and decision-making process of which care partner measure was most suitable and acceptable to include in the trial.

EQ-5D-5L

The EQ-5D-5L is a simple questionnaire regarding perceived health on the day of completion within 5 domains (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), each answered according to 5 response levels (no problems, some problems, moderate problems, severe problems,

extreme problems) and a visual analogue scale capturing overall health[46,47]. The EQ-5D-5L allows calculation of utility scores, which are used to calculate quality-adjusted life-years (QALYs), and thus enable standardised health economic analyses to be performed. As a means for calculating QALYs, it is useful for providing evidence to decision makers such as NICE that rely on this type of information in the form of a cost-utility analysis for approval of new therapies and resource allocation decisions.

10.2.5 Withdrawal from Partner Sub-Study

Partners can participate in the trial for as long as the participant with Parkinson's takes part and continues follow-up assessments, even if the participant discontinues trial treatment. If the participant with Parkinson's withdraws from both trial treatment and follow-up then their partner must also withdraw.

As the participant of the partner is dependent on the consent of the participant with Parkinson's, if the participant with Parkinson's withdraws consent for their partner to take part in the trial, then the partner must withdraw from the trial.

If the partner decides to withdraw at any point, then the participant with Parkinson's can continue, without their participation in the trial being affected.

The participation of a partner must be in place so that the partner is able to contribute data from the participant with Parkinson's baseline visit. Therefore, a new partner or late-joining partner would not be able to participate after the participant with Parkinson's baseline visit window is completed.

10.3 Digital Measures Sub-study

Please refer to the sub-study specific Appendix.

10.4 Biosamples Sub-study

Please refer to the sub-study specific Appendix.

10.5 Genetics Sub-Study (PD Frontline collaboration)

PD Frontline is an existing ethically approved research study in which consenting participants will provide samples for DNA extraction and testing for genes known to be associated with PD risk. PD Frontline participants also consent to their DNA samples being tested in the GP2 study- a global genotyping consortium seeking to identify new genes associated with PD.

All EJS ACT-PD participants will be invited to register for PD Frontline using the PD Frontline approved PIS and informed consent forms at their EJS ACT-PD screening visit.

EJS ACT-PD will collaborate with PD Frontline to obtain the results of the genetic testing to link with the EJS ACT-PD data set to:

- Check if any of the treatments tested in EJS ACT-PD work better in people with different genetic risks for PD.
- Identify any other genetic factors which may influence response to the treatments tested.

- Look at how differences in genetic makeup (or DNA) may make someone more or less likely to develop PD, or impact how PD affects the body.

If the participant consents to PD Frontline during the EJS ACT-PD screening visit, the blood sample collection can take place alongside the EJS ACT-PD screening and research bloods. The PD Frontline sample will be shipped by sites to PD Frontline.

If the participant consents to PD Frontline after their EJS ACT-PD screening visit, the blood or saliva sampling kit will be taken home by the participants. The participant will then return their sample directly to PD Frontline.

The samples received by PD Frontline will be analysed (including analysis by GP2). The PD Frontline trial processes will be followed. The results of genotyping of EJS ACT-PD participants will be shared with the EJS ACT-PD team and linked with the EJS ACT-PD data set.

Further details regarding sample collection, processing and shipping will be outlined in the Sample Collection & Handling Manual.

11. REGULATORY & ETHICAL ISSUES

11.1 COMPLIANCE

11.1.1 REGULATORY COMPLIANCE

The EJS ACT-PD Trial will be conducted in compliance with the approved protocol, the Declaration of Helsinki 1996,[63] the principles of Good Clinical Practice (GCP) as laid down by the ICH topic E6 (R2) as amended, Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) as amended and The Human Medicines (Amendment) (EU Exit) Regulations 2019 (SI 2019/775), the UK Data Protection Act 2018 (DPA number: Z6364106), and the UK Policy Framework for Health and Social Care Research.

11.1.2 SITE COMPLIANCE

An agreement will be in place between the site and the CTU, setting out respective roles and responsibilities (see **Section 13 - Finance**).

All sites will inform the EJS ACT-PD Trial Team as soon as they are aware of a possible serious breach of compliance, so that the Trials Unit can report this breach if necessary within 7 days as per the UK regulatory requirements. For the purposes of this regulation, a 'serious breach' is one that is likely to affect to a significant degree either:

- The safety or physical or mental integrity of the participants in the trial
- The scientific value of the trial

11.1.3 DATA COLLECTION & RETENTION

Trial data will be inputted directly into the trial database and should be securely stored electronically for a minimum of 25 years after the end of the trial. During this period, all data should be accessible, with suitable notice, to the competent or equivalent authorities, the Sponsor, and other relevant parties in accordance with the applicable regulations. The data may be subject to an audit by the competent authorities. Medical files of trial participants should be retained in accordance with the maximum period of time permitted by the hospital, institution or private practice.

11.2 ETHICAL CONDUCT

11.2.1 ETHICAL CONSIDERATIONS

The following ethical considerations, problems and/or dilemmas relating to the trial have been considered:

- Participants are required to attend in-person or remotely for additional visits to their normal standard of care. This is for safety and trial conduct. Participants will be contacted 5 times in first year and twice yearly thereafter compared to once per year or less in standard care.
- Use of placebo and when and/or whether its use would be revealed. The trial is placebo controlled and can be seen as receiving no drug by participants. This could lead to reduced compliance. It will be confirmed to all participants they will also be receiving their current care standard. This will be expanded in the PIS. After the final efficacy analysis (stage 3 or 4 depending on outcome), it would be appropriate to reveal the arm the participants were randomised to.
- Following a stage 1 or stage 2 analyses, treatment arms may be closed early if showing a lack of activity. The participants on these arms would cease trial treatment and follow-up and

exit the trial. However, these participants would be able to be re-randomised into another active treatment arm (see Sections 4.4, 6.10 and 11.5.1 for further details regarding re-randomisation following closure of arms at stage 1 and stage 2 analyses).

- Washout period after trial treatment will be 6 weeks for arms ceased due to futility, and 26 weeks for arms that proceeded to primary analysis to avoid any residual biological activity (reduced to 6 weeks should the primary analysis be negative). After washout (if appropriate and eligible) a participant can be re-randomised into the trial.
- The IMP are re-purposed with excellent safety records. The possible side-effects and mitigations are described in **section 5.7.1**.
- Participants will be reimbursed for travel expenses (up to £40 per visit or reviewed on a case-by-case basis if insufficient)
- The collection of sensitive or personal samples will not occur without informed consent and samples will be pseudo anonymised
- Publication of data and feedback of overall results (not individual results) to participants (including participants who have withdrawn but consented to continue to receive trial communications)
- Coincidental findings:
    - blood tests may uncover some other previously unknown condition. If these are uncovered by the trial, these will be communicated back to their Primary Care physician as appropriate.

Steps that have been taken to minimise these issues will be included within the risk assessment and other quality management documents. Any issues raised here will be included in the PIS (see Participant Information Sheet). Issues relating to confidentiality can be found in **Section 8.3.2**.

11.2.2 Favourable Ethical Opinion

Following Main REC approval and Health Research Authority (in England) approvals and before initiation of the trial at each clinical site, the protocol, all informed consent forms, and information materials to be given to the prospective participant will be submitted to each Trust's Research and Development (R&D) office. In Wales, Scotland and Northern Ireland, the R&D office will be asked to give approval. In England, the R&D office will be asked to confirm capacity and capability. Any further substantial amendments will be submitted and approved by the Main REC and HRA.

If further sites in non-UK countries do participate in later stages, the national ethics requirements for those countries will also be required.

The EJS ACT-PD Trial has been developed with Patient and Public Involvement and Engagement (PPIE) to ensure that its design is feasible and acceptable to potential participants, and to ensure its outcomes and potential impact are relevant to the population who may benefit from its results. PPIE also helps to ensure transparency and accountability throughout this research. PPIE activity will continue for the duration of the study, including dissemination of study results.

The rights of the participant to refuse to participate in the trial without giving a reason must be respected. After the participant has entered into the trial, the trial clinician must remain free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the participant. The reason for doing so, however, should be recorded; the participant will remain within the trial for the purpose of follow-up and for data analysis by the treatment option to which they have been allocated. Similarly, the participant must remain free to change their mind at any time about the protocol treatment and trial follow-up without giving a reason and without prejudicing his/her further treatment.

11.3 Competent Authority Approvals

This protocol will be submitted to the MHRA in the UK for review and approval, prior to protocol release.

This is a Clinical Trial of an Investigational Medicinal Product (IMP) as defined by the Medicines for Human Use (Clinical Trials) Regulations 2004. Therefore, a CTA is required in the UK.

The progress of the trial and safety issues will be reported to the MHRA in accordance with local requirements and practices in a timely manner.

Safety reports, including expedited reporting and SUSARS will be submitted to the competent authority in accordance with each authority's requirements in a timely manner.

11.4 Other Approvals

The protocol will be submitted by those delegated to do so to the relevant R&D department of each participating site or to other local departments for approval as required in each country. A copy of the local R&D approval (or other relevant approval as above) and of the PIS and Consent Form (CF) on local headed paper should be forwarded to the CTU before participants are entered.

11.5 End of Trial and Comparison Closure

11.5.1 Closure of arms at stage 1 and stage 2 analyses

At the stage 1 and stage 2 analyses, a decision will be made to determine whether the treatment arm will proceed to the efficacy analyses (stage 3 & stage 4). Applicable arms will close if it is decided to no longer proceed with them. Therefore, in this case or for the closure of other arms, all participants in the applicable arm(s) will be notified to stop taking any trial treatment, and complete a final follow-up visit at which they will discuss the decision and potential options for re-randomisation **(Section 4.4 and Section 6.10)**. No further requirement for safety reporting is required following arm closure for participants on that arm, other than those stipulated in the safety follow-up visit, 9 weeks after treatment discontinuation and to the point of resolution or stability of any SAEs. Any subsequent events that may be attributed to trial treatment should be reported to the MHRA using the yellow card system.

Further linkage for long-term analysis for these participants may occur through routinely collected medical data for up to 20 years after arm closure for participants who have consented for their data to be used.

11.5.2 Closure of arms at stage 3 and stage 4 analyses

The stage 3 efficacy analysis will take place to determine whether a treatment shows enough efficacy after 104 weeks post first dose of study medication to end the treatment arm and start the approval process to introduce the treatment into standard of care. If the initial efficacy analysis at stage 3 does not show efficacy, then a final primary analysis (stage 4) will take place following 156 weeks post first dose of study medication.

When a treatment arm ends at the stage 3 or the stage 4 analysis, all participants in this treatment arm will be notified of the trial's decisions and complete their final trial follow-up visit, at which there will be a discussion of their future treatment. This will be their final trial follow-up visit and no further

safety reporting is required, except for point of resolution or stability of any SAEs. Any subsequent events that may be attributed to trial treatment should be reported to the MHRA using the yellow card system.

Participants in other active treatment arms (that are still recruiting or in follow-up) will be notified of the trial's decisions / the outcome of ended arms, and continue in the trial as per the study visit schedule.

11.5.3 End of Trial Definition

The EJS ACT-PD Trial end of trial definition is when all arms are closed and all the data entered into the trial's eDC system, and once the database is checked and locked. Closure will be notified to MHRA, ethics and each R&D department according to local applicable laws and regulations.

12 INDEMNITY

The sponsor of the trial is the University College London (UCL). The EJS ACT-PD Trial is co-ordinated by the MRC CTU at UCL. UCL holds insurance against claims from participants for injury caused by their participation in this clinical trial. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this clinical trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical trial.

UCL does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise. Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of UCL or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigators, who will pass the claim to the UCL's Insurers, via the UCL office.

Healthcare provider organisations selected to participate in the EJS ACT-PD Trial must provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary can be provided on request.

13 FINANCE

The EJS ACT-PD Trial (Edmond J Safra Parkinson's Disease Multi-arm, Multi-stage Trial Platform) is funded by a collaboration of funding parties, including:

- The Efficacy and Mechanism Evaluation (EME) Programme, an MRC and NIHR partnership
- Cure Parkinson's Trust
- The Michael J Fox Foundation
- Parkinson's UK
- John Black Charitable Foundation
- Gatsby Charitable Foundation
- Van Andel Institute

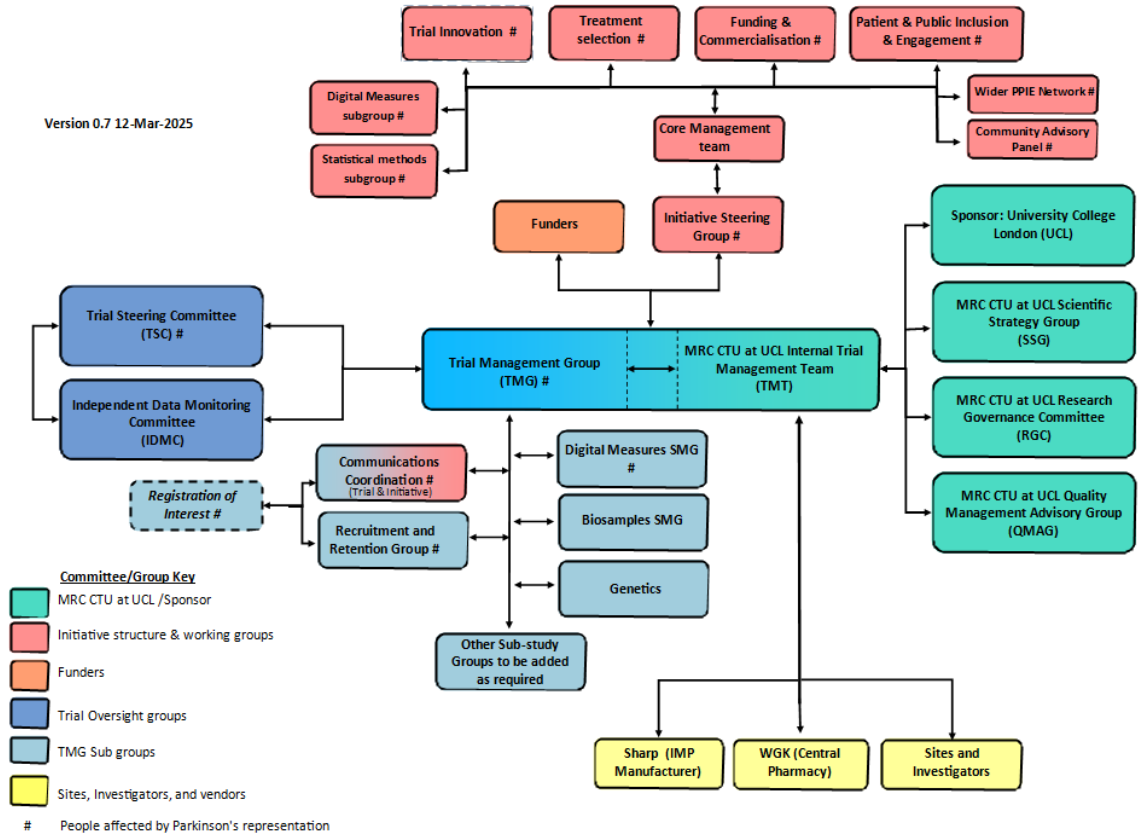
All Trial treatment (IMPs) will be provided. SoC therapies will not be provided by the trial. Participants will be reimbursed for trial travel expenses. Core-funded research site staff members (e.g., Research Nurses / Research Practitioners) will be hired and based at selected participating sites to assist with the recruitment and delivery of the trial in their region. Sites will also receive payments to cover other research activity costs. This will be documented in the non-commercial model agreement (mCTA) that will be in place between UCL and each participating site.

