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The needs of patients with parkinsonism and their caregivers: a protocol for the PRIME-UK cross-sectional study

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Manuscripts

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5 The needs of patients with parkinsonism and their caregivers: a
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7 protocol for the PRIME-UK cross-sectional study
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Abstract

Introduction

People with parkinsonism (PwP) are a highly heterogeneous group and the condition encompasses a spectrum of motor and nonmotor symptoms which variably emerge and manifest across the disease course, fluctuate over time and negatively impact quality of life. Whilst parkinsonism is not directly the result of ageing, it is a condition that mostly affects older people, who may also be living with frailty and multimorbidity. This study aims to describe the broad range of health needs for PwP and their carers in relation to their symptomatology, disability, disease stage, comorbidities and sociodemographic characteristics.

Methods and analysis

In this single site cross-sectional study, PwP will be sent a study information pack for themselves and their primary informal caregiver, if relevant. Data are collected via questionnaire, with additional support, if required, to maximise participation. A specific strategy has been developed to target and proactively recruit patients lacking capacity to consent, including those in residential care settings, with input from a personal consultee prior to completion of a bespoke questionnaire by a representative. Caregivers are also recruited to look at various health outcomes. Results will be displayed as descriptive statistics and regression models will be used to test simple associations and interactions.

Ethics and dissemination

This protocol was approved by the London - Brighton & Sussex Research Ethics Committee (REC reference 20/LO/0890). The results of this protocol will be disseminated through publication in an international peer-reviewed journal; presentation at academic meetings and conferences; and a lay summary uploaded to the PRIME-Parkinson website.

Article summary

Strengths and limitations of this study

- This study aims to recruit typically under-represented individuals with parkinsonism, specifically those who lack capacity, in order to describe a more representative sample and address an area of unmet need
- This study involves a detailed and holistic phenotyping of people with parkinsonism, rather than focusing on any one motor or non-motor domain in conjunction with data from the perspective of a caregiver
- Despite efforts to design a specific approach to promote inclusion of hard-to-reach individuals, we acknowledge that non-response bias may impact the findings

- Given the cross-sectional design, it will not be possible to establish causality of any associations observed

Introduction

Parkinson's disease (PD), the most common cause of parkinsonism, is the second most frequent neurodegenerative disease after Alzheimer's disease and is estimated to affect around 0.3% of the population in industrialised countries, rising to 1% in those aged over 60 years [1]. A meta-analysis of worldwide data on prevalence of Parkinson's disease showed rising prevalence with age from 41 per 100,000 people in those aged 40-49 years to 1,903 per 100,000 in those aged over 80 years [2].

People with parkinsonism (PwP) are a highly heterogeneous group [3] and the disease encompasses a spectrum of motor and non-motor symptoms, including fatigue, sleep disturbance, neuropsychiatric complications and cognitive impairment, which manifest across the disease course and fluctuate over time [4]. Whilst PD is not directly the result of ageing, it is a condition that more commonly affects older people [1], who are more likely to also be living with frailty and multimorbidity. Frailty and multimorbidity act synergistically to drive clinical complexity [5] and heighten the risk of adverse outcomes for older people with PD. The impact of multimorbidity on an individual's risk profile may be greater than the sum of conditions [6]. In order to fully appreciate the level of clinical complexity of people with PD, it is necessary to integrate the multifaceted problems they may experience, together with their frailty status and additional comorbidities.

PD impacts negatively on the physical and psychosocial wellbeing of those who care for or support these individuals [7]. As PD progresses, many individuals will require care and a large proportion of this is provided informally. In one study of patients with moderate to advanced parkinsonism, over 80% were receiving input from an informal caregiver, whilst only a quarter of people received formal domestic or personal care [8]. Increasing age, Hoehn and Yahr stage, non-motor symptom burden, and declining cognitive and physical function is associated with greater care need and, in turn, with worsening caregiver quality of life [9]. Caregivers are often older adults [9], so may themselves be living with frailty and multimorbidity, making them vulnerable to negative health outcomes which can limit their ability to provide informal support; thus studying the needs of, and supporting, caregivers is important to optimise the wellbeing of PwP.

The extent to which findings from many large observational studies of PwP can be extrapolated is limited as patients are frequently excluded on the bases of age, comorbidities, cognitive impairment or inability to consent. The COPPADIS (COhort of Patients with PARKinson's Disease in Spain) study restricted inclusion to those aged 30- 75 years and excluded patients with dementia (defined as a Mini-Mental State Examination score < 26) or who were unable to provide informed consent [10]. The international, multicentre Non-motor International Longitudinal Study (NILS) excluded patients with dementia or who were unable to consent [11]. Similarly, existing UK-based PD cohort studies have generally focused on patients with idiopathic PD, including the Discovery cohort which recruited from neurology clinics and excluded individuals if they were suspected to have non-idiopathic PD, Lewy Body dementia or had cognitive impairment which precluded consent [12]. The prospective, multicentre

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3 Tracking Parkinson's cohort excluded those with other forms of parkinsonism or severe comorbid illness
4 [13]. Even studies focusing on later stage PD are often not wholly inclusive: a Dutch cross-sectional study
5 of nursing home residents with PD opted to exclude individuals with moderate to severe cognitive
6 decline [14] and a cross-sectional study investigating the clinical burden of advanced PD required
7 patients to be able to provide written informed consent [15]. This limits the generalisability of the
8 findings and likely provides an overly optimistic clinical picture of PD.
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13 In this study we aim to quantitatively describe the overall symptomatology and phenomenology of PwP,
14 rather than focus on any one motor or non-motor symptom of the disease. Early studies focussed
15 almost exclusively on the motor manifestations of Parkinson's with more recent work better profiling
16 the non-motor aspects. However, more global aspects such as patient activation, nutritional risk, well-
17 being and exploration of wider impacts on caregivers have been under-evaluated. [13]. We will recruit
18 PwP who are additionally living with frailty, multimorbidity and cognitive impairment, in order to
19 describe a representative population and address this area of unmet need. We will also gain vital
20 information on the lived experience of caregivers by co-enrolling individuals who live with, care for, or
21 support someone with parkinsonism. Understanding the profile of PwP in terms of their disease stage,
22 symptom burden and multimorbidity, as well as characterising the population of caregivers associated
23 with PwP will inform the development of a person-centered and individualised multi-component
24 intervention and allow us to target patients and caregivers most at risk of adverse outcomes [16]. We
25 will also use this cross-sectional study as a sampling frame whereby information on disease stage and
26 health needs is utilised to stratify a subgroup of participants into a future randomised controlled trial of
27 a new care model (PRIME) with an intervention that is targeted according to clinical complexity [17].
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32 Methods and analysis