The EJS ACT-PD Trial is included in the UKCRN portfolio and support will be available for participating UK centres in the usual way.

14 OVERSIGHT & TRIAL COMMITTEES

There are a number of committees involved with the oversight of the trial. These committees are detailed below, and the relationship between them expressed in **figure 7**.

Figure 7: Outline of the EJS ACT-PD Trial committees and interaction:



14.1. TRIAL MANAGEMENT GROUP (TMG)

A Trial Management Group (TMG) has been formed comprising the Co-Chief Investigators, Senior Health Economist, Senior Statistician, Clinical Trials Pharmacist, co-investigators (clinical and non-clinical), members of the MRC Clinical Trials Unit (CTU), the Project Manager from the EJS ACT-PD Initiative and PPIE contributors. A representative of the trial's core-funded nurses will be appointed as a TMG member once recruitment is complete. The membership of the TMG may be expanded if other groups of trialists wish to participate. It will also be amended during the trial if other circumstances require e.g. retirement.

The Trial Management Team (TMT) at MRC CTU will be responsible for the day-to-day running and management of the trial. The TMG will be responsible for the operational oversight and management of the trial. The TMG will meet by teleconference approximately monthly and in person if needed. The full details can be found in the TMG Charter.

14.2. Trial Steering Committee (TSC)

The Trial Steering Committee (TSC) has membership from the TMG plus independent members, including the Chair and PPIE contributors. The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chair. The ultimate decision for the continuation of the trial lies with the TSC. Further details of TSC functioning are presented in the TSC Charter.

14.3. (Independent) Data Monitoring Committee (I[DMC])

An Independent Data Monitoring Committee (IDMC) will be formed. The IDMC will be the only group who sees the confidential, accumulating data for the trial. Reports to the IDMC will be produced by the CTU statisticians. The IDMC will meet within 6 months of recruitment starting; the frequency of meetings will be dictated in the IDMC charter, with timings of meetings later in the follow-up adapted to coincide with the milestones for analysis set out in **Table 11**. The IDMC will consider data using the statistical analysis plan (see **Section 9.6**) and will advise the TSC. The IDMC can recommend premature closure or reporting of the trial, or that recruitment to and follow-up within any research arm be discontinued.

Further details of IDMC functioning, and the procedures for interim analysis and monitoring are provided in the IDMC Charter.

14.4. Sample access committee (post-trial completion)

Following trial completion, the governance and ownership of the biorepository will be as outlined in a collaboration agreement between the relevant trial parties and the FCI. Proposals for sample access post-trial will be reviewed by an EJS ACT-PD sample access committee which will be run by the FCI and include the EJS ACT-PD CI's. The possible outcomes of proposal review will be the same as those listed in **section 10.1.1.** See **Section 17** for further information on data sharing.

14.5 Communications Coordination Group

The Communications Group membership will comprise a range of expertise, ensuring comprehensive input across relevant areas. The membership will include: patient and public representatives, members of the EJS ACT-PD trial team and initiative, members of the Join Parkinson's Research (JPR) team, communication officers from the MRC CTU at UCL, UCL and funder (charity) representatives. The purpose of the group is to oversee the trial's communication strategy and outputs, ensuring the development, review and approval of clear, effective communication and engagement materials that support trial objectives. In relation to the EJS ACT-PD initiative, an overarching communications strategy which aligns with the EJS ACT-PD trial will be developed.

14.6 Recruitment and Retention Group:

The Recruitment and Retention group will include both professional and patient representatives to assist with recruitment monitoring and identify ongoing recruitment strategies and support for sites as required. Members will be identified via current members participating in the EJS ACT-PD initiative to design the trial and the core-funded research site staff members. Additional members will be identified via an online recruitment campaign as needed and will be asked to submit information on their relevant experience and interest in participation.

14.7 Registration of Interest

The Registration of Interest (RoI) process will use an online form to collect basic demographic, contact, and eligibility information for all interested people with Parkinson's. This information will be shared with the registrants preferred study site to enable the study team to initiate the pre-screening telephone call. The RoI will ensure that all sites have the same basic information of data about potential participants and can quickly identify any points of eligibility which require further discussion or clarification. People with PD who complete the registration of interest form will have their data held within the Join Parkinson's Research registry hosted by Research+Me (JPR@Research+Me) and will be contacted with updates about the trial and site opening timeframes.

14.8 Sub-study groups

For each sub-study with external collaborations part of the EJS ACT-PD trial, a Study Management Group (SMG) will be formed to oversee the implementation and ongoing delivery of the sub-study. All groups will include members from the EJS ACT-PD trial team, relevant representatives from the external collaborators, and PPIE representatives.

14.9 The EJS ACT-PD Initiative

The EJS ACT-PD initiative was set-up to design and produce the protocol for the EJS ACT-PD Trial. The initiative has a pre-existing consortium of more than 90 members from a range of key stakeholders in Parkinson's. The initiative will continue to run as a separate but linked entity after the EJS ACT-PD Trial launches. The initiative will include the following groups which will be chaired individually but report to the TMG to support the sustainability of the trial:

14.9.1 Trial Innovation Working Group (TDOM WG)

The TDOM WG will include professional experts and input from trial TMG members to:

- Develop methodological innovations and trial design adaptations as required when adding new treatments to the trial
- Oversee the development of protocols and funding applications for the incorporation of trial sub-studies
- Manage future trial design developments based on inclusion of validated novel outcome measures

14.9.1.1 Digital Measures Subgroup

The Digital Measures subgroup will develop and apply a robust and sustainable selection process to review and prioritise digital measures for inclusion as exploratory measures in the EJS ACT-PD trial. This will include determining the most appropriate and relevant concept of interest to capture via an digital measures and considering how the measure can be implemented in future trial adaptations. Group membership will include a range of professional experts and PPIE representatives.

14.9.1.2 STATISTICAL METHODS SUBGROUP

The Statistical Methods Subgroup will use the trial dataset to perform new statistical modelling to inform how randomisation and treatment comparisons may occur in smaller groups, or how certain groups can be enriched for patients more likely to respond. These adaptations can then potentially be incorporated into the next stage of the trial design. Additional statistical innovations may also be used for other possible trial amendments including using trial emulation techniques to predict whether future treatments are likely to be effective, and modelling work to consider design practicalities of future sub-studies or updated outcome measures. The Statistical Methods Subgroup will include statistical experts, input from EJS ACT-PD Research Fellows, and PPIE representatives.

14.9.2 TREATMENT SELECTION WORKING GROUP (TS WG)

The TS WG will include a range of professional experts and patient input to:

- Oversee continued iteration and improvement of the treatment selection process to ensure it is consistently responding to new developments, innovative selection tools and expert feedback
- Implement the treatment selection process to identify the most promising treatments for future trial arms
- Liaise with the EJS ACT-PD funding panel secure funding for future treatment arms and collaborate with commercial organisations

14.9.3 FUNDING AND COMMERCIALISATION WORKING GROUP (FCWG)

The FCWG will include a range of professional experts and patient input to:

- Review currently selected treatments to determine all potential options for patient access, should they prove effective.
- Work closely with the Treatment Selection Working Group to identify appropriate new compounds for future inclusion in the trial, considering all contractual and funding requirements including those specific to industry partners.
- Identify future funding sources and pathways to support future trial arms and core trial infrastructure to maintain the trial past the first 3 treatment arms and include additional future sub-studies.

14.9.4 PATIENT AND PUBLIC INCLUSION AND ENGAGEMENT WORKING GROUP (PPIE WG)

The PPIE WG will consist of patient and care partner representatives alongside professionals with expertise in patient input to:

- Provide input into future treatment selection, trial design and sub-study development decisions considering acceptability, feasibility and meaningfulness for people with Parkinson's and their care partners
- Assist with the development and incorporation of SWAT (study within a trial) protocols to evaluate novel recruitment and retention methodologies, particularly those targeting under-served populations
- Liaise with a communications subgroup to devise a communications strategy for global awareness of the EJS ACT-PD Initiative and support the trial with additional recruitment and retention resources

14.9.4.1 WIDER PPIE NETWORK

The Wider PPIE Network consists of people with Parkinson's and carers / partners of people with Parkinson's to include a broader perspective on topics that the PPIE WG feel require additional input. This provides additional perspectives for the PPIE WG members to consider and increases the representativeness of trial decisions using PPIE input. The Wider Network form a mailing list used to

request input in a number of different formats e.g., via email response, survey completion, volunteering for focus groups etc.

14.9.4.2 COMMUNITY ADVISORY PANEL (CAP):

The CAP will consist of up to 11 patient and public members who have experience of either living with or caring for a person with a chronic health condition. The aim is for CAP members to be from a diverse range of backgrounds and experiences, with representatives from under-served groups in PD research (including ethnic and racial minorities, individuals living in rural or remote areas, research-naïve individuals and individuals from various socioeconomic backgrounds / locations). CAP members will be recruited via an online application process requesting details on their demographics, previous research experience and interest in participation. The CAP's remit will include to discuss, input and feedback on trial decisions with regards to their accessibility and inclusivity.

14.10 OTHER COMMITTEES

MRC CTU at UCL requires a number of internal working groups to run a platform protocol. These internal groups assist the TMT (or EJS ACT-PD Trial Team) in the operation of the trial, providing guidance on scientific strategies of research and publication, research governance in regulatory information and protocol review and the management of research quality within the EJS ACT-PD Trial.

14.11 ROLE OF STUDY SPONSOR

University College London is the sponsor of the EJS ACT-PD Trial. It is the employer of the staff coordinating the trial at the MRC CTU at UCL. The MRC CTU at UCL is delegated Sponsor responsibilities for the trial.

15 PATIENT AND PUBLIC INVOLVEMENT

Patient and Public Involvement (PPI) in research is defined by INVOLVE (an advisory group established by the NIHR) as research being carried out 'with' or 'by' members of the public rather than 'to', 'about' or 'for' them. INVOLVE intends 'public' to include patients, potential patients, carers and other users of health and social care services, as well as people from organisations that represent people who use services. In some cases, this may include involvement of a trial's participants in guidance or oversight of a trial.

People with Parkinson's (PwP) and care partners have been an integral part of the trial design process from its outset in 2021 via the EJS ACT-PD initiative. Two to three PPIE contributors work together to act as advisors to each of initiative's Working Groups, contributing to discussions and decisions on trial design, outcome measures, infrastructure, treatment selection and funding. To provide additional support and understanding, the PPIE contributors form a PPIE working group (WG) together with other stakeholders including representatives from patient organisations, trial delivery experts and researchers with a particular interest in patient engagement. PPIE members have also been present in all trial sub-groups, to ensure their input and perspectives have been included in all trial communications and sub-study considerations.

To ensure that the trial is accessible and inclusive as possible, an 'Community Advisory Panel' (CAP) was established. The CAP consists of 10 members, from a range of diverse backgrounds and experiences, with experience with PD or a chronic health condition either as a patient or care partner. The CAPs remit includes providing feedback and guidance to support the trial in engaging with and recruiting from under-served groups, by identifying and overcoming barriers to research and effectively communicating with different communities.

Cure Parkinson's and Parkinson's UK have been key members throughout the study concept development, and are committed to assisting the trial with regards to advertising the trial for recruitment and disseminating updates.

The EJS ACT-PD Initiative and trial are committed to continue including PPIE representation across all groups, discussions and decisions to ensure that all aspects of the trial are patient-centred, and reflect patient concerns and priorities. This includes the TMG, TSC, Communications Coordination, Recruitment and Retention Panel and any future Study Management Groups set-up for trial purposes.

15.1 POTENTIAL IMPACT OF PPI

Involving people affected by PD has strengthened the quality and relevance of the design and will continue to impact the management of the EJS ACT-PD Trial. PwP and their care partners offer unique insights from their lived experience that enhance the expert knowledge of trial clinicians and researchers. PPI is an essential component of all aspects of the research process, and has already been embedded in the preparatory work for the trial. PPIE input has guided the evolution of the trial design, highlighting areas that need further thought or input and ensuring that the Parkinson's population is at the heart of protocol decisions. This has ensured that when applying for the funding and ethical approval, the opinions of PwP and care partners have been forefront of project.

The trial design decisions related to inclusion criteria, trial delivery and outcome measures will ensure the trial is acceptable and meaningful to participants, to encourage participation and provide results that are relevant to PwP daily life.

PPIE and CAP input has been crucial to our recruitment, retention and communications strategy to assist with how the trial is advertised, how we support participants throughout their journey in the trial and how we engage with under-served groups. This will ensure that recruitment is timely and our participant population is representative of the wider Parkinson's community. It will also enable updates regarding trial progress and dissemination of research findings to be given to appropriate forums and in an efficient, understandable delivery.

The input from all patient and public members has led directly to:

- The Primary Outcome Measure including a focus on non-motor symptoms of PD and patient-reported outcomes
- The broad inclusion criteria with regards to age and disability
- The use of 'ON' medication assessments
- The inclusion of remote trial assessments
- The length and frequency of selected secondary outcome measures
- The drafting of the resource use questionnaire, which was developed for this study based on the CSRI and iVICQ questionnaires.
- Increasing the readability of the trial documents including consent form and PIS
- Production of a communications strategy targeting under-served groups with PD
- The recruitment and retention strategy
- The dissemination strategy

15.2 Identifying PPI Contributors

The EJS ACT-PD Trial has a number of panels, oversight committees and TMG working groups associated with it as described in **Section 14** (see **Figure 7**). There is active involvement of people with PD (PwP) and care partners in each group, where appropriate.

The Trial Management Group includes two people with Parkinson's and one care partner, all of whom have been involved in the EJS ACT-PD initiative to design the trial. The two PwP on the TMG are also co-applicants on the programme grant.

Further PPIE members PwP/care partners will sit on the following committee and TMG working groups:

Trial-related

- Trial Steering Committee (TSC)
- Recruitment and Retention Panel (RRP)
- Sub-study management groups (SMGs)
-

Initiative-related

- Treatment Selection Working Group (TS WG)
- Funding and commercialisation collaboration committee (FCC)
- Trial Innovation Working Group (TIWG).
- JPR Steering Group
- Statistical methods
- Initiative Steering Group

Trial and initiative-related

Community Advisory Panel (CAP)

-
- Communications Group
- Broader PPIE network
- PPIE Working Group

Duration, rotation and responsibilities of the PPI representatives will be defined in the relevant Charters to prevent PwP exhaustion and burden.

15.3 PROTOCOL DESIGN AND STUDY SETUP

PwP and care partners have been involved in the EJS ACT-PD initiative to design the trial, since it first launched in 2021. Members have been active throughout the entire design process and will remain involved during the set-up and delivery.

Reimbursement for ongoing patient and public involvement has been included in the trial costings as the recommended rates provided by the NIHR.

15.4 PPI IN THE ONGOING RUNNING OF STUDY

PwP who participate in the trial will be recruited to assist in the creation of communication resources to share their experience of participation in the trial with other PwP. This will include creating videos, written blogs and assisting with hosting webinars alongside the trial team.
Please refer to **section 15** for more information on PPI in the ongoing running of the EJS ACT-PD Trial.

15.5 INTERPRETING AND PLANNING DISSEMINATION OF STUDY RESULTS

PwP and care partners have contributed to the recruitment, retention and overall communication strategies for the trial. PPIE members will continue to be included in the interpreting, planning and dissemination of study results via their representation on the TMG, TSC, CAP and RRP. PPIE members will lead on the creation of lay summaries detailing trial results, as well as additional communications throughout the trial to provide updates on trial progress and amendments (e.g., recruitment updates, stage analysis outcomes etc.).

Regular communication with participants will be provided throughout the trial duration via several possible formats including email / postal updates, newsletters, online webinars, in-person events, social media posts and website updates. PPI representatives on the various trial committees will help to ensure that EJS ACT-PD Trial participants are kept up-to-date, by helping to plan and draft the relevant communications to make sure that the language used is appropriate and engaging for different audiences.

15.6 REPORTING AND EVALUATING IMPACT OF PPI

The processes of including PPIE input and feedback in the trial design process, via the EJS ACT-PD initiative have been evaluated for feasibility and impact. The evaluation included a longitudinal, mixed methods approach to evaluate PPIE embedded within EJS ACT-PD. The Patient Engagement in Research Scale[64] (PEIRS) was administered six monthly to allow quantitative analysis of engagement quality. Semi-structured interviews were conducted at the project's mid-way and end point to identify areas for improvement and collect overall impressions of engagement. Process fidelity was measured by capturing adherence to processes co-designed with PPI representatives. A document

review will capture impact of PPI on project outputs and an analysis integrating all data sources will be conducted to address study aims.

A feedback process will be implemented throughout the trial, in which participants can submit anonymous feedback regarding their experience to the trial management team. This will provide the trial team with a better understanding of the participant experience, to identify areas that can be improved and to implement methods to improve participation for both PwP and sites. Updates on when participant feedback leads to trial amendments or improvements will be included in future participant communications so that participants are aware of how their feedback is being used.
The EJS ACT-PD Trial will include details of their PPI activities and the impact in the main publications coming out of the trial.

16 PUBLICATION AND DISSEMINATION OF RESULTS

The results for each stage of the EJS ACT-PD Trial will be analysed separately when appropriate and according to pre-defined criteria developed from the MAMS design. The results from the trial will be published in peer-reviewed journals, as well as being presented at national and/or international conferences, when appropriate and possible. Individual groups and clinicians must not publish data concerning their participants that are directly relevant to questions posed by the study until the TMG has published its manuscript. The TMG will form the basis of the Writing Committee and will advise on the nature of all publications. Any release of efficacy or safety data, presentation or publication will be agreed with the TSC according to the terms of their charter.

There are expected to be a number of resulting publications and the authorship will vary for each. Individual authors will include relevant members of the TMG and collaborators, as well as investigators/key site staff where possible. All participating sites and corresponding PIs, Sub-Is and key members of the study delivery teams in the relevant cohort will be acknowledged in all relevant publications, along with members of the IDMC and TSC.

With the manuscript, a full list of sites and the number of participants recruited will be provided. In the presentations, this list of sites will also be shown. The term “the EJS ACT-PD Trial investigators” will clearly be stated and relevant names included in the presentation credits.

Results from the analyses may be available at different times, as will results from the sub-studies. In order not to jeopardise the integrity of the ongoing trial, careful consideration (in discussion with the IDMC and TSC, as appropriate) will be given to the data to be released from each analysis for presentation/publication. Similarly, if at any point it is felt to be justified and appropriate to release specific data from an analysis, this would require discussion and agreement from the IDMC, who would be asked to provide guidance regarding the data to be released and how widely they should be disseminated.

17 DATA AND/OR SAMPLE SHARING

Data and/ or samples will be shared during the trial according to the CTU's controlled access approach, based on the following principles:

- No data and / or samples should be released that would compromise an ongoing trial or study.
- There must be a strong scientific or other legitimate rationale for the data and /or samples to be used for the requested purpose.
- Investigators who have invested time and effort into developing a trial or study should have a period of exclusivity in which to pursue their aims with the data and /or samples, before key trial data are made available to other researchers.
- The resources required to process requests should not be under-estimated, particularly successful requests which lead to preparing data for release. Therefore, adequate resources must be available in order to comply in a timely manner or at all, and the scientific aims of the study must justify the use of such resources.
- Data and/ or sample exchange complies with Information Governance and Data Security Policies in all of the relevant countries.
- Data and/ or sample exchange is only provided following execution of a valid material transfer agreement (MTA).

Data and / or samples will be available for sharing following the end of a trial arm and the unblinding of participants. Researchers wishing to access the EJS ACT-PD Trial data should contact the Trial Management Group in the first instance.

Following trial completion, requests for data and/ or sample sharing will be reviewed by an EJS ACT-PD access committee which will include the trial's Chief Investigators.

18 PROTOCOL AMENDMENTS

Please check with the EJS ACT-PD Trial Team or website to confirm the most recent version of the trial protocols, appendices and associated documents.

Amendments made from Protocol version 1.0 12-Nov-2024 to version 2.0

1. Throughout – version and date updated to v2.0 11-Feb-2025.
2. Throughout – addition of ISRCTN, CTA and MREC numbers.
3. Page ii – addition of REC name and Research Network Portfolio.
4. Section 3 – Selection of Participants – clarification regarding contraception effectiveness and use to the inclusion criteria.
5. Section 3 – Selection of Participants – Addition of bilirubin value, including Gilbert's disease exception, to the exclusion criteria.
6. Section 5 – Treatment of Participants - Clarification of emergency unblinding process.
7. Section 7 – Safety Reporting – Updated table referencing RSI documentation.
8. Appendix 1 – Appropriate Contraceptive Treatments - clarification regarding contraception effectiveness and use.
9. Appendix 1 - Appropriate Contraceptive Treatments – lists for 'highly effective methods of contraceptive methods' and 'Contraception methods not used…' updated.

Amendments made from Protocol version 2.0 11-Feb-2025 to version 3.0

Throughout:

1. Update of visit months into weeks
2. Correction of minor typos and wording updates
3. Correction of 'community pharmacy' to 'central pharmacy'
4. Correction of 'Pharmacy Manual' to 'Site IMP Management Guidance Document'
5. New references added and reference numbering updated
6. Correction of 'Lab manual' to 'Sampling Handling Manual'
7. Addition of Clinical Global Impression Scale (CGI) as a secondary outcome measure
8. Removal of the Participant Exit Interview

General Information:

9. Notable Events added to SAE reporting details
10. Update to MRC CTU at UCL Staff

Summary of Trial:

11. Addition of Biosamples, Digital Measures and Genetics sub-studies.
12. Research blood samples removed from Ancillary section
13. Clarification of capability and quality of life secondary outcome measures

Trial Assessment Schedule:

14. Clarification that all study visits can be conducted remotely and in-person
15. Removal of blood pressure requirement at follow-up visits (weeks 13, 26, 52, 78, 104 and 103)
16. Addition of sitting blood pressure and clarification when blood pressure should be taken (and section 6.7.3)
17. Clarification that all assessments at early termination and unscheduled visits are not compulsory.
18. Additional footnote explaining in-person visit requirement for the end of study visit (week 156) for the purpose of research blood collection *(also updated in Section 6.2.6)*

19. Addition of footnote clarifying the translation requirements of MDS-UPDRS Parts Ib and III
20. Partner EQ-5D-5L additional timepoint at week 13 added
21. Further footnote details added regarding where the safety bloods should be completed
22. Addition of coagulation factor (for Biosamples sub-study participants) and cholesterol.
23. Clarification regarding pregnancy testing completion
24. Clarification of completing the H&Y staging remotely

Abbreviations

25. Addition of new abbreviations (CGI-S and CGI-C)

Glossary:

26. Update to H&Y stage definitions (*also updated in section 6.5.3*)
27. Correction of 'Assessing clinician' to 'blinded rater' and clarification of definition

Section 3:

28. Removal of overall inclusion criteria statement *'The inclusion criteria are relevant at all stages of the trial, unless where stated e.g., MoCA and PHQ-9 cut-off scores only apply at the screening timepoint.'*
29. Updates to exclusion criteria Points 5 and 8
30. Clarification added to treatment specific exclusion criteria regarding treatments to be used with caution
31. Clarifications added to telmisartan specific exclusion criteria point 3
32. Addition of a terazosin specific exclusion critera
33. Addition of sub-study consent process
34. Removal of reference to signing via proxy

Section 5:

35. Removal of IMP bottle details for all treatment arms
36. Update to Terazosin titration schedule
37. Update to the definition of Orthostatic hypotension
38. Addition of Hypotension
39. Clarification added regarding restarting trial medication in relation to contraindicated medication
40. Clarifications added to medications and treatments to be used with caution

Section 6:

41. Long term follow-up data updated to 20 years
42. Updated wording from 'Assessing clinician' to 'blinded rater' and further details of the role added
43. Clarification on how to record medical history
44. MDS-UPDRS clarification regarding completion in translated languages
45. Addition of sitting blood pressure and clarification when blood pressure should be taken
46. Assessment details added for SPFQ, Falls and Participant Expectations Questionnaire
47. Update to advice regarding continuation for participants who start DBS or infusion therapy during trial

Section 7:

48. Addition of CTCEA footnotes
49. Update to the timing of reporting AEs from consent to randomisation
50. Removal of RSI Document dates

Section 8:

51. Additional source document exceptions and further clarification added

Section 10:

52. Removal of potential research blood studies
53. Additional details of research blood sample processing added
54. Removal of Partner Three Letter Code
55. Details of Genetics Sub-study added

Section 14:

56. Updated EJS ACT-PD Organogram
57. Details of new trial groups added (Communications Coordination Group, Registration of Interest, Sub-Study Groups)
58. Details amended or added for Initiative groups

Section 15:

59. Additional details and clarification of PPI involvement in the trial and initiative

Appendices

60. Addition of the Digital Measures Sub-study Appendix V1.0
61. Addition of Biosamples Sub-study Appendix V1.0

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APPENDIX 1: APPROPRIATE CONTRACEPTIVE TREATMENTS

EJS ACT-PD Trial female participants who are WOCP must agree to use a highly effective method of contraception while taking trial treatment and for 70 days after the last dose of trial treatment.

For the purpose of EJS ACT-PD, a woman is considered of childbearing potential (WOCP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause and being aged ≥60 years old. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy if aged <60 years old. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

EJS ACT-PD Trial male participants and their partners (if WOCP) must agree to use one of the highly effective methods of contraception listed below while taking trial treatment, during dose interruptions and for at least 70 days after the last dose of treatment.

The contraception methods which may be considered as highly effective are listed below:

HIGHLY EFFECTIVE METHODS OF CONTRACEPTIVES

1. Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation which can be oral, intravaginal or transdermal
2. Progestogen-only hormonal contraception associated with inhibition of ovulation which can be oral, injectable or implantable
3. Intrauterine device (IUD)
4. Intrauterine hormone-releasing system (IUS)
5. Bilateral tubal occlusion
6. Vasectomised or vasectomised sexual partner - this is a highly effective birth control method provided that partner is the sole sexual partner of the WOCP trial participant and that the vasectomised partner has received medical assessment of the surgical success.
7. True heterosexual abstinence (which is in line with the preferred and usual lifestyle of the participant i.e. not just stopping intercourse for the duration of the trial)

Condom use is mandatory for men if their partner is a WOCP in combination with contraceptive methods 1-5.

CONTRACEPTION METHODS NOT CONSIDERED HIGHLY EFFECTIVE INCLUDE:

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- Sole use of a cap, diaphragm or sponge with spermicide, or male and female condom with or without spermicide.
- Fertility awareness methods
- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus)
- Spermicides only
- Lactational amenorrhoea method (LAM)

OTHER CONSIDERATIONS

- A urine HCG pregnancy test is required for WOCBP/WOCP. See **Schedule of Assessment Table 1 and section 6.6.4** for details.
- If a pregnancy occurs in a trial participant or a partner of a trial participant, it is a reportable event and female trial participants must stop trial treatment please refer to Protocol **section 6.6.4** and **section 7.2** for how it must be reported.
- Contraceptive history should be rechecked throughout the trial at follow up visits, clinical discretion exercised if pregnancy tests are required prior to dispensing. Participants should be made aware of the availability of emergency “post-coital” contraception if there is an indication for it (for example missing IUD threads or a late injection).
- Gastro-intestinal side effects: diarrhoea is unlikely to affect oral contraceptive absorption unless cholera-like. Vomiting within 3 hours of taking oral contraception does pose a risk equivalent to a missed pill and participants should follow the guidelines for a missed pill. Neither diarrhoea nor vomiting will affect non-oral routes for hormones.