33 Study design and population

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35 This is a single centre, cross-sectional study. PwP living in the catchment area of Royal United Hospital
36 Bath NHS Foundation Trust (RUH Bath), a district general hospital in the United Kingdom, will be
37 recruited to the study over approximately 12-24 months from September 2020. We will also enrol
38 primary informal caregivers of a patient with parkinsonism. A caregiver may participate in the study
39 regardless of whether the person with parkinsonism, for whom they care, wishes to take part.
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43 The catchment area for the RUH Bath includes North-East Somerset, parts of South Gloucestershire and
44 West Wiltshire. PwP are cared for by the separate Parkinson's specialist clinicians in the Older Person's
45 Unit (OPU) and neurology teams with outpatient clinics at the RUH site; St Martin's Hospital in Bath; and
46 Chippenham and Devizes in Wiltshire. Home visits to patients in residential care are also undertaken by
47 the OPU Parkinson's clinicians.
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50 Inclusion/exclusion criteria

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Patient participants

Inclusion criteria

- Have a diagnosis of parkinsonism (including idiopathic Parkinson's disease, progressive supranuclear palsy, corticobasal degeneration, multisystem atrophy, dementia with Lewy Bodies, vascular parkinsonism), made by a movement disorder specialist
- Be willing to participate
- Have the ability to provide informed consent to participate or, where unable to do so due to cognitive impairment, availability of a close friend or relative to act as a personal consultee.
- Be aged 18 years or over
- Live in the catchment area of RUH Bath

Exclusion criteria

- Individuals with drug-induced parkinsonism
- Individuals who lack capacity to consent to participate but do not have anyone who can be a consultee to provide advice regarding their wishes and views
- Current medical, cognitive or psychosocial issue or co-enrolment in another study that, in the opinion of the site investigator, would interfere with adherence to study requirements

Caregiver participants

Inclusion criteria:

- Provide informal care or support for a patient with parkinsonism and, where a patient has more than one informal caregiver, be considered by the patient to be their primary caregiver
- Be willing to participate
- Have the ability to provide informed consent to participate
- Be aged 18 years or over

Exclusion criteria:

- Professional carers, who are paid to deliver care

Sampling and recruitment procedures

Potentially eligible participants will be identified from clinical lists and from lists of patients seen as new referrals within the movement disorder service at RUH Bath.

Patients who meet the eligibility criteria will be sent an invitation letter in the post, together with information about the study for them and for any informal caregiver. Willing patients/caregivers will be asked to complete the written consent form and return it by post to the study team at RUH Bath. Participants who do not respond to this invitation letter will receive one or more telephone calls from the clinical team. The purpose of these calls will be to answer any questions the patient may have about study participation; ascertain how the team can support the patient to participate should they wish to; and, where necessary, assess capacity to consent to taking part in the study. If the patient declines to participate, they will not receive further contact about this study.

Adults lacking capacity to consent to participation in research

Patients will be assumed to have capacity to consent to the study unless there is evidence to suggest otherwise. If a capacity assessment is triggered, this will be conducted by telephone by a trained member of the team in accordance with the Mental Capacity Act 2005 two-stage test. If the potential participant does not have capacity to give consent to participate in the study, a personal consultee will be sought to review the requirements for study participation and offer advice on the wishes and views of the patient, including the patient's view on taking part in research at the time they had capacity. If the consultee advises that the person would have consented at a time they had capacity, they will be asked to sign the consultee declaration form. The personal consultee, or another close friend or relative of the person with parkinsonism, will be asked to complete questionnaires on behalf of the patient, acting as their "representative." We will not involve nominated consultees such as healthcare professionals or paid carers. Where no personal consultee is available, for example because the person lacking capacity has no family member or friend, or they are not willing to act as a personal consultee, the patient shall be excluded from the study.

Data collection

Methods of assessment

Recruited participants will complete a single questionnaire booklet at home during the study period. Where able, participants will self-complete the questionnaires. Questionnaire completion can also be facilitated over the telephone or in person to support individuals with, for example, visual impairment or tremor/dyskinesia limiting ability to write, to participate. Where participants have capacity but have a physical inability to mark responses on the questionnaire (e.g. due to tremor or bradykinesia), assistance with making a physical response can be undertaken by another person, which could include their paid carer, with the answer communicated by the participant.

PwP, who can provide informed consent to the study, will be asked to complete a full patient questionnaire booklet. For PwP who are unable to consent to the study, a specially designed and adapted patient questionnaire booklet, will be provided for their representative to complete on their behalf. Caregivers will be asked to complete the caregiver questionnaire booklet. A caregiver may, in some instances, complete a questionnaire booklet acting as the patient's representative and also complete a booklet answering questions about their experience of being a caregiver. The contents of all three questionnaire booklets are detailed in table 1.

Table 1: Contents of questionnaire booklets

METRIC	DATA	PPT +	PPT -	CG
Demographics	Gender	✓	✓	✓
	Date of birth	✓	✓	✓
	Ethnicity	✓	✓	✓
	Employment status	✓		✓
	Highest qualification	✓	✓	✓
	Marital status	✓	✓	✓
	Living situation	✓	✓	✓
Medication	Medication (name, dose, frequency, route)	✓	✓	
Parkinson's history	Diagnosis	✓	✓	
	Year of diagnosis	✓	✓	
	Laterality of first symptoms	✓	✓	
	Advanced therapies	✓	✓	
General medical history	Past medical history	✓	✓	
	Healthcare contacts	✓	✓	
	Falls and near falls	✓	✓	
	Height, weight, weight 3-6 months ago	✓	✓	✓
	Health status question			✓
About the care	Relationship to recipient			✓
	Living with recipient			✓
	Intensity of caring and tasks of caring			✓
	Duration of caring			✓
Information about care recipient (if the patient is not participating)	Gender			(✓)
	Age			(✓)
	Living situation			(✓)
	Diagnosis			(✓)
	Year of diagnosis			(✓)
Nutritional risk	Seniors in the community: Risk Evaluation for Eating and Nutrition (SCREEN II)-14 item version [18-20]	✓	✓	✓
Frailty	Survey of Health, Ageing and Retirement in Europe (SHARE-FI) 75+ [21]	✓	✓	✓
Sarcopenia screen	SARC-F questionnaire [22]	✓	✓	✓
Covid-19 questions	Symptoms, self-isolation/shielding, access to care	✓	✓	✓
Lifestyle	Smoking	✓	✓	
	Alcohol intake	✓	✓	
	Physical activity	✓	✓	
Capability/wellbeing	ICEpop CAPability measure for Older People [23]	✓	✓ (proxy version)	
Quality of life	Parkinson's Disease Questionnaire-39 (PDQ-39) [24]	✓		
Non-motor symptom burden	Non-Motor Symptom Questionnaire (NMSQ) [25]	✓		
Autonomic symptoms	Scales for Outcomes in Parkinson's disease- autonomic dysfunction (SCOPA-AUT) [26]	✓		
Depression	Beck depression inventory-II (BDI-II) [27]	✓		
Bowel function	Neurogenic bowel dysfunction score [28]	✓		
Urinary tract symptoms	International Consultation on Incontinence Questionnaire: ICIQ-mLUTS (for men) and ICIQ-fLUTS (for women) [29]	✓		
Cognition	Test Your Memory [30]	✓		

Motor symptom burden	Motor rating scale- adapted from Parveen [31]	✓		
Freezing of gait	New Freezing of Gait (N-FOG) [32]	✓		
Patient activation	Patient Activation Measure [33]	✓		
Symptoms and behaviour	Neuropsychiatric Inventory [34]		✓	
Activities of daily living	Bristol Activities of Daily Living Scale [35]		✓	
Quality of life	Parkinson's Disease Questionnaire (PDQ) carer [36]			✓
Caregiver burden	Zarit Burden Interview [37]			✓
Caregiver activation	Caregiver PAM			✓
Caregiver coping strategies	Brief Coping Orientation to Problems Experienced (BriefCOPE) [38]			✓
Perceived social support	Multidimensional scale of perceived social support [39]			✓
PPT +	Participant with parkinsonism with capacity to consent to research			
PPT-	Participant with parkinsonism without capacity to consent to research (questionnaires completed by a representative)			
CG	Caregiver participant			

Rationale for selected questionnaires

Measures for people with parkinsonism

In order to capture the other comorbidities affecting PwP, we are using a list designed as a research tool for the self-report of chronic conditions in primary care [40].

The 39-item Parkinson's Disease Questionnaire (PDQ-39) is a Movement Disorder Society-recommended, PD-specific measure of health-related quality of life and has been well-validated and utilised in this population [41]. A well-being measure, ICECAP-O will be used to capture the broader impact of PD on participants. ICECAP-O is a relatively new measure of capability in older people which has been previously used in patients with PD [42]. A proxy version has been used to assess capability in older adults with cognitive impairment [43, 44] so this measure will be completed by a representative for PwP lacking capacity and unable to complete questionnaires.

Non-motor symptoms can be particularly troubling for patients and can negatively influence quality of life [45] and so are important to capture as part of this holistic and in-depth assessment. Whilst the Parkinson's Disease Nonmotor Symptoms Questionnaire (NMSQ) is a screening tool, rather than a rating instrument, it was selected for this study because it does not require rater administration and is relatively quick for participants to self-complete [46]. The Beck Depression Inventory (BDI-II) has been validated for use in PwP and is widely used to screen for depression and assess the severity of depression symptoms in the group [47].

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3 The SCOPA AUT questionnaire has been included to characterise the burden of autonomic symptoms
4 that are responsible for many non-motor symptoms. These can be diffuse and wide-reaching and
5 include important yet seldom considered issues such as sexual function, as well common phenomena
6 including orthostatic hypotension. Bladder symptoms contribute significantly to quality of life and will
7 be further explored in more depth using the International Consultation on Incontinence Questionnaire
8 male and female short form Lower Urinary Tract tools (mLUTS and fLUTS), which have been
9 recommended for use in PD [29]. These broadly cover all urinary symptoms specific to each gender.
10 Bowel symptoms will be similarly explored using the neurogenic bowel score [28].
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13 Test Your Memory (TYM) is a self-administered cognitive screening test [48] which has been used
14 amongst PwP and compared to the Montreal Cognitive Assessment (MoCA) [30].
15

16 Self-reported motor symptoms will be captured using questions adapted from a motor rating form
17 based on motor tasks from the Movement Disorder Society-Unified Parkinson's Disease Rating Scale
18 (MDS-UPDRS) [31].
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21 Freezing of gait is a common symptom, particularly in the advanced phases of PD, which can cause
22 disability, negatively impact quality of life [49] and increase falls risk [50]. The New-Freezing of Gait
23 Questionnaire (NFOG-Q) is a self-reported tool to assess the impact and severity of freezing symptoms
24 [32].
25

26 The Patient Activation Measure is a metric used to quantify the self-management capabilities of patients
27 [51]. There is an increasing awareness that patients who have the knowledge, skills, and confidence to
28 look after their health and feel empowered to do so have better health outcomes [51] and so it is
29 important to gain an understanding of activation levels amongst PwP and their caregivers.
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32 The Bristol Activities of Daily Living (Bristol ADL) has been shown to have good content and construct
33 validity when used with people with dementia [35] and was one of only two scales rated as moderate
34 quality in a systematic review of Activities of Daily Living scales in dementia and, of these, the only one
35 suitable for self-completion by a caregiver [52]. This will allow the quantification of functional ability in
36 participants who take part with a representative. Neuropsychiatric symptoms are a common feature of
37 PD dementia and can negatively impact caregiver burden [53], hence particularly important to measure
38 for participants with cognitive impairment. The questionnaire form of the Neuropsychiatric Inventory
39 (NPI-Q) is a brief proxy-completed assessment [54].
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42 Measures which have not been validated for proxy report, or for which it would not be feasible for
43 someone to complete on behalf of the PwP, have not been included in the shorter patient questionnaire
44 booklet for completion by a representative.
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49 *Measures for caregivers*