APPENDIX 2: DRUG-SPECIFIC APPENDIX FOR ACTIVE TREATMENTS

TELMISARTAN:

1. BACKGROUND:

1.1. BACKGROUND AND MECHANISM FOR TELMISARTAN

Telmisartan is an angiotensin II (AT-II) type 1 receptor (AT1R) blocker (ARB) licensed as an antihypertensive drug. The renin–angiotensin–aldosterone system is a modulates blood pressure, fluid and electrolyte balance, and vascular resistance, hence telmisartan exerting a blood pressure-lowering effect by blocking AT1R.

There is extensive preclinical data supporting the neuroprotective properties of ARBs in PD, and epidemiological data shows that exposure to these compounds is associated with a reduced risk of developing PD. Of all the ARBs, telmisartan has the best pharmacokinetics (bioavailability, blood-brain barrier (BBB) penetration, and half-life).

1.2. RATIONALE FOR THE USE OF TELMISARTAN

Telmisartan has broad preclinical evidence of neuroprotection, both in cell and animal models. In the former, a regulatory role in oxidative stress and inflammation via IL-1ß has been described[1]. Among the latter, apart from confirmation of its anti-inflammatory role in an alpha-synuclein rodent model[2], the inhibition of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced microglial response[3] and an improvement of mitochondrial[4], astroglial and dopaminergic functions[5] have been reported, as well as the inhibition of apoptosis[6], with subsequent motor improvement in several of those studies. Furthermore, a reduction in angiotensin type 1 receptors (AT1R) has been shown to correlate with the loss of dopaminergic neurons over time in postmortem PD brains[7], and a dopaminergic nigral cell subpopulation expressing that receptor's gene (AGTR1) is highly susceptible to PD[8].

Epidemiological data on ARBs has suggested a reduced risk of PD among users of this group of drugs[9], especially the blood-brain barrier (BBB)-crossing ones[10], such as telmisartan. More recently, AT1R autoantibodies (AA) were found to be higher in PD patients when compared to matched controls, and these also increased levels of neuroinflammation markers, which could be ameliorated by a similar drug, candesartan[11]. This opens the possibility of a *post hoc* analysis of subgroups of patients according to AT1R AA levels at baseline and after treatment with telmisartan.

Although there have been no PD trials using telmisartan, a small trial of candesartan in patients with PD and hypertension showed good tolerability and a significant motor and non-motor improvement, as measured by the Hospital Anxiety and Depression (HAD) scale, the Unified Parkinson's Disease Rating Scale (UPDRS) scale (parts I to IV), and a subsequent improvement in quality of life reflected in the 39-item Parkinson's Disease Questionnaire (PDQ-39) ratings[12]. There are various ongoing trials on ARB in other neurodegenerative conditions, such as Alzheimer's disease (AD).

Telmisartan has the best pharmacokinetics (in terms of bioavailability, CNS penetrance, and half-life) of all ARBs with an excellent side-effect profile and there is long-term experience of its use.

1.3. TELMISARTAN DOSE JUSTIFICATION

The proposed dose of telmisartan (i.e. 40mg once daily titrated from 20mg daily) is based on the candesartan trial in PD, in which a dose of 8mg/day was used[12]. According to NICE guidelines, maintenance doses of candesartan are 8mg/day whereas telmisartan maintenance doses are usually 40mg/day[13]. Various guidelines report an equivalence between candesartan 8mg and telmisartan 40mg[14,15] and as such we expect good CNS penetration and target engagement at this dose, as well as tolerability in people with Parkinson's.

For the titration schedule, please see **Section 5.4.2** of the protocol.

1.4. TELMISARTAN TOXICITY AND SAFETY

1.4.1. TELMISARTAN: COMMON OR VERY COMMON SIDE-EFFECTS

Orthostatic hypotension:

Any patient developing new or worsening symptomatic or significant asymptomatic OH at any point after randomisation will be given clinical advice to manage the symptoms, tailored according to the clinician's judgement.

To facilitate remote BP monitoring, each participant will be given and taught to use a home BP measuring device.

1.4.2. OTHER COMMON OR VERY COMMON SIDE-EFFECTS

Side-effects described as common or very common in the British National Formulary (BNF) for all ARBs are abdominal and/or back pain, asthenia, cough, diarrhoea, dizziness, headache, postural hypotension (more common in patients with intravascular volume depletion, e.g. those taking high-dose diuretics), nausea, renal impairment, vertigo, and vomiting[16].

Additional uncommon side-effects of telmisartan listed in the BNF are: anaemia; arrhythmias; chest pain; cystitis; depression; dyspnoea; flatulence; gastrointestinal discomfort; hyperhidrosis; increased risk of infection; insomnia; muscle spasms; sciatica; syncope.

For information on the monitoring and management of medically significant toxicities while on telmisartan, please see **Section 5.7.1.2** of the protocol.

To reduce the risk of the most serious side-effects from the list above, treatment-specific exclusion criteria for the telmisartan trial arm have been established and are detailed in **Section 3.2.1.1** of the protocol.

2. SELECTION OF PARTICIPANTS

2.1. PARTICIPANT CORE INCLUSION AND EXCLUSION CRITERIA

Please see **Sections 3.1** and **3.2** of the protocol for core inclusion and exclusion criteria, respectively.

2.2. TELMISARTAN-SPECIFIC EXCLUSION CRITERIA

Please see **Section 3.2.1.1**. for telmisartan-specific exclusion criteria.

3. TREATMENT OF PARTICIPANTS: TELMISARTAN

3.1. PRODUCT INFORMATION: TELMISARTAN

- This trial will test telmisartan.
- Telmisartan is a licenced product used in hypertension and in prevention of cardiovascular events in patients with established atherosclerotic cardiovascular disease, or type 2 diabetes mellitus with target-organ damage[17], with a well-established safety profile. There is however no data in this particular indication nor any direct safety data of telmisartan in PD, and the closest data is from a trial of candesartan in PD[12], as mentioned above.

- Telmisartan 20mg and 40mg tablets over-encapsulated in size 00 capsules with Microcrystalline Cellulose will be packaged, labelled and shipped to the central pharmacy by Sharp Clinical Services (UK) Ltd.
- Telmisartan will be dispensed and distributed by the central pharmacy and shipped directly to participants' homes at baseline (5-week titration pack), end of titration and every 6 months after for a total treatment duration of 36 months.
- Blinding will be maintained in in appearance via over encapsulation.
- The elimination half-life of telmisartan is 21-38 hours[18-19]

3.2. HANDLING CASES OF TRIAL TREATMENT OVERDOSE: TELMISARTAN

Management of trial treatment overdose is covered in **Section 5.8** of the protocol.

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TERAZOSIN:

1. BACKGROUND:

1.1. BACKGROUND AND MECHANISM

Terazosin is an α1-adrenergic receptor (α1-AR) antagonist, licensed for the treatment of hypertension and benign prostatic hyperplasia. Independent of the aforementioned mechanism of action, it also activates phosphoglycerate kinase 1 (PGK1), an enzyme which is central in glycolysis, thus enhancing energy (adenosine triphosphate (ATP) production in cells.

1.2. RATIONALE FOR THE USE OF TERAZOSIN

Preclinical data highlights the glycolysis-enhancing action of terazosin and its subsequent potential to protect dopaminergic neurons in different toxin-based PD animal models[1,2], as well as in patient-derived induced pluripotential stem cells (iPSCs)[2], attenuating PD progression.

In general, epidemiological studies have shown a reduced incidence of PD among people taking terazosin and other PGK1 activators, as opposed to those taking α1-AR antagonists which do not activate PGK1[2-5], as well as a milder disease progression (less symptoms and complications – falls, dementia, gait problems –) in people with PD taking PGK1 activators[2].

Importantly, a pilot study of target engagement of terazosin in PD has shown significantly increased βATP to inorganic phosphate ratio in the brain as measured by 31-phosphorus magnetic resonance spectroscopy (31P-MRS) as well as a significant increase in blood ATP levels compared to the placebo group[6]. Another study showed a significant motor improvement as measured by part 3 of the Unified Parkinson's Disease Rating Scale (UPDRS) in PD patients versus placebo[7].

1.3. TERAZOSIN DOSE JUSTIFICATION

The pilot study of terazosin in PD administered 5mg daily to participants[6], as such we are confident that this dose will provide CNS penetration and target engagement with biological activity being demonstrated, as well as being tolerated in people with Parkinson's.

For the titration schedule, please see **Section 5.5.2** of the protocol.

1.4. TERAZOSIN TOXICITY AND SAFETY

1.4.1. SIDE-EFFECTS OF TERAZOSIN (FREQUENCY NOT KNOWN)

The following side-effects of terazosin are listed in the British National Formulary[8] (BNF) with an unknown frequency:
Angioedema; anxiety; arrhythmias; arthritis; asthenia; chest pain; conjunctivitis; constipation; cough; depression; diarrhoea; dizziness; drowsiness; dry mouth; dyspnoea; epistaxis; fever; flatulence; gastrointestinal discomfort; gout; headache; hyperhidrosis; increased risk of infection; insomnia; joint disorders; myalgia; nasal congestion; nausea; oedema; pain; palpitations; paraesthesia; postural hypotension; sexual dysfunction; skin reactions; syncope; thrombocytopenia; tinnitus; urinary disorders; vasodilation; vertigo; vision disorders; vomiting; weight increase.

In the BNF, the only contraindications for terazosin are history of micturition syncope (in benign prostatic hyperplasia) and history of postural hypotension (in benign prostatic hyperplasia).

Therefore, the main potential side-effect to monitor on participants in this treatment arm would be orthostatic hypotension. Participants with significant concomitant medical conditions would not be included, as per **Section 3.2** of the protocol, potentially reducing the risk of many of the above-listed side-effects.

In line with BNF recommendations, treatment-specific exclusion criteria for the terazosin arm have been established and are detailed in **Section 3.2.1.2** of the protocol.

For information on the monitoring and management of medically significant toxicities while on terazosin, please see **Section 5.7.1.2** of the protocol.

2. SELECTION OF PARTICIPANTS

2.1. PARTICIPANT CORE INCLUSION AND EXCLUSION CRITERIA

Please see **Sections 3.1** and **3.2** of the protocol for core inclusion and exclusion criteria, respectively.

2.2. TERAZOSIN-SPECIFIC EXCLUSION CRITERIA

Treatment-specific exclusion criteria for terazosin are detailed in **Section 3.2.1.2** of the protocol.

3. TREATMENT OF PARTICIPANTS: TERAZOSIN

3.1. PRODUCT INFORMATION: TERAZOSIN

- This trial will test terazosin hydrochloride.
- It is a licenced product used in hypertension and in benign prostatic hyperplasia[8], with a well-established safety profile. Data on terazosin in PD is available from two studies[6,7].
- Terazosin 1mg, 2mg, and 5mg tablets/capsules over-encapsulated in size 00 capsules with Microcrystalline Cellulose will be packaged, labelled and shipped to the central pharmacy by Sharp Clinical Services (UK) Ltd.
- Terazosin will be dispensed and distributed by the central pharmacy and shipped directly to participants homes at baseline (5-week titration pack), end of titration and every 6 months after for a total treatment duration of 36 months.
- Blinding will be maintained in appearance via over-encapsulation.
- The mean beta-phase half-life (the rate of decline due to the process of drug elimination due to metabolism) of terazosin is approximately 12 hours[9]

3.2. HANDLING CASES OF TRIAL TREATMENT OVERDOSE: TERAZOSIN

Management of trial treatment overdose is covered in **Section 5.8** of the protocol.

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EJS ACT-PD

Edmond J. Safra Accelerating Clinical Trials in Parkinson's disease: A Multi-arm Multi-stage Platform Trial for potential disease modifying approaches

Protocol Sub Study Appendix:
EJS ACT-PD Biosamples Sub-study

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ABBREVIATIONS

Abbreviation	Term
CI	Chief Investigator
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
DMP	Data Management Plan
DNA	Deoxyribonucleic Acid
EJS ACT-PD	Edmond J. Safra Accelerating Clinical Trials in Parkinson's Disease
FCI	Francis Crick Institute
GDPR	General Data Protection Regulation
GSL	Guilford Street Labs
LC	Liquid Chromotography
MAMS	Multi-Arm Multi-Stage
MS	Mass Spectrometry
MRC CTU	Medical Research Council Clinical Triaks Unit
PBMC	Peripheral Blood Mononuclear Cells
PD	Parkinson's Disease
PI	Principal Investigator
PIS	Participant Information Sheet
PwP	People with Parkinson's
SAA	Seed Amplification Assay
SSAC	Scientific Sample Access Committee
SNP	Single Nucleotide Polymorphism
STR	Short Tandem Repeat Profling
TMG	Trial Management Group
TMT	Trial Management Team
UCL	University College London

CONTENTS

1 BACKGROUND

Testing Disease Modifying Approaches in PwP remains significantly limited by (i) the lack of clarity in PD diagnostics, (ii) lack of confirmation of target engagement by the candidate intervention, (iii) the uncertainty regarding the utility and validity of stratification, and (iv) the absence of biomarkers that can detect and/or predict motor and non-motor progression (in routine clinical use).

This phase III multi-centre, interventional, multi-arm, multi-stage, randomised, double-blind, placebo-controlled MAMS platform trial, through its scale, design and associated rich datasets, is well suited to testing a range of innovations and advances in fluid biomarkers - this trial based research will ultimately set a precedent for how we may in future, 1) recruit precise populations of Parkinson's disease patients according to confirmed contributory biological processes related to genotype, alpha synuclein, tau, amyloid and other potential proteins or processes, 2) accurately measure disease progression and its modification in response to disease modifying interventions, and 3) predict which individuals may be better suited for which potential disease modifying interventions.

We have adopted a similar approach used by other longitudinal repositories that support biomarker research in PD, namely the Parkinson's Progression Markers Initiative[1] (established by the Michael J Fox Foundation), which aims to identify biological markers of Parkinson's risk, onset and progression that can be used for the development of new and better treatments, and to provide the broad research community a comprehensive, standardized, longitudinal data set and biosample library to enable validation toward clinical application of new findings.