50 Several tools will be used to measure caregiver burden and experience. The number of hours spent
51 caregiving will be captured using a grid which allows the caregiver to document the hours spent on each
52 of four categories of tasks, which are based on the categories included within the Caregiver Indirect and
53 Informal Care Cost Assessment Questionnaire, developed by Landfeldt and colleagues [55]. Caregivers
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3 can report the hours spent on each day of the week to account for the fact that their input may differ
4 throughout the week.
5

6 The 21-item Zarit Burden Inventory is the most commonly used measure of caregiver burden amongst
7 family caregivers of PwP [56]. The Parkinson's Disease Questionnaire (PDQ) carer has been specifically
8 designed to measure quality of life amongst caregivers of PwP [36] and will be used in this study.
9

10 The BriefCOPE is a frequently used coping scale and its subscales have been shown to predict distress
11 and wellbeing [57]. The Multidimensional Scale of Perceived Social Support is a subjective assessment of
12 social support [39]. Coping style may alter the way an informal caregiver deals with the challenges and
13 stresses of caring and a caregiver's perception that they have good social support may have a protective
14 effect [56].
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16

17 18 19 *Measures used in all three groups* 20

21 There is evidence to suggest that PwP are at risk of weight loss and malnutrition [58]. Moreover,
22 malnutrition is prevalent in older adults and is responsible for many significant health-related negative
23 outcomes [59-61]. We will quantify nutrition risk using the Seniors in the community: risk evaluation for
24 eating and nutrition, Version II (SCREEN-II) scale which is a valid and reliable tool to measure nutritional
25 status.
26

27 Frailty is a syndrome of loss of physiological reserve which confers greater vulnerability to negative
28 health outcomes; it is considered to be a dynamic condition in which individuals may transition to an
29 improved, as well as more advanced, frailty state [62]. The Frailty Instrument for Primary Care of the
30 Survey of Health, Ageing and Retirement in Europe (SHARE) is a phenotypic frailty assessment tool; in
31 this study, we have opted to use the SHARE tool which was developed and validated in those aged 75
32 years and over, in which assessment of handgrip strength was substituted with a question about walking
33 [21]. In the SHARE cohort, walking was assessed by a clinician; in this study, we have adapted the
34 SHARE-FI75+ for self-reported completion. Sarcopenia, a disease characterised by low muscle strength,
35 together with low muscle quantity or quality, may contribute to the development of physical frailty [63].
36 SARC-F is a rapid screening tool for sarcopenia [22] which will be used.
37
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40 Caregivers are often older adults [9] and may themselves be living with frailty, sarcopenia and risk of
41 malnutrition, hence the SARC-F, SHARE-FI75+ and SCREEN-II questionnaires will also be included in the
42 caregiver questionnaire booklet, as well as the patient and representative-completed booklets.
43

44 In order to contextualise the responses to other questionnaires collected in this study, we have
45 compiled some questions to gather information about any symptoms of Covid-19 infection experienced
46 by participants, whether they have had to self-isolate or shield, and their experience of accessing care
47 during the pandemic.
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50 *Sample size* 51

52 The sample size is pragmatic based on the total available number of potentially eligible PwP at this
53 single centre. There are approximately 1,200 PwP who are within the geographical catchment of the
54 RUH Bath. The likely response rate is unclear but we anticipate we will achieve a response rate of
55 between 40- 70% which would result in 480- 840 completed patient questionnaires.
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3 A previous cross-sectional postal survey noted a mean Parkinson's Disease Questionnaire-39 (PDQ-39)
4 summary index score of 44.6 (SD 17.6) [64]. With a sample size of 480 we can estimate a mean PDQ-39
5 score with the following precision of approximately +/- 3.3 points. This 95% confidence interval range is
6 sufficiently precise for descriptive purposes. Further sub-groups e.g., by age group and gender will be
7 less precise.
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10 Statistical analysis

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12 Results will be displayed as descriptive statistics using mean plus standard deviation for normally
13 distributed variables and median plus interquartile range for skewed variables. Linear and logistic
14 regression models will be used to test simple associations. We presume we will show worse health
15 needs and greater disability with increasing age and disease duration. However, we are specifically
16 interested to test how these factors could potentially interact with gender, socioeconomic status and
17 geography. Interaction tests will be specified a priori. We will use multiple imputation methods and
18 other methods to deal with missing data.
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23 Patient and public involvement statement

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25 This study has been designed and performed in conjunction with the study public involvement advisory
26 group (PIAG). The PIAG been critical to the design and content of participant information leaflets and
27 consent forms. Changes made as a result of the valuable contribution from PIAG contributors, all of
28 whom have Parkinson's disease, includes:
29

- 30 - Improved sensitivity around terminology for those who care for someone with PD,
31 acknowledging that they may live with someone who has PD but not see themselves as a
32 carer/caregiver, but may 'provide support'. The term 'caregiver' was preferred over 'carer' and
33 therefore used throughout the study documentation.
- 34 - Inclusion of an approximate time to complete the questionnaires in the participant information
35 leaflet and we further emphasized that the questionnaires are intended to be completed at
36 home
- 37 - Inclusion of information for plans regarding dissemination of results to participants.
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44 Ethics and dissemination

45 This protocol was approved by the London - Brighton & Sussex Research Ethics Committee on 27 July
46 2020 (REC reference 20/LO/0890).
47

48 All participants will either provide written informed consent or, in the case of patient participants who
49 lack capacity to consent to participation in the study, a consultee will provide advice on their prior
50 wishes and will sign a consultee declaration if they believe the patient would be willing to participate.
51
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53 If the person with parkinsonism has opted not to participate themselves, it is necessary, so far as
54 possible, for us to collect some basic information about who the caregiver supports. In this case, the
55 person with PD (or their personal consultee if they lack capacity to make decisions about the study) is
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3 asked to sign a section on the back of the caregiver consent form if they are happy for their caregiver to
4 provide basic information about them.
5

6 Participants can choose to withdraw for any reason at any time during their involvement in the study
7 and will not be followed up after withdrawal from the study. They will be asked their reason for
8 withdrawal but do not have to provide this. Data collected up to the time of withdrawal will be used.
9

10 We plan to publish the results of this protocol in an international peer-reviewed journal and at academic
11 national and international meetings and conferences. When we share the results of key findings, we will
12 upload a lay summary to the PRIME-Parkinson website.
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15

16 17 18 Authors' contributions

19 ET, FEL, YBS and EJH were responsible for the concept of the study and contributed to study
20 development and design. ET, DEB and MDS contributed to patient recruitment. ET drafted the
21 manuscript and all authors provided critical revision and approved the final protocol.
22
23

24 25 Funding statement

26 This work was supported by the Gatsby Charitable Foundation, grant number 3676.
27
28

29 30 Data statement

31 Access to the data will be available through application to the Chief Investigator. Pseudo-anonymised
32 data may be shared with other researchers to enable meta-analyses.
33
34

35 36 Competing Interests Statement

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44
45

46 All other authors declare that they have no competing interests.
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51 None
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The needs of patients with parkinsonism and their caregivers: a protocol for the PRIME-UK cross-sectional study

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Manuscripts

The needs of patients with parkinsonism and their caregivers: a protocol for the PRIME-UK cross-sectional study

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Abstract

Introduction

People with parkinsonism are a highly heterogeneous group and the disease encompasses a spectrum of motor and nonmotor symptoms which variably emerge and manifest across the disease course, fluctuate over time and negatively impact quality of life. Whilst parkinsonism is not directly the result of ageing, it is a condition that mostly affects older people, who may also be living with frailty and multimorbidity. This study aims to describe the broad range of health needs for people with parkinsonism and their carers in relation to their symptomatology, disability, disease stage, comorbidities and sociodemographic characteristics.

Methods and analysis

In this single site cross-sectional study, people with parkinsonism will be sent a study information pack for themselves and their primary informal caregiver, if relevant. Data are collected via questionnaire, with additional support, if required, to maximise participation. A specific strategy has been developed to target and proactively recruit patients lacking capacity to consent, including those in residential care settings, with input from a personal consultee prior to completion of a bespoke questionnaire by a representative. Caregivers are also recruited to look at various health outcomes. Results will be displayed as descriptive statistics and regression models will be used to test simple associations and interactions.

Ethics and dissemination

This protocol was approved by the London - Brighton & Sussex Research Ethics Committee (REC reference 20/LO/0890). The results of this protocol will be disseminated through publication in an international peer-reviewed journal; presentation at academic meetings and conferences; and a lay summary uploaded to the PRIME-Parkinson website.

Article summary

Strengths and limitations of this study

- This study aims to recruit typically under-represented individuals with parkinsonism, specifically those who lack capacity, in order to describe a more representative sample and address an area of unmet need
- This study involves a detailed and holistic phenotyping of people with parkinsonism, rather than focusing on any one motor or non-motor domain in conjunction with data from the perspective of a caregiver
- Despite efforts to design a specific approach to promote inclusion of hard-to-reach individuals, we acknowledge that non-response bias may impact the findings

- Given the cross-sectional design, it will not be possible to establish causality of any associations observed

Introduction

Parkinson's disease (PD), the most common cause of parkinsonism, is the second most frequent neurodegenerative disease after Alzheimer's disease and is estimated to affect around 0.3% of the population in industrialised countries, rising to 1% in those aged over 60 years [1]. A meta-analysis of worldwide data on prevalence of Parkinson's disease showed rising prevalence with age from 41 per 100,000 people in those aged 40-49 years to 1,903 per 100,000 in those aged over 80 years [2].

People with parkinsonism are a highly heterogeneous group [3] and the disease encompasses a spectrum of motor and non-motor symptoms, including fatigue, sleep disturbance, neuropsychiatric complications and cognitive impairment, which manifest across the disease course and fluctuate over time [4]. Whilst PD is not directly the result of ageing, it is a condition that more commonly affects older people [1], who are more likely to also be living with frailty and multimorbidity. Frailty and multimorbidity act synergistically to drive clinical complexity [5] and heighten the risk of adverse outcomes for older people with PD. The impact of multimorbidity on an individual's risk profile may be greater than the sum of conditions [6]. In order to fully appreciate the level of clinical complexity of people with PD, it is necessary to integrate the multifaceted problems they may experience, together with their frailty status and additional comorbidities.

PD impacts negatively on the physical and psychosocial wellbeing of those who care for or support these individuals [7]. As PD progresses, many individuals will require care and a large proportion of this is provided informally. In one study of patients with moderate to advanced parkinsonism, over 80% were receiving input from an informal caregiver, whilst only a quarter of people received formal domestic or personal care [8]. Increasing age, functional disability, non-motor symptom burden, and declining cognitive and physical function are associated with greater care need and, in turn, with worsening caregiver quality of life [9]. Caregivers are often older adults [9], so may themselves be living with frailty and multimorbidity, making them vulnerable to negative health outcomes which can limit their ability to provide informal support; thus studying the needs of, and supporting, caregivers is important to optimise the wellbeing of people with parkinsonism.

The extent to which findings from many large observational studies of people with parkinsonism can be extrapolated is limited as patients are frequently excluded on the bases of age, comorbidities, cognitive impairment or inability to consent. The COPPADIS (COhort of Patients with PARKinson's Disease in Spain) study restricted inclusion to those aged 30- 75 years and excluded patients with dementia (defined as a Mini-Mental State Examination score < 26) or who were unable to provide informed consent [10]. The international, multicentre Non-motor International Longitudinal Study (NILS) excluded patients with dementia or who were unable to consent [11]. Similarly, existing UK-based PD cohort studies have generally focused on patients with idiopathic PD, including the Discovery cohort which recruited from neurology clinics and excluded individuals if they were suspected to have non-idiopathic PD, Lewy Body dementia or had cognitive impairment which precluded consent [12]. The prospective, multicentre