The key aim of the EJS ACT-PD Biosample Sub-study is to create a large longitudinal biofluid resource that can be used as a biomarker discovery research platform. Critically, there are no available, verified biomarkers for CNS drug target engagement, for PD disease progression and its modification – therefore there are no objective biofluid markers that can contribute to the primary or secondary outcomes of the EJS ACT-PD trial. This sub-study aims to discover fluid biomarkers that will enable us to evaluate the impact of candidate interventions on Parkinson's disease.

The EJS ACT PD Biosample Sub-study will create the EJS ACT-PD Biorepository from the full trial through two sources (i) the collection of blood samples from all trial participants at screening and at the end of the trial, and the collection of these samples is included in the Main Trial protocol. (ii) the collection of additional blood samples and cerebrospinal fluid, and peripheral blood mononuclear cells samples from a subset of participants at multiple timepoints throughout the trial.

1.1 RATIONALE FOR INCLUSION INTO EJS ACT-PD

The generation of the repository of biofluids from the EJS ACT-PD trial will have three areas of impact:

- Understanding the trial population for precision medicine approaches – *See section 1.1.1*
- Confirming target engagement, and target pathway modification – *See section 1.1.2*

- Measuring disease progressions simultaneously with digital and molecular biomarkers – *see section 1.1.3*

1.1.1 UNDERSTANDING THE TRIAL POPULATION FOR PRECISION MEDICINE APPROACHES:

The EJS ACT-PD trial is an inclusive trial, and does not currently use any form of stratification. However the research sub-study will help to define whether there are subgroups of individuals who may have responded differently to other groups of individuals. One reason for variable responses to drugs is the underlying genetic basis, that can affect the type of PD that an individual has, and also can affect the way in which an individual responds to certain drugs. Genetic stratification is not used routinely in disease modifying therapy trials, although it has the potential to provide an important approach to stratify individuals for specific treatments in the future, as has been shown for other diseases where specific genotypes can predict disease progression, drug specific responses, and drug side-effects. All EJS ACT-PD participants are invited to undergo genotyping through the existing PD genotyping studies "PD Frontline"[3] and "GP2"[4], to enable such analyses to inform future stratification. This data will also be important to analyse in the context of the Biosamples sub-study where the genetic data and the the fluid biomarker data will together provide information that could be used in the future.

A precise biological definition of PD currently requires confirmation of alpha synuclein pathology using a seed amplification assay (SAA)[5] applied to cerebrospinal fluid collected at lumbar puncture. While lumbar puncture is not uniformly acceptable to trial participants (which would limit inclusivity), it is anticipated that within 2 years, there will be an equivalently sensitive test that can be performed on serum/plasma[6,7]. Approximately 90% of clinically diagnosed PD patients test positive for the alpha synuclein SAA. It is therefore evident that any therapy targeting alpha synuclein aggregation would have greater chances of success if recruitment/analysis were restricted to those testing positive for the SAA. By analogy, agents targeting other factors contributing to neurodegeneration, e.g. neuroinflammation or mitochondrial or lysosomal dysfunction may have greater chance of success among those with evidence of these processes being active at baseline. Thus the Biosamples sub-study has the potential to provide information on whether stratification could be performed based on pathways targeted by specific drugs.

1.1.2 CONFIRMING TARGET ENGAGEMENT, AND TARGET PATHWAY MODIFICATION:

By clearly identifying the process/target through which a disease modifying intervention is expected to act, it should be possible to get early confirmation of target engagement through accurate measurement of the relevant process/pathway using appropriate biofluids. Formal confirmation of CNS penetration of the candidate interventions will add to the confidence that the drug reached the target compartment, and then in the mechanism of action of these approaches.

1.1.3 MEASURING DISEASE PROGRESSION SIMULTANEOUSLY WITH DIGITAL AND MOLECULAR BIOMARKERS:

In parallel with this, the validation of digital biomarkers to provide the most sensitive capture of data related to human movement, is of enormous value in the evaluation of people with PD and agents that might slow down the rate of disease progression. It is increasingly clear that early changes in digital wearable measures can be useful predictors of long term clinically measurable worsening and patient reports of change in their function and/or quality of life. Furthermore, the integration of

digital disease progression with gene scores and molecular biomarkers of disease progression provides a unique and enriched dataset with the sensitivity to detect disease modification that is not captured by current methods (e.g., clinical scales).

1.2 JUSTIFICATION FOR SUB-STUDY

The aim is to create a large longitudinal resource to facilitate the early and long term evaluation of the impact of the candidate interventions on a range of objective candidate wet biomarkers, time-locked to detailed longitudinal clinical phenotypic data. The EJS ACT-PD MAMS Platform Trial design provides the ideal infrastructure to assess this impact in a large participant population.

This longitudinal resource will be generated from two sources of samples:

(a) The EJS ACT-PD biorespository has been created from the full trial with research samples (plasma, serum, buffy coat) from all trial participants collected at screening and end of trial/early termination (0 and 156 weeks). This will allow us to explore existing and novel emerging biomarkers and link them to a comprehensive clinical dataset. Details of the core EJS ACT-PD research samples can be found in the Main Trial Protocol.

(b) The EJS ACT-PD Biosamples sub-study utilises and adopts SOPs for sample collection that are harmonised with the Michael J Fox PPMI programme to ensure the most productive and standardised use of findings. It comprises sample collection from 400 trial participants, across a variety of different optional biofluids at multiple timepoints;

1) additional Interim 26ml blood samples at week 13, 26, 52
2) additional approximately 20ml blood samples at week 0 and at the end of trial participation (week 156) to allow storage of PBMCs (Peripheral Blood Mononuclear Cells), taken as 2x10mls tubes
3) cerebrospinal fluid at baseline visit and week 52 and at the end of trial participation (week 156)

The exact processes for collection and transfer of all samples to the central storage location at The Francis Crick Institute (FCI) are outlined in the EJS ACT-PD Sample Collection and Handling Manual.

Storage and analysis and PBMC processing of Biosample sub-study samples at The Francis Crick Institute will be done for exploratory research and will follow the principles and standards of sample processing, handling and biorepositories whilst not being required to meet the standards of Good Clinical Practice/Good Laboratory Practice.

1.3 EJS ACT-PD BIOSAMPLES SUB-STUDY OBJECTIVES

A. Standardised collection of wet biomarker samples from both the main trial and from the Biosample sub-study will be combined to generate a repository of samples to allow retrospective/prospective research studies and analyses to be performed.

B. Detection of CNS and peripheral drug levels will establish posthoc dose-efficacy relationships in both the periphery and in the CNS.
C. Evidence of candidate target and target pathway engagement will generate/establish biomarkers of target engagement to establish posthoc their relation to clinical outcomes.
D. Evidence of disease modification using candidate disease associated biomarkers and their relationship to clinical progression, and effects of treatment will improve the way in which we evaluate disease modifying therapies in trials in future.

2 SELECTION OF SITES AND SET UP

2.1 SITE INCLUSION CRITERIA

Sites will have the opportunity to participate in the EJS ACT-PD Biosamples sub-study, if they demonstrate the site capability and infrastructure to comply with SOPs for the collection of blood and/or collection of CSF samples. It is likely that sub-study participating sites will have high levels of experience with both blood and CSF collection (for example, Tier 3 sites). Specific Tier 3 sites with appropriate skills/infrastructure to perform PBMC processing will participate in the PBMC collection and processing aspect of the sub-study.

2.1 SET-UP REQUIREMENTS

Staff will be trained to undertake the Biosamples sub-study and named on the EJS ACT-PD Signature and Delegation Log of Responsibilities at trial sites. Biosamples sub-study training will be delivered by the EJS ACT-PD trial team as part of their trial site training. It will include practical guidance for sub-study delivery sample collection, processing, storage and shipment. This information will also be available to sites in the Sample Collection and Handling Manual. Training will be logged locally on the main trial Training Log. Only staff that have completed and documented this training should be responsible for Biosample sub-study related tasks. Sites should follow their local practice for venepuncture and observe safety practices including those in relation to discarding clinical waste and sharps.

All site personnel involved in the collection of samples for this sub-study should have previous training and experience in phlebotomy and/or lumbar puncture and CSF collection.

All training or documentation or approvals required to set up and activate the site to recruit for the sub-study will be obtained before the sub-study is activated at site.

3 PARTICIPANTS

3.1 PARTICIPANT INCLUSION CRITERIA

All trial participants attending Tier 3 sites (outlined in the main protocol) will be invited to participate in the EJS ACT-PD Biosamples sub-study. All participants will have been given the EJS ACT-PD Biosamples sub-study Patient Information Sheet and will have signed the EJS ACT-PD Biosamples sub-study Informed Consent Form and will have been given a copy.

At screening, eligibility for the EJS ACT-PD Biosamples sub-study will be confirmed after the screening visit based on:

1. Confirmation that the participant can attend for face to face visits for Interim blood sample collection at Week 13, 26, 52.
2. If consenting to PBMC collection, the participant will need to attend for face to face visits at Baseline and week 156.
3. If consenting to lumbar puncture, the participant will need to have confirmation of normal blood coagulation and platelet count > 50, and will need to attend for face to face visits at Baseline and week 156.

3.2 PARTICIPANT EXCLUSION CRITERIA

1. Participants that are unable to attend for face to face visits at the relevant timepoints.

2. Participants with contraindications to lumbar puncture will not be able to contribute Cerebrospinal fluid
   - This may include participants on anticoagulants, who have thrombocytopenia, or have undergone previous surgical fusion of the lumbar spine.
   - Any participants suspected of having raised intracranial pressure would not undergo lumbar puncture until investigations confirm this is a safe procedure.

3.3 NUMBER OF PARTICIPANTS

There is a target of 400 participants who will contribute the additional Interim blood sample collection at 13, 26, 52 weeks. There is a minimum target of 200 participants who will have both blood and CSF collection for the downstream assays. Progress on recruitment will be monitored regularly by the Trial Management Group, who, in turn will update and inform the MJFF of the recruitment progress.

The target for recruitment for PBMCs (Peripheral Blood Mononuclear Cells) is 200 participants. Due to the complex processing requirments for these samples, only a limited number of Tier 3 sites will be able/expected to participate.

The Biosample sub-study collection will be reviewed at intervals of 6 months in meetings with the sub-study leads, the project manager at the Crick, and representatives from the MRC CTU. The recruitment to the sub-study, and progress to these targets, and the demographic diversity of the sub-study participants will be reviewed, and any necessary changes will be made to amend the target, the site level recruitment, and delivery of the project. Any risks are outlined in the risk register to ensure proper mitigation steps are implemented if required.

3.4 SCREENING AND CONSENT PROCEDURES

The Biosamples sub-study participant information sheet (PIS) should be provided to participants at the same time as the main trial PIS (i.e. at least 72 hours prior to the in-person screening) to give participants sufficient time to read the sub-study information. The PIS will also be available on the trial website.

4 ASSESSMENT OF PARTICIPANTS

4.1 ASSESSMENT SCHEDULE

All EJS ACT-PD participants will have a blood sample collected at the screening visit as described in the core trial protocol. If the participant is found to be ineligible for the EJS ACT-PD trial subsequent to the screening visit, and does not proceed to randomisation, the participant will be informed as outlined in the main trial protocol and their samples will be destroyed.

Following completion of the Biosamples sub-study consent form and screening, eligible participants will have samples collected irrespective of, and blinded to their trial randomisation allocation.

Additional blood samples will be taken at subsequent in person visits visits at weeks 13, 26, 52 and 156. Assessment schedule and dates are shown in Table 1 below, and Appendix 1.

Eligible participants will have their additional CSF and/or PBMC samples collected (if applicable) at their trial baseline visit (in-person).

Sample collection data will be recorded as per the instructions outlined in the Sample Collection and Handling Manual.

4.2 PROVISION AND STORAGE

The EJS ACT-PD trial team will provide the kits and return envelopes/dry ice courier shipments to each study site as part of the set-up process and as needed. The kits will have been constructed by The Francis Crick Institute and checked to ensure all consumables have an adequate expiry date.

Biosample sub-study kits should be stored securely at study site in a locked facility.

Any expired kits should be disposed of as per local practice and EJS ACT-PD trial team and The Francis Crick team should be informed so that replacements can be provided.

4.3 SAMPLE COLLECTION

All participants consenting to Biosamples sub-study blood sample collection will have the following samples collected:

- Two tubes of 10ml blood and 1 tube of 6ml blood will be collected, centrifuged and aliquoted to generate:

(i) Plasma divided into 10 x 0.5ml aliquots
(ii) Serum divided into 10 x 0.5ml aliquots
These plasma and serum samples will provide a resource for future analyses of candidate diagnostic/prognostic/ pathophysiological investigations - these measures

will, in future, aid the mechanistic stratification of participants to enrich for those most likely to respond to a known DMT's mechanism of action.

(iii) One 6ml aliquot of whole blood (frozen) will be stored, and utilised for DNA extraction for a SNP panel analysis (STR profiling) to confirm the identity of the samples matches the sample identity from previous timepoints.

(iv) One Buffy Coat sample- Using the blood sample collected for the plasma aliquots and following centrifuge and aliquoting plasma samples, the residual contents of the blood sample will contain Red blood cells beneath a "Buffy Coat" layer containing a mixture of white blood cells. This buffy coat layer will be collected into a separate aliquot and stored.

Participants consenting to optional Cerebrospinal fluid (CSF) sample collection will have the following samples collected at baseline and 156 weeks :

- 15 mls CSF taken in a polypropylene container for centrifugation, then divided into 30x 0.5ml aliquots in 2ml polypropylene vials (max 30 x 0.5 aliquots per participant).

Participants consenting to optional PBMC sample collection will have the following samples collected at Baseline and 156 weeks;

- 20 mls whole blood to yield a total of 3 x 0.5ml of PBMC (total 1.5ml)

Due to the interference of lipid content in CSF specimens collected for biomarker evaluation, it is strongly advised that CSF samples be collected after an 8 hour fast (no food or drink except fluids such as water, tea, black coffee). If fasting is not achievable, a participant should be on a low-fat diet for at least 8 hours prior to sample collection.

Note: Processing of these samples must follow the instructions in the EJS ACT-PD Sample Collection & Handling Manual

Table 1: Schedule of Biosamples sub-study blood panels for consented participants

		Baseline	Week 13	Week 26	Week 52	Week 156
Sample type	**Recruitment Target**					
Blood samples☐	400 participants		✓	✓	✓	
CSF samples	200 participants	✓			✓	✓
Peripheral blood mononuclear cell samples (PBMCs)	200 participants	✓				✓

☐Taken in addition to screening and 156 week/End of trial main trial research bloods

4.4 ASSESSMENT DATA COLLECTION

Standard operating procedures for sample collection will reproduce the methods used in the PPMI biosample collection protocol to ensure quality and consistency and allow comparability across studies and samples.