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3 Tracking Parkinson's cohort excluded those with other forms of parkinsonism or severe comorbid illness
4 [13]. It is, however, encouraging to note that some ongoing biomarker development cohorts are taking
5 an inclusive approach towards recruitment, including the Cincinnati Biomarker Program which is
6 enrolling participants with any form of parkinsonism or dementia, at any disease stage, though
7 participant burden may implicitly exclude some participants [14]. Even studies focusing on later stage PD
8 are often not wholly inclusive: a Dutch cross-sectional study of nursing home residents with PD opted to
9 exclude individuals with moderate to severe cognitive decline [15] and a cross-sectional study
10 investigating the clinical burden of advanced PD required patients to be able to provide written
11 informed consent [16]. This limits the generalisability of the findings and likely provides an overly
12 optimistic clinical picture of PD.
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18 In this study we aim to quantitatively describe the overall symptomatology and phenomenology of
19 people with parkinsonism, rather than focus on any one motor or non-motor symptom of the disease.
20 Early studies focussed almost exclusively on the motor manifestations of Parkinson's with more recent
21 work better profiling the non-motor aspects [17]. However, more global aspects such as patient
22 activation, nutritional risk, well-being and exploration of wider impacts on caregivers have been under-
23 evaluated. We will recruit people with parkinsonism who are additionally living with frailty,
24 multimorbidity and cognitive impairment, in order to describe a representative population and address
25 this area of unmet need. We will also gain vital information on the lived experience of caregivers by co-
26 enrolling individuals who live with, care for, or support someone with parkinsonism. Understanding the
27 profile of people with parkinsonism in terms of their disease stage, symptom burden and
28 multimorbidity, as well as characterising the population of caregivers associated with people with
29 parkinsonism will inform the development of a person-centered and individualised multi-component
30 intervention and allow us to target patients and caregivers most at risk of adverse outcomes [18]. We
31 will also use this cross-sectional study as a sampling frame whereby information on disease stage and
32 health needs is utilised to stratify a subgroup of participants into a future randomised controlled trial of
33 a new care model (PRIME) with an intervention that is targeted according to clinical complexity [19].
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39 Methods and analysis

40 Study design and population

41 This is a single centre, cross-sectional study. People with parkinsonism living in the catchment area of
42 Royal United Hospital Bath NHS Foundation Trust (RUH Bath), a district general hospital in the United
43 Kingdom, will be recruited to the study over approximately 12-24 months from September 2020. We will
44 also enrol primary informal caregivers of a patient with parkinsonism. A person with parkinsonism may
45 take part in the study regardless of whether they have an informal caregiver and, if they do, whether
46 this person wishes to take part. Likewise, a caregiver may participate regardless of whether the person
47 with parkinsonism, for whom they care, wishes to take part.
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52 The catchment area for the RUH Bath includes North-East Somerset, parts of South Gloucestershire and
53 West Wiltshire. People with parkinsonism are cared for by the separate Parkinson's specialist clinicians
54 in the Older Person's Unit (OPU) and neurology teams with outpatient clinics at the RUH site; St Martin's
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Hospital in Bath; and Chippenham and Devizes in Wiltshire. Home visits to patients in residential care are also undertaken by the OPU Parkinson's clinicians.

Inclusion/exclusion criteria

Patient participants

Inclusion criteria

- Have a diagnosis of parkinsonism (including idiopathic Parkinson's disease, progressive supranuclear palsy, corticobasal degeneration, multisystem atrophy, dementia with Lewy Bodies, vascular parkinsonism), made by a movement disorder specialist (a physician sub-specialising in neurology or geriatric medicine)
- Be willing to participate
- Have the ability to provide informed consent to participate or, where unable to do so due to cognitive impairment, availability of a close friend or relative to act as a personal consultee.
- Be aged 18 years or over
- Live in the catchment area of RUH Bath

Exclusion criteria

- Individuals with drug-induced parkinsonism
- Individuals who lack capacity to consent to participate but do not have anyone who can be a consultee to provide advice regarding their wishes and views
- Current medical, cognitive or psychosocial issue or co-enrolment in another study that, in the opinion of the site investigator, would interfere with adherence to study requirements (e.g. individuals in the last days/weeks of life)

Caregiver participants

Inclusion criteria:

- Provide informal care or support for a patient with parkinsonism and, where a patient has more than one informal caregiver, be considered by the patient to be their primary caregiver
- Be willing to participate
- Have the ability to provide informed consent to participate
- Be aged 18 years or over

Exclusion criteria:

- Professional carers, who are paid to deliver care

Sampling and recruitment procedures

Potentially eligible participants will be identified from lists of patients coded with parkinsonism during an inpatient admission and from lists of patients followed up or seen as a new referral within the movement disorder services at the main regional hospital (RUH Bath) and ancillary clinics within the surrounding area.

Patients who meet the eligibility criteria will be sent an invitation letter, by the study team on behalf of their Parkinson's clinician, in the post, together with information about the study for them and for any informal caregiver. Willing patients/caregivers will be asked to complete the written consent form and return it by post to the study team at RUH Bath. Participants who do not respond to this invitation letter will receive one or more telephone calls from the study team, after they have had at least 1 week to consider the information. The purpose of these calls will be to answer any questions the patient may have about study participation; ascertain how the team can support the patient to participate should they wish to; identify if there are any requirements for translation and, where necessary, assess capacity to consent to taking part in the study. Research participants do not receive any remuneration or incentive for taking part, but all postal costs are covered. If the patient declines to participate, they will not receive further contact about this study.

Identification of caregivers

The envelope sent to potential patient participants will contain an information booklet and consent form for people who provide care or support to someone with parkinsonism. The invitation letter asks the person with parkinsonism to pass this information to the person who is their main source of help or support, where relevant. Potential caregiver participants may also be identified from the 'About Me' form, which willing patient participants are asked to return together with their completed consent form. If they tick that they live with someone or that they receive support from family or friends, the patient participant will receive a telephone call to clarify whether this individual is eligible and willing to take part as caregiver.

Adults lacking capacity to consent to participation in research

Patients will be assumed to have capacity to consent to the study unless there is evidence to suggest otherwise. Situations which will prompt capacity assessment include return of incomplete or partially completed consent forms; an individual (such as care home staff or a family member), who answers the phone on behalf of a patient during a follow-up call, expressing concern that the patient may struggle to understand the study information. If a capacity assessment is triggered, this will be conducted by telephone by a trained member of the team in accordance with the Mental Capacity Act 2005 two-stage test [20]. This individual will take all possible steps to facilitate the potential participant to make a capacitous decision (e.g. by calling back on another occasion; by ensuring that a family member or friend is with the potential participant during the assessment, if possible).

Identification and involvement of a personal consultee

If the potential participant does not have capacity to give consent to participate in the study, a personal consultee, usually a close family member or friend who knows the potential participant in a personal capacity, will be sought to review the requirements for study participation and offer advice on the

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3 wishes and views of the patient, including the patient's view on taking part in research at the time they
4 had capacity. Personal consultees will be identified from next of kin details held within clinical records,
5 discussion with care home staff and, where relevant, asking to speak to anyone who lives with or is
6 supporting the potential patient participant.
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9 If the consultee advises that the person would have consented at a time they had capacity, they will be
10 asked to sign the consultee declaration form. The personal consultee, or another close friend or relative
11 of the person with parkinsonism, will be asked to complete questionnaires on behalf of the patient,
12 acting as their "representative." We will not involve nominated consultees such as healthcare
13 professionals or paid carers. Where no personal consultee is available, for example because the person
14 lacking capacity has no family member or friend, or they are not willing to act as a personal consultee,
15 the patient shall be excluded from the study.
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20 Data collection

21 Methods of assessment

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23 Recruited participants will complete a single questionnaire booklet at home during the study period and
24 will be asked to return this to the research team in the pre-paid envelope provided. Where able,
25 participants will self-complete the questionnaires and can do this over a number of days. Questionnaire
26 completion can also be facilitated over the telephone or in person to support individuals with, for
27 example, visual impairment or tremor/dyskinesia limiting ability to write, to participate. Where
28 participants have capacity but have a physical inability to mark responses on the questionnaire (e.g. due
29 to tremor or bradykinesia), assistance with making a physical response can be undertaken by another
30 person, which could include their paid carer, with the answer communicated by the participant.
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34 People with parkinsonism, who can consent to the study, will be asked to complete a full patient
35 questionnaire booklet, which may take up to 2 hours to complete. Representatives of those unable to
36 consent to the study will complete a specially designed and adapted patient questionnaire booklet on
37 their behalf; this may take up to 1 hour to complete. Caregivers will be asked to complete the caregiver
38 questionnaire booklet, about their own perspective, which is estimated to take up to 1 hour to
39 complete. The contents of all three questionnaire booklets are detailed in table 1.
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42 If questionnaire booklets have not been received by the research team within 2 weeks of them being
43 posted to participants, the research team will telephone the participant to answer any queries and to
44 offer support. If the participant returns a questionnaire with one or more questions left blank or
45 incorrectly completed (e.g. multiple options are selected for a question which requires only one
46 answer), the participant will be contacted by telephone and asked if they are willing to clarify their
47 answers.
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Table 1: Contents of questionnaire booklets

METRIC	DATA	Items	PPT +	PPT -	CG
Demographics	Gender	1	✓	✓	✓
	Date of birth	1	✓	✓	✓
	Ethnicity	1	✓	✓	✓
	Employment status	1	✓		✓
	Highest qualification	1	✓	✓	✓
	Marital status	1	✓	✓	✓
	Living situation	1	✓	✓	✓
Medication	Medication (name, dose, frequency, route)	1	✓		
Parkinson's history	Diagnosis	1	✓	✓	
	Year of diagnosis	1	✓	✓	
	Laterality of first symptoms	1	✓	✓	
	Advanced therapies	3	✓	✓	
General medical history	Past medical history	1	✓	✓	
	Healthcare contacts	2	✓	✓	
	Falls and near falls	2	✓	✓	
	Height, weight, weight 3-6 months ago	3	✓	✓	✓
	Health status question	1			✓
About the care	Relationship to recipient	1			✓
	Living with recipient	1			✓
	Intensity of caring and tasks of caring	2			✓
	Duration of caring	1			✓
Information about care recipient (if the patient is not participating)	Gender	1			(✓)
	Age	1			(✓)
	Living situation	1			(✓)
	Diagnosis	1			(✓)
	Year of diagnosis	1			(✓)
Nutritional risk	Seniors in the community: Risk Evaluation for Eating and Nutrition (SCREEN II)-14 item version [21-23]	17	✓	✓	✓
Frailty	Survey of Health, Ageing and Retirement in Europe (SHARE-FI) 75+ [24]	5	✓	✓	✓
Sarcopenia screen	SARC-F questionnaire [25]	5	✓	✓	✓
Covid-19 questions	Symptoms, self-isolation/shielding, access to care	13	✓	✓	✓
Lifestyle	Smoking	1	✓	✓	
	Alcohol intake	2	✓	✓	
	Physical activity	3	✓	✓	
Capability/wellbeing	ICEpop CAPability measure for Older People [26]	5	✓	✓ (proxy version)	
Quality of life	Parkinson's Disease Questionnaire-39 (PDQ-39) [27]	39	✓		
Non-motor symptom burden	Non-Motor Symptom Questionnaire (NMSQ) [28]	30	✓		
Autonomic symptoms	Scales for Outcomes in Parkinson's disease- autonomic dysfunction (SCOPA-AUT) [29]	25	✓		
Depression	Beck depression inventory-II (BDI-II) [30]	21	✓		

Bowel function	Neurogenic bowel dysfunction score [31]	11	✓		
Urinary tract symptoms	International Consultation on Incontinence Questionnaire: ICIQ-mLUTS (for men) and ICIQ-fLUTS (for women) [32]	12 (female) 13 (male)	✓		
Cognition	Test Your Memory [33]	16	✓		
Motor symptom burden	Motor rating scale- adapted from Parveen [34]	4	✓		
Freezing of gait	New Freezing of Gait (N-FOG) [35]	9	✓		
Patient activation	Patient Activation Measure [36]	13	✓		
Symptoms and behaviour	Neuropsychiatric Inventory [37]	12		✓	
Activities of daily living	Bristol Activities of Daily Living Scale [38]	20		✓	
Quality of life	Parkinson's Disease Questionnaire (PDQ) carer [39]	29			✓
Caregiver burden	Zarit Burden Interview [40]	22			✓
Caregiver activation	Caregiver PAM	13			✓
Caregiver coping strategies	Brief Coping Orientation to Problems Experienced (BriefCOPE) [41]	28			✓
Perceived social support	Multidimensional scale of perceived social support [42]	12			✓
PPT +		Participant with parkinsonism with capacity to consent to research			
PPT-		Participant with parkinsonism without capacity to consent to research (questionnaires completed by a representative)			
CG		Caregiver participant			

Rationale for selected questionnaires

Measures for people with parkinsonism

In order to capture the other comorbidities affecting people with parkinsonism, we are using a list designed as a research tool for the self-report of chronic conditions in primary care [43].