The serum/plasma samples will allow confirmation of peripheral target engagement by the active treatments, and the CSF samples will allow confirmation of central target engagement by the active treatments. Samples will be batched and sent to the partner Guildford Street Labs from FCI, for the following drug level analyses:

A. drug levels in CNS and serum at a single timepoint (52 weeks)
B. target engagement at a single timepoint (52 weeks)
C. sustained target engagement across three timepoints (0 - baseline, 52, 156 weeks)

This research an relevant assays and therefore results of these drug level analyses are entirely exploratory, and have not been validated as directly causative in the neurodegenerati processes of Parkinson's disease and will not be used for the primary or secondary outcomes in the trial.

Drug Arm B, TELMISARTAN[8]: Telmisartan drug levels will be measured using Liquid Chromotography/ Mass spectrometry (LC/MS) in serum and CSF, confirming the CNS penetration of telmisartan. Successful target and target pathway engagement will result in consistent changes in a Neuroinflammatory panel (CRP, TNF-alpha, Ifn-Gamma, IL-1ß, IL-6, IL-8, IL-10), as well as levels of phospho AkT in brain derived extracellular vesicles isolated from serum. AT1R antibody levels will be measured to assess whether Telmisartan efficacy is influenced by their presence.

Drug Arm C, TERAZOSIN[9]: Terazosin drug levels will be measured using LC/MS in serum and CSF, confirming the CNS penetration of terazosin. Successful target engagement will result in higher levels of blood ATP and HSP-90 will be measured in serum and CSF. Terazosin has anti-inflammatory effects, and therefore the neuroinflammatory panel will capture target pathway engagement. PGK1: PGK1 activity levels will be measured.

Mechanistic Studies

These samples will be used for baseline confirmation of the major biological processes of PD, namely alpha synuclein aggregation (exosomal, and/or SAA), testing for co-pathology (phospho-tau and beta amyloid), and understanding the baseline associated pathogenic pathways on an individualised level (e.g. presence of active neuroinflammation, or mitochondrial dysfunction). Biomarker identification utilises a wide range of detection technologies, including measurements of RNA transcripts, the proteome, lipidome, and metabolome, and these will be used for (i) detection of markers of disease modifying therapy mechanism of action, (ii) detection of subtypes of Parkinson's disease within the trial cohorts, and (iii) progression of Parkinson's disease. We anticipate that these measures will, in future, aid the mechanistic stratification of participants to enrich for those most likely to respond to a known disease modifying therapy's mechanism of action[10].

One 6ml aliquot of whole blood (frozen) will be stored, and utilised for DNA extraction for an STR profile analysis which includes a minimum number of loci markers to confirm the identity of the samples matches the sample identity from previous timepoints.

4.5 DISTRIBUTION, STORAGE AND ACCESS TO BIOSAMPLES

The EJS ACT-PD biorepository will form a unique resource that will be of value to researchers internationally, fulfilling objectives;

A. Standardised collection of wet biomarker samples for storage to allow retrospective/prospective analyses.

B. Detection of CNS and peripheral drug levels to establish posthoc dose-efficacy relationships in both the periphery and in the CNS, serum, plasma and CSF sub-study and core trial protocol samples will be provided to the sub-study partner, Guildford Street Laboratories to perform drug level testing in the CSF and in the serum/plasma.

C. Generate evidence of target and target pathway engagement to establish biomarkers of target engagement and their posthoc relation to clinical outcomes (for research purposes only) for the serum/plasma and CSF samples, will be provided to Guildford Street Laboratories for target pathway analyses for the interventions telmisartan and terazosin. Additionally, samples will be provided to other third parties, external laboratories, partners and academic collaborators, for biomarker research analyses that include target/target pathway biomarkers and disease biomarkers.

D. Generate evidence of disease modification using candidate disease associated biomarkers and their relationship to clinical progression, and effects of treatment, samples may be provided to third parties, external laboratories, partners and academic collaborators for biomarker analyses that include disease specific biomarkers. Specific EJS ACT-PD Biomarker sub-study contracts and agreements will be established between the Biorepository and the relevant third parties/external labs/academic collaborators prior to sample provision. All analyses performed by third parties, that are related to the sub-study objectives B-D will be shared with the EJS ACT-PD Biosample Team.

Community Access to the Biorespository: Access to the biorepository for academic collaborators during, and following the completion of the trial, will be established for the purposes of advancing Parkinson's research. Access will be under the governance of the Trial Access Committee (see Section 17 of the Main Trial Protocol).

Workflow for access to the EJS ACT-PD Biorepository: Briefly, a project application form is completed and submitted to the Biorepository Manager. This will include a sample/data release request.

While the EJS ACT-PD trial is open, the Trial Management Group (TMG) will determine the potential eligibility and feasibility, and undertake a technical, logistical and governance review of the proposed study for access, ensuring correct documentation is submitted, and that the proposed project aligns with the main trial protocol (Section 10.1.1) regarding access, consent, and ethical approval. If approved, a sample and data sharing agreement will be completed.

On completion of the trial, scientific and statistical review will be carried out by a Scientific Sample Access Committee. The processes will be overseen by the Biorepository Manager. See Appendix 2 for post trial closure sample access requests flow chart.

A 5 year review of the research biorepository will be performed to ensure (i) it is a relevant Research Tissue Bank (researchers still access it) (ii) its running costs (staffing and freezer storage) are appropriately allocated (iii) a review of all projects (meta-analysis) to determine direction of research (iv) it is appropriately costed/resourced for the following 5 years.

4.6 INTERVENTION MODIFICATIONS

There are no planned modifications to the Storage and Access schedule.

4.7 COMPLIANCE AND ADHERANCE

All sites will be given training for sample collection, and will follow EJS ACT-PD Sample Collection & Handling Manual for sample collection.

Plasma, serum, and buffy coat aliquots collected for the EJS ACT-PD trial will be stored frozen at participating sites at -70, or -80˚ C. All sites will ship their frozen plasma & serum microtubes in batches periodically to The Francis Crick Institute.

Sites will be monitored to ensure appropriate SOPs are being followed. Samples received will be subject to routine testing for quality assurance, including random checks for sample identity to mitigate any risks of sample labelling errors.

4.8 PROTOCOL DEVIATIONS

A protocol deviation is defined as any change, divergence, or departure from study design or procedures. Sites will be trained on identifying, categorisation and recording protocol deviations during the site initiation training. Protocol deviations should be handled and reported according to the timelines given in the relevant section of the main study protocol. Any deviations which impact the Biosamples sub-study will be communicated between the main trial and sub-study teams for discussion and appropriate action.

4.9 EARLY STOPPING AND COMPLETION OF FOLLOW UP

All participants are free to withdraw at any time from the Biosamples sub-study without giving a reason. Participants may withdraw from the Biosamples sub-study without affecting their participation in the main trial. Early cessation of the sub-study follow-up will be recorded in participant medical record.

Participants who are discontinued on the main trial treatment (e.g. due to change in diagnosis or starting specific treatment) but remain in the main trial follow-up, may remain in the Biosamples sub-study.

Participants who are stopped on a treatment arm due to lack of activity can be re-randomised to either a new treatment or placebo. Participants should be re-screened and enrolled to the Biosamples sub-study. The Biosamples Study Management Group, in collaboration with EJS ACT-PD trial team will advise when recruitment to Biosamples sub-study will cease.

Participants who withdraw or are removed from the main trial will be removed from the Biosamples sub-study. Information about participants who withdraw from the main trial will be provided to the Biosamples sub-study team by the main trial team.

Previously collected Biosamples sub-study data from participants who stop follow-up early will be kept and included in the analysis, in line with the GDPR exemption which states that the ‘right to erasure’ of data does not apply where data processing is necessary for the performance of a task in the public interest in the area of public health, with the appropriate safeguards in place.

5 STATISTICAL CONSIDERATIONS

5.1 METHODS

All the assays performed on biosamples collected from EJS ACT-PD will be exploratory. The 13 week timepoint samples and associated data will be used to estimate the effect size and associated variance for each potential measure of target engagement. These estimates can then inform on the number of samples needed to confirm sustained target engagement at subsequent timepoints.

5.2 OUTCOME MEASURES

The outcome measures include the following metrics, which will be compared in placebo vs active drug across the trial period:

1. Drug Levels in peripheral fluids (serum/plasma) compared with CSF and compared to baseline.
2. Target engagement markers in peripheral fluids (serum/plasma) compared with CSF and compared to baseline.
3. Target pathway markers in peripheral fluids (serum/plasma) compared with CSF and compared to baseline.
4. Disease progression markers in peripheral fluids (serum/plasma) compared with CSF and compared to baseline.

5.3 SAMPLE SIZE

The EJS ACT-PD Biosamples sub-study will include a minimum 400 participants. There have been no formal sample size calculations for the Biosamples sub-study. This is exploratory study, and therefore is not powered for confirmatory biomarker effects. To estimate the power of the whole study, the data from the analyses from the first batch of 40 samples collected at the 13 week timepoint will allow estimation of effect sizes for drug levels/target engagement, and indivudal variation, and thus will allow the team to generate a formal power calculation to estimate the number of participants required for formal confirmation of the effect size of drug levels/target engagement.

5.4 ANALYSIS AND ANALYSIS PLAN

Analysis will be performed by an unblinded statistician following 13 week analysis. Unblinding will be confined to the arm (A – SoC plus placebo, B – SoC plus telmisartan or C – SoC plus terazosin) only. These analyses will be exploratory only and will not be used to make definitive decisions regarding continuing/stopping recruitment or follow up of trial arms, but will inform research regarding differential responses from subgroups of participants, and how such information can be used to inform on future trial design planning.

Linear mixed-effect regression analyses with a random effect per subject will evaluate changes in outcomes as a function of Randomisation allocation. Covariates will include Age at Baseline, Sex and disease duration.

Subsequent analyses will be repeated once sufficient numbers of samples from later timepoints have been collected, based on the variance observed at the 13 week timepoint.

Data required for the analyses of the substudies, for example participant metadata held at CTU, and biosample analyses held at the FCI will be shared between the EJS ACT-PD project team leads at the MRC CTU, UCL and FCI locations. Data can be shared with collaborators of the sub-study under data sharing agreements.

Access to samples for mechanistic studies will continue beyond the length of the trial

Sample integrity will be monitored throughout the sub-study using STR profiling to confirm sample identity

5.5 MONITORING

Monitoring will be conducted according to the EJS ACT-PD main trial monitoring plan, which will also cover monitoring responsibilities for the sub-study.

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APPENDIX 1 – SCHEDULE OF ASSESSMENT

Activity	**Screening**	**Randomisation**	**Week**												**Early Termination**	**Unscheduled Visit**
			Week 0 (Baseline)	**Weeks 1-5 (Titration)**	**Week 13 (month 3)**	**Week 26 (month 6)**	**Week 39 (month 9)**	**Week 52 (month 12)**	**Week 65 (month 15)**	**Week 78 (month 18)**	**Week 104 (month 24)**	**Week 130 (month 30)**	**Week 156 End of study visit (month 36)**	**Week 165 Safety follow-up visit (month 38)**		
Window		Ideally within 3 weeks of screening visit *(maximum of 4 weeks)*	within 4 weeks of screening visit *(maximum of 6 weeks)*	Ideally within 48 hours of completing baseline	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks		
Location	In-person	Telephone call+	Remote ~ or in-person	Telephone call (weekly)	In-person	In-person	Telephone Call	In-person	Telephone Call	Remote ~ or in-person	Remote ~ or in-person	Remote ~ or in-person	In-person	Remote ~ or in-person	As required	As required
Sub-Study activities:																
Informed consent	x															
Blood panel (Research boods) [A]					X	X		X								
Cerebrospinal Fluid [B]			x					X					X			
Peripheral blood mononuclear cells [C]			x										X			

Activity	Screening	Randomisation	Week												Early Termination	Unscheduled Visit
			Week 0 (Baseline)	Weeks 1-5 (Titration)	Week 13 (month 3)	Week 26 (month 6)	Week 39 (month 9)	Week 52 (month 12)	Week 65 (month 15)	Week 78 (month 18)	Week 104 (month 24)	Week 130 (month 30)	Week 156 End of study visit (month 36)	Week 165 Safety follow-up visit (month 38)		
Coagulation factor[B]	X												X			

Notes / Annotations:

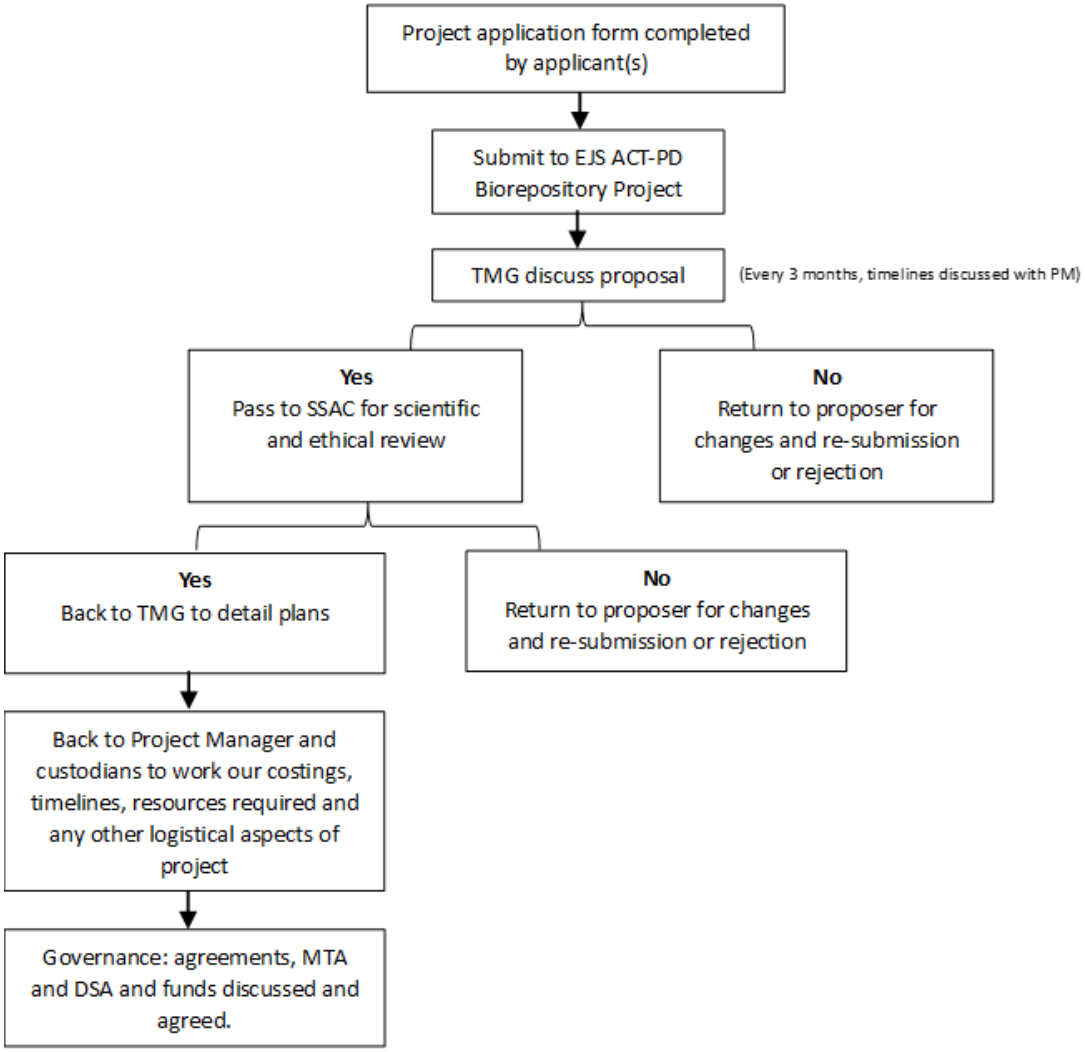
~: Remote visit should ideally be conducted as a video call to complete assessments, but if needed the visit can be conducted via a telephone call with abbreviated assessment and will be encouraged to have an in person visit at 52 weeks, 104 weeks and 156 weeks.

A: Taken in addition to screening and Week 156 Core trial research bloods

B: If consented to CSF sample collection

C: If consented to PBMC sample collection

APPENDIX 2 – SAMPLE ACCESS REQUEST FLOW CHART



EJS ACT-PD

Edmond J. Safra Accelerating Clinical Trials in Parkinson's disease: A Multi-arm Multi-stage Platform Trial for Potential Disease Modifying Approaches

Digital Measures Sub-study Appendix

Version: **1.0**
Date: **19-May-2025**

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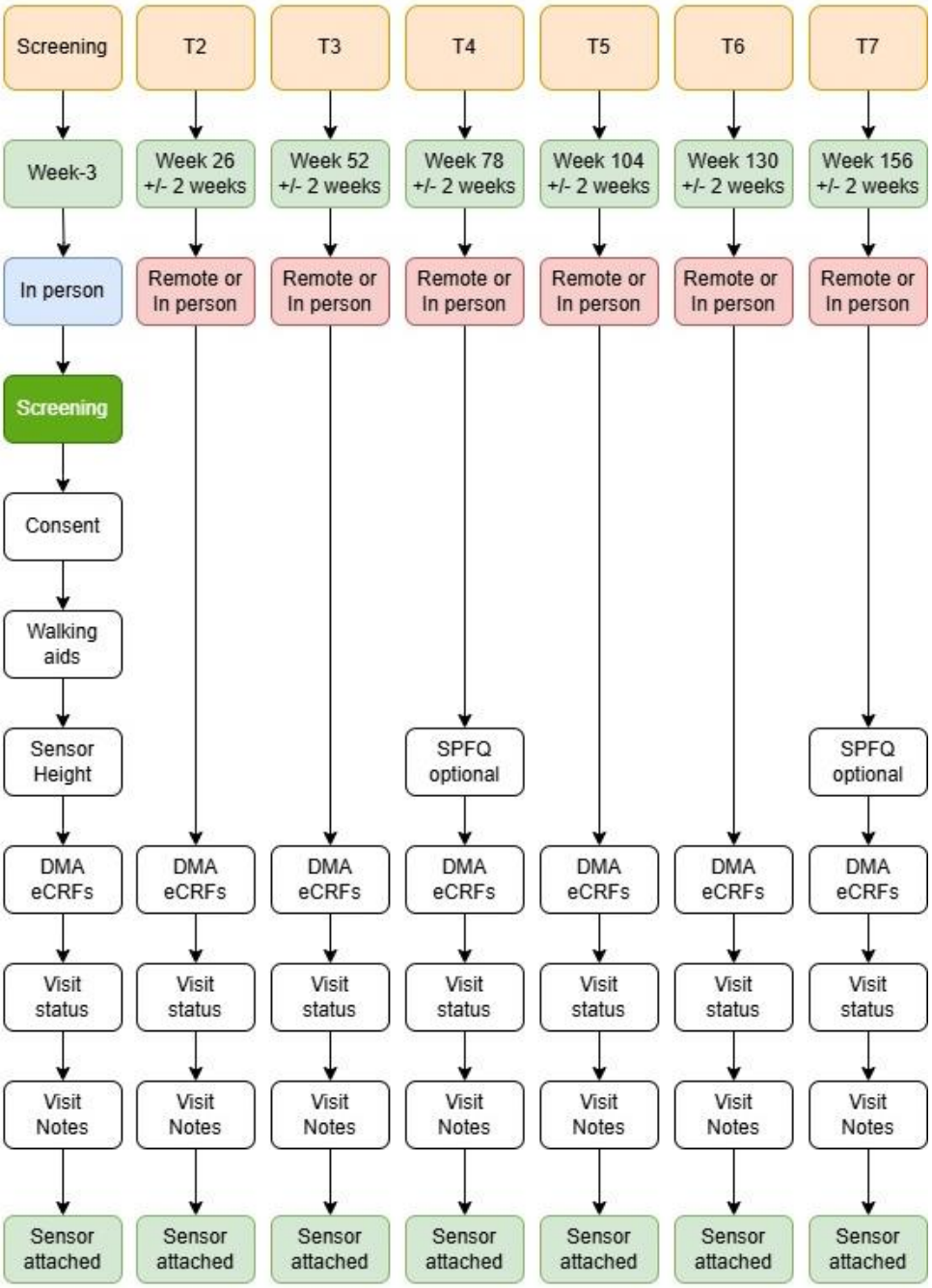
Date: 20-May-2025

ABBREVIATIONS

Abbreviation	Term
CI	Chief Investigator
DMA	Digital Mobility Assessment
DMO(s)	Digital Mobility Outcome(s)
DMP	Data Management Plan
EJS ACT-PD	Edmond J. Safra Accelerating Clinical Trials in Parkinson's Disease
EU IMI	European Union Innovative Medicines Initiative
GDPR	General Data Protection Regulation
MAMS	Multi-Arm Multi-Stage
MDS-UPDRS	Movement Disorders Society Unified Parkinson's Disease Rating Scale
MRC CTU	Medical Research Council Clinical Research Unit
MRI	Magnetic Resonance Imaging
NU	Newcastle University
OSM	Observational Study Management
PD	Parkinson's Disease
PI	Principal Investigator
PIS	Participant Information Sheet
PwP	People with Parkinson's
SMG	Study Management Group
SPFQ	Study Participant Feedback Questionnaire
TMG	Trial Management Group
TMT	Trial Management Team
UCL	University College London

ASSESSMENT SCHEDULE

Fig 1. EJS-ACT-PD Digital Mobility Assessment (DMA) Timelines



Notes:
The SPFQ is completed at Baseline which does not show on the chart here (3-4 weeks after T1). This will include questions related to the digital mobility assessment (DMA).
There is a DMA eCRF which is completed when issuing the device and one completed when the device is returned (both will be available in the same visit).

CONTENTS

1 BACKGROUND:

Parkinson's disease (PD) is the fastest growing neurological condition in the Western world, with over 8.5 million people estimated to be affected worldwide[1]. Over the last 30 years the global burden has more than doubled due to the ageing population, optimised management of motor disease and environmental factors[2]. PD can thus be considered an age-associated condition, in which gait disorders and their consequences, most notably falls, are common manifestations. Even at the diagnosis stage, gait impairments can be evident and may respond only selectively to treatment[3]. Gait disturbance can have significant consequences, as discrete gait characteristics predict future falls, even in those who are falls naïve [4]. Activity levels are significantly lower in people with Parkinson's (PwP) compared to controls[5] and decline annually[6]. Gait impairment, activity reduction and subsequent falls risk results in loss of independence, loss of mobility and fear of falling; all of utmost importance to people with Parkinson's[7].

Existing tools to assess PD outcomes, including gait and mobility loss, are based on performance, patient self-reporting and one-off assessments (using rating scales such as the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS[8])); these are resource intensive and lack sensitivity, which limits therapeutic development and clinical management. The fluctuating nature of PD further reduces reliability and validity of these measures due to the intermittent nature of assessment. There is a lack of effective assessments of gait and wider mobility in PD and in other conditions with significant similar impacts, reflected by the paucity of mobility outcomes used in the decision-making process relating to market authorisation of drugs by the European Medicines Agency[9]. This is despite the accepted importance of mobility and the recognition that mobility loss – through gait impairment and postural control – is a fundamental feature of PD.

Recent work has explored quantitative assessment of gait (both in the laboratory and in free-living conditions) to complement clinical assessment of PD. Gait impairment is observed in the prodromal period[10-13], and deteriorates over time[3, 14]. Gait can thus be used to monitor progression in PD and is sensitive to change in both laboratory[15] and real-world settings[16-18], with some evidence that it may be more sensitive to change than using established gold standard instruments such as the MDS-UPDRS[15, 17]. However, significant evidence gaps remain, with requirement for validation of existing gait and mobility measurement tools in larger and generalisable data sets, to enable evolution of use of these tools to clinical trials and clinical care[19].

The five-year EU IMI funded Mobilise-D study (GA No. 820820, www.mobilise-d.eu) aimed to address these gaps by developing and validating tools to objectively measure mobility and gait using a digital device to measure digital mobility outcomes (DMOs) in individuals living with chronic conditions, including PD[20]. The Mobilise-D project established a large biobank of DMO data and developed validated tools and methods for DMO collection. The work of Mobilise-D has removed barriers to adoption of mobility assessment through generic solutions for implementation that are standardised, acceptable, feasible and scalable. These methods have been endorsed and informed by the patients who will use them.

1.1 RATIONALE FOR INCLUSION INTO EJS ACT-PD

The aim of this Digital Measures sub-study within the EJS ACT-PD trial is to establish the validity and practical utility of DMOs in a clinical trial, both cross-sectionally and longitudinally. The sub-study will determine whether objectively measured DMOs are able to detect or predict PD progression as measured by the trial's primary outcome measure – MDS-UPDRS parts I and II, which may inform design of future trial arms.

The validation of digital biomarkers to provide the most sensitive capture of data related to human movement is of enormous value in the evaluation of people with PD and agents that might slow down the rate of disease progression. It is increasingly clear that early changes in digital wearable measures can be useful predictors of long term clinically measurable worsening/patient reports of change in their function/quality of life. Furthermore, the integration of digital measures of disease progression with genetic and molecular biomarkers provides a unique and enriched dataset with the sensitivity to detect disease modification that is not captured by current methods (e.g., clinical scales).

1.2 JUSTIFICATION FOR DIGITAL MEASURES SUB-STUDY

The aim of this sub-study is to understand whether a digital measure of motor performance will detect changes over time reflective of Parkinson's disease progression with greater sensitivity than traditional rating scales. This sub-study will utilise the Mobilise-D digital mobility outcome (DMO) algorithms using a digital device in all trial participants, to objectively capture indices reflective of real-world mobility performance. The EJS ACT-PD MAMS Platform Trial provides the perfect infrastructure to assess the usefulness of these measures in a large participant population. This will provide extensive data to:

(a) support development and validation of a digital biomarker to inform Go/No-go decisions at early analysis points;
(b) support regulatory qualification of novel surrogate digital study endpoints.

Both objectives could greatly speed up the process of assessing the effectiveness of an intervention and more rapidly improve patient lives.

1.3 SUB-STUDY OBJECTIVES

1. To establish the validity (as measured by correlation with the primary and secondary outcomes, prediction of primary and secondary outcomes and change over time) and practical utility (as assessed by compliance and adherence measures) of the DMO.
2. To evaluate the participant experience of the digital measure study, as assessed by the Study Participant Feedback Questionnaire (SPFQ).

1.4 OUTCOME MEASURES

Validity will be measured as:

1. Correlation of DMOs with the main trial outcomes
2. Ability of DMOs to predict the main trial outcomes

3. Correlation of changes in DMOs with change in the main trial outcome
4. Progression of DMOs over time
5. Difference in DMOs between different treatment arms

Practical utility will be measured as:

1. Number of participants who agree to wear the digital device
2. Compliance with digital device, as measured by number of days of meaningful data per participant
3. Adherence, as measured by the number of digital assessments undertaken by participants

Acceptability will be measured using the SPFQ (embedded questions within the main trial SPFQ).

2. SELECTION OF SITES AND SET UP

2.1 SITE INCLUSION CRITERIA

All sites selected to participate in EJS ACT-PD are eligible to take part in the Digital Measures sub-study.

2.2 SET-UP REQUIREMENTS

Staff will be trained to undertake the Digital Measures sub-study and named on the EJS ACT-PD Signature and Delegation Log of Responsibilities at trial sites. Digital Measures sub-study training sessions will be delivered by Newcastle University (NU) staff as part of their trial site training. It will include practical guidance for study delivery including device set-up, attachment, data upload and device returns. Training and delegation will be logged locally on the main trial Training Log and Signature and Delegation of Responsibilities Log. Only staff who have competed this training will be granted access to the sub-study database, the Inkspot Observational Study Management (OSM) Platform.

Once the study training is complete, sites must complete and return a Digital Measures sub-study set-up checklist, confirming training of staff involved in the digital sub-study, storage of associated documentation and any paper forms, receipt and storage of digital mobility devices and staff access to Inkspot OSM platform. NU will review the study set up checklist and issue approval for the sub study to commence once activated to EJS ACT-PD. At activation, access to the Inkspot platform will be provided to trained and delegated site staff.
New staff who join a trial site after initial training must also complete the sub-study training and be appropriately delegated prior to working on the Digital Measures sub-study and to obtain access to the Inkspot platform. This training will be recorded on an NU New Staff Form and sent to NU. The training and delegation should also be documented on the main trial Training Log and Signature and Delegation of Responsibilities Log.

The Digital Measures sub-study will be managed by the Digital Measures Project Manager at NU. This will involve organisation of study set-up and training, oversight of recruitment and data collection, management of digital devices and study resources, and study close-down.

The Data Manager and Statistician at Newcastle University will perform regular data monitoring checks as documented in Data Management Plan and Monitoring Plan.

3. PARTICIPANTS

3.1 PARTICIPANT INCLUSION CRITERIA

All EJS ACT-PD participants are eligible to take part in the Digital Measures sub-study. Participants must additionally:

1. Be able to walk 2 metres with or without walking aids
2. Have intact skin on the lower back

3.2 PARTICIPANT EXCLUSION CRITERIA

1. Known allergy to adhesives

3.3 NUMBER OF PARTICIPANTS

We will recruit 1200 participants to the Digital Measures Study, up to 400 participants per arm. There have been no formal sample size calculations for the Digital Measures Study.

3.4 SCREENING AND CONSENT PROCEDURES

The Digital Measures sub-study participant information sheet (PIS) should be provided to participants at the same time as the main trial PIS (i.e. at least 72 hours prior to the in-person screening) to give participants sufficient time to read the sub-study information. The PIS will also be available on the trial website.

Written informed consent to participate in the Digital Measures sub-study should be obtained at the main trial in-person screening.

Participants who are ineligible for the main trial and are not randomised will not be consented to the sub-study. If a participant has been randomised in the main trial without being consented to the Digital Measures sub-study, screening and consent for the Digital Measures sub-study can take place at the 26-week follow-up visit, provided this is conducted by appropriately delegated personnel. This visit should be in-person but can be a home visit by a study nurse/practitioner where local arrangements allow.

All aspects of the Digital Measures sub-study should be discussed with potential participants including a review of the eligibility criteria. It must be made clear that the participant may refuse to participate in the Digital Measures sub-study, and that declining will not affect participation in the main trial or their standard clinical care in any way. Participants must also be informed that they are free to stop their participation in the Digital Measures sub-study at any time, and that withdrawing will not affect their participation in the main trial, or their standard clinical care.

The full consent process must be documented in the participant's medical notes and confirmation of receipt of the PIS and consent was obtained on the Inkspot Platform. The participant ID used in the

main trial will be recorded on the Digital Measures sub-study consent form and on the Inkspot Platform.

Participants whose trial participation ceases following treatment arm closure due to lack of activity can attend a new screening visit and be considered for re-randomisation as documented in main trial protocol. Participants who attend a new screening visit for the main trial should also be screened and re-enrolled in the Digital Measures sub-study under their new participant ID. The Digital Measures Study Management Group, in collaboration with MRC CTU will advise when recruitment to Digital Measures Study will cease.

4 ASSESSMENT OF PARTICIPANTS

4.1 BASELINE DMO ASSESSMENT (at main study screening visit)

Following completion of the Digital Measures sub-study consent form and screening, the participant will be provided with a digital device for their first DMO data collection and trained in its application. Instructions for attaching the device are provided as an appendix to the PIS (including a link to the video) and should be provided to and discussed with the participant. This includes instructions on how and when to remove and reattach the device, wear instructions, how to return the device, and whom to contact if there are any questions or issues.

If the participant is able to reach their lower back, the site study team will observe the participant attaching the device, providing guidance and assistance if required (supervised application). This should be used as training for future device application, and to identify whether the participant is able to do this without assistance. Alternatively, the site study team may supervise a friend or family member attaching the device to the participant. If the participant is unable to reach their lower back, and does not have assistance, the site study team should attach the device to the participant. The date and time the device should be removed must be documented on the instruction sheet by the site study team.

Clinical data required for processing DMO data will be collected (sensor height from the ground) and entered into the Inkspot Platform. Participant height will be obtained from main trial database. The site study team should provide the participant with a pre-paid return envelope to return the device to the study site.

The device should be worn continuously for seven days, including during sleep and washing. Additional adhesives should be provided in case the participant needs to remove and reattach the device. It should be noted that the device must be removed for MRI scanning or prior to lumbar puncture procedure. The participant will then remove the device on the date and time provided by the site study team and send back to them in the pre-paid envelope along with the completed Digital Device Log.

If the participant is found to be ineligible for the EJS ACT-PD trial subsequent to the screening visit, and does not proceed to randomisation, the participant will be informed as outlined in the main trial protocol. The participant will be asked to return the device using the pre-paid return envelope.

4.2 ASSESSMENT SCHEDULE

The baseline DMO data collection will be initiated at the main trial screening appointment. Follow-up DMO data collection will be at the 26-weekly main trial appointments (Weeks 26, 52, 78, 104, 130 and 156). Assessment schedule and dates are shown in Figure 1, above and Appendix 1, below.

The DMO data collection should commence on the day of the study appointment. The measurement may be delayed by up to 14 days after the study appointment or completed up to 14 days in advance of the study appointment. If it is not possible to complete the measurement within 14 days of the appointment, the DMO should not be completed and the reason recorded on the Inkspot Platform by the site study team.

If the DMO data collection is interrupted (e.g. device not working properly or participant is unwell), the measurement may be repeated (up to 14 days after the appointment date).

If a follow-up appointment for the main trial is not completed for any reason, participants may still wear the device for the 7-day period and contribute DMO data relating to the missed appointment.

4.3 PROVISION AND STORAGE

NU will provide the devices, adhesives and return envelopes to each study site as part of the set-up process and as needed. The devices will have been checked and calibrated by the NU team to confirm adequate battery function and labelled to show the correct orientation for affixing to the body.

Digital devices should be stored securely at study site in a locked cabinet.

Any broken or faulty devices should be taken out of use and returned to the Digital Measures sub-study team at NU who will provide a replacement. To protect the life of the devices' lithium batteries, devices should be used on rotation and stored in a fully charged state, as leaving uncharged for long periods may reduce battery longevity.

4.4 DATA COLLECTION

For all in-person appointments the device may be applied by the participant, with site study team supervision as required. A family member or friend may also assist with the device application, or a member of the site study team can apply device for the participant. Device instructions, spare adhesives and a pre-paid return envelope will be provided to participants. Participants will be advised when to remove the device; the date and time of removal will be recorded on the instruction sheet.

For all remote appointments, the digital device, instructions, adhesives and a pre-paid return envelope will be sent out to participants by the site study team ahead of the appointment date. The time and date the device should be attached and removed will be documented on the instruction sheet. The device attachment (positioning and orientation) should be checked by the study team during the main trial video call.

In the exceptional circumstance that the participant is unable to apply the device, and there is nobody available to assist, a home visit by site staff may be required.

Before each appointment (remote or in-person), site staff will:

- Ensure the device is fully charged and in good working order.
- Log the device ID against the participant ID and study timepoint on Inkspot Platform.
- Provide adequate spare adhesives.
- Provide a pre-paid return envelope.
- Provide written instructions including date and time device should be attached/removed.

Once device is returned, site staff will:

- Clean the device and check carefully for any damage (e.g. cracks, tears in casing etc).
- Check file size and remaining battery charge. A full AX6 7-day file should be approximately 750MB. If the measurement is incomplete, this is likely due to battery not being fully charged or battery failure.
- Upload DMO data to the Inkspot Platform within 24 hours of device return. Upload can take up to an hour.
- Record DMO data collection details and dates on the Inkspot Platform (outlined in the Digital Measure Study manual, including data collection started/ended, device/visit status).
- Record walking aid data on Inkspot platform.

Detailed instructions for uploading data from digital device and using the Inkspot Platform is outlined in the Digital Measures sub-study Assessor Manual.

4.5 COMPLIANCE AND ADHERENCE

The NU Data Manager will monitor the upload of DMO data to the Inkspot Platform, ensuring expected data have been uploaded within a month of the scheduled visit date and contacting sites where this has not occurred, or missing data not accounted for. These checks are documented in sub-study Data Management Plan (DMP) and Monitoring Plan. For monitoring and compliance purposes the main trial team may be granted access to the Inkspot platform as required and access to the main trial database granted to the NU Data Manager, if required.

4.6 COMPLIANCE AND ADHERENCE

A protocol deviation is defined as any change, divergence, or departure from study design or procedures. Sites will be trained on identifying, categorisation and recording protocol deviations during the site initiation training. Protocol deviations should be handled and reported according to the timelines given in the relevant section of the main study protocol. Any deviations which impact the digital measures sub-study will be communicated between the main trial and sub-study teams for discussion and appropriate action.

4.7 EARLY STOPPING AND COMPLETION OF FOLLOW UP

All participants are free to withdraw at any time from the Digital Measures sub-study without giving a reason. Participants may withdraw from the Digital Measures sub-study without affecting their

participation in the main trial. Early cessation of the sub-study follow-up will be recorded in participant medical record and on the Inkspot OSM Platform. If a participant provides a reason for withdrawal this should be documented in the Inkspot OSM Platform

Participants who are discontinued on the main trial treatment (e.g. due to change in diagnosis or starting specific treatment) but remain in the main trial follow-up, may remain in the Digital Measures sub-study.

Participants who are stopped on a treatment arm due to lack of activity can be re-randomised to either a new treatment or placebo. Participants should be re-screened and enrolled to the Digital Measures sub-study. The Digital Measures Study Management Group (SMG), in collaboration with EJS ACT-PD trial team will advise when recruitment to Digital Measures Study will cease.

Participants who withdraw or are removed from the main trial will be removed from the Digital Measures sub-study. Information about participants who withdraw from the main trial will be provided to the Digital Measures Study team by the main trial team.

Previously collected Digital Measures sub-study data from participants who stop follow-up early will be kept and included in the analysis, in line with the GDPR exemption which states that the 'right to erasure' of data does not apply where data processing is necessary for the performance of a task in the public interest in the area of public health, with the appropriate safeguards in place.

4.8 MONITORING

Monitoring will be conducted according to the EJS-ACT PD main trial monitoring plan, which will also cover monitoring responsibilities for the sub-study.

5 STATISTICAL CONSIDERATIONS

5.1 OUTCOME MEASURES

Validity will be measured as:

1. Correlation of DMOs with the main trial outcomes
2. Ability of DMOs to predict the main trial outcomes
3. Correlation of changes in DMOs with change in the main trial outcome
4. Progression of DMOs over time
5. Difference in DMOs between different treatment arms

Practical utility will be measured as:

1. Number of participants who agree to wear the digital device
2. Compliance with digital device, as measured by number of days of meaningful data per participant
3. Adherence, as measured by the number of digital assessments undertaken by participants

Acceptability will be measured using the SPFQ.

5.2 SAMPLE SIZE

There have been no formal sample size calculations for the Digital Measures Study as we are not attempting to make definitive assessments of any specific DMO. Rather we aim to explore the validity, reliability and feasibility, for a range of proposed DMOs.

5.3 ANALYSIS AND ANALYSIS PLAN

The goals relating to validity will be assessed using suitable statistical models applied in turn to the list of main trial outcomes under consideration. Firstly, transformations to normality will be made to the DMOs if necessary and with the primary outcome standardised to the baseline mean and standard deviation. Specifically, for each DMO, EJS ACT-PD will fit a joint linear mixed model to the data from each DMO and main trial outcome for each available timepoint, adjusting for gender, age at baseline, time since diagnosis and site tier, with a term also included for treatment per outcome. The random effect structure will include slope and intercept terms for both outcomes with all covariances freely estimated, including covariances between error terms. Other co-variates may be considered, including cognitive score, walking aid use, levodopa equivalent dose.

The post-estimation 'working' correlation matrix can be used to assess correlations between the DMO and main trial outcome across timepoints[1] and compared with the raw correlations. The correlation between random slopes for both outcomes can be used to assess[3]. The correlation of individuals' post-estimation slopes (best linear unbiased predictions- BLUPs) can also be used to confirm this. Checking if progression over time is as anticipated[4] can be made looking at the DMO mean slope. Comparison can also be made to the primary outcome mean slope. The joint aspect of the modelling allows for straightforward estimation of the difference in slopes with confidence intervals. The difference in

mean DMO slope between arms[5] can be taken from the treatment term coefficient for DMO portion of the model. How this compares to the treatment term coefficient for the main trial outcome can be presented if this information is publicly available at the time of publication.

For[6] the variance components of the model can be used to assess reliability (intra-class correlation) of the DMO as the ratio of true variance to total variance, conditioning for time. This reliability estimate may again be compared to the equivalent for the main trial outcome, taken from the joint model. A separate linear mixed model solely of the main trial outcome with the DMO as a time-varying predictor can be used to assess[2].

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Appendix 1 – Schedule of Assessment

Activity	**Screening**	**Randomisation**	**Week**											**Early Termination**	**Unscheduled Visit**
			0 (Baseline)	**1-5 (Titration)**	**13 (M3)**	**26 (M6)**	**39 (M9)**	**52 (M12)**	**65 (M15)**	**78 (M18)**	**104 (M24)**	**130 (M30)**	**156 (M36) End of study visit**	**165 (M38) Safety follow-up visit**		
Window		Ideally within 3 weeks of screening visit *(maximum of 4 weeks)*	within 4 weeks of screening visit *(maximum of 6 weeks)*	Ideally within 48 hours of completing baseline	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks		
Location	In-person	Telephone call+	Remote ~ or in-person	Telephone call (weekly)	Remote ~ or in-person	Remote ~ or in-person	Telephone Call	Remote ~ or in-person	Telephone Call	Remote ~ or in-person	Remote ~ or in-person	Remote ~ or in-person	Remote or in-person	Remote ~ or in-person	As required	As required
Sub-Study activities:																
Informed consent	x					x*										
Device supplied to participant and applied [A]	x					x		x		x	x	x	x			
DMO data collection	x					x		x		x	x	x	x			

Notes / Annotations:

~: Remote visit should ideally be conducted as a video call to complete assessments, but if needed the visit can be conducted via a telephone call with abbreviated assessment and will be encouraged to have an in person visit at 52 weeks, 104 weeks and 156 weeks.

*: If a participant has been randomised in the main trial without being consented to the Digital Measures sub-study, screening and consent for the Digital Measures sub-study can take place at the 26-week follow-up appointment, provided this is conducted by appropriately delegated personnel and must be in-person.

[A]: at the screening visit the participant will be provided the digital device and trained in its application. At all remote follow-up appointments, the device will be posted to the participant ahead of the appointment date – devices should be posted out 10 days before the appointment date.