The 39-item Parkinson's Disease Questionnaire (PDQ-39) is a Movement Disorder Society-recommended, PD-specific measure of health-related quality of life and has been well-validated and utilised in this population [44]. A well-being measure, ICECAP-O will be used to capture the broader impact of PD on participants. ICECAP-O is a relatively new measure of capability in older people which has been previously used in patients with PD [45]. A proxy version has been used to assess capability in older adults with cognitive impairment [46, 47] so this measure will be completed by a representative for patients lacking capacity and unable to complete questionnaires.

Non-motor symptoms can be particularly troubling for patients and can negatively influence quality of life [48] and so are important to capture as part of this holistic and in-depth assessment. Whilst the Parkinson's Disease Nonmotor Symptoms Questionnaire (NMSQ) is a screening tool, rather than a rating

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3 instrument, it was selected for this study because it does not require rater administration and is
4 relatively quick for participants to self-complete [49]. The Beck Depression Inventory (BDI-II) has been
5 validated for use in people with PD and is widely used to screen for depression and assess the severity of
6 depression symptoms in the group [50].
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9 The SCOPA AUT questionnaire has been included to characterise the burden of autonomic symptoms
10 that are responsible for many non-motor symptoms. These can be diffuse and wide-reaching and
11 include important yet seldom considered issues such as sexual function, as well common phenomena
12 including orthostatic hypotension. Bladder symptoms contribute significantly to quality of life and will
13 be further explored in more depth using the International Consultation on Incontinence Questionnaire
14 male and female short form Lower Urinary Tract tools (mLUTS and fLUTS), which have been
15 recommended for use in PD [32]. These broadly cover all urinary symptoms specific to each gender.
16 Bowel symptoms will be similarly explored using the neurogenic bowel score [31].
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19 Test Your Memory (TYM) is a self-administered cognitive screening test [51] which has been used
20 amongst people with PD and compared to the Montreal Cognitive Assessment (MoCA) [33].
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22 Self-reported motor symptoms will be captured using questions adapted from a motor rating form
23 based on motor tasks from the Movement Disorder Society-Unified Parkinson's Disease Rating Scale
24 (MDS-UPDRS) [34].
25

26 Freezing of gait is a common symptom, particularly in the advanced phases of PD, which can cause
27 disability, negatively impact quality of life [52] and increase falls risk [53]. The New-Freezing of Gait
28 Questionnaire (NFOG-Q) is a self-reported tool to assess the impact and severity of freezing symptoms
29 [35].
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32 The Patient Activation Measure is a metric used to quantify the self-management capabilities of patients
33 [54]. There is an increasing awareness that patients who have the knowledge, skills, and confidence to
34 look after their health and feel empowered to do so have better health outcomes [54] and so it is
35 important to gain an understanding of activation levels amongst people with PD and their caregivers.
36

37 The Bristol Activities of Daily Living (Bristol ADL) has been shown to have good content and construct
38 validity when used with people with dementia [38] and was one of only two scales rated as moderate
39 quality in a systematic review of Activities of Daily Living scales in dementia and, of these, the only one
40 suitable for self-completion by a caregiver [55]. This will allow the quantification of functional ability in
41 participants who take part with a representative. Neuropsychiatric symptoms are a common feature of
42 PD dementia and can negatively impact caregiver burden [56], hence particularly important to measure
43 for participants with cognitive impairment. The questionnaire form of the Neuropsychiatric Inventory
44 (NPI-Q) is a brief proxy-completed assessment [57].
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47 Measures which have not been validated for proxy report, or for which it would not be feasible for
48 someone to complete on behalf of the patient, have not been included in the shorter patient
49 questionnaire booklet for completion by a representative.
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Measures for caregivers

Several tools will be used to measure caregiver burden and experience. The number of hours spent caregiving will be captured using a grid which allows the caregiver to document the hours spent on each of four categories of tasks, which are based on the categories included within the Caregiver Indirect and Informal Care Cost Assessment Questionnaire, developed by Landfeldt and colleagues [58]. Caregivers can report the hours spent on each day of the week to account for the fact that their input may differ throughout the week.

The 21-item Zarit Burden Inventory is the most commonly used measure of caregiver burden amongst family caregivers of people with PD [59]. The Parkinson's Disease Questionnaire (PDQ) carer has been specifically designed to measure quality of life amongst caregivers of people with PD [39] and will be used in this study.

The BriefCOPE is a frequently used coping scale and its subscales have been shown to predict distress and wellbeing [60]. The Multidimensional Scale of Perceived Social Support is a subjective assessment of social support [42]. Coping style may alter the way an informal caregiver deals with the challenges and stresses of caring and a caregiver's perception that they have good social support may have a protective effect [59].

Measures used in all three groups

There is evidence to suggest that people with PD are at risk of weight loss and malnutrition [61]. Moreover, malnutrition is prevalent in older adults and is responsible for many significant health-related negative outcomes [62-64]. We will quantify nutrition risk using the Seniors in the community: risk evaluation for eating and nutrition, Version II (SCREEN-II) scale which is a valid and reliable tool to measure nutritional status.

Frailty is a syndrome of loss of physiological reserve which confers greater vulnerability to negative health outcomes; it is considered to be a dynamic condition in which individuals may transition to an improved, as well as more advanced, frailty state [65]. The Frailty Instrument for Primary Care of the Survey of Health, Ageing and Retirement in Europe (SHARE) is a phenotypic frailty assessment tool; in this study, we have opted to use the SHARE tool which was developed and validated in those aged 75 years and over, in which assessment of handgrip strength was substituted with a question about walking [24]. In the SHARE cohort, walking was assessed by a clinician; in this study, we have adapted the SHARE-FI75+ for self-reported completion. Sarcopenia, a disease characterised by low muscle strength, together with low muscle quantity or quality, may contribute to the development of physical frailty [66]. SARC-F is a rapid screening tool for sarcopenia [25] which will be used.

Caregivers are often older adults [9] and may themselves be living with frailty, sarcopenia and risk of malnutrition, hence the SARC-F, SHARE-FI75+ and SCREEN-II questionnaires will also be included in the caregiver questionnaire booklet, as well as the patient and representative-completed booklets.

In order to contextualise the responses to other questionnaires collected in this study, we have compiled some questions to gather information about any symptoms of Covid-19 infection experienced by participants, whether they have had to self-isolate or shield, and their experience of accessing care during the pandemic.

Sample size

The sample size is pragmatic based on the total available number of potentially eligible people with parkinsonism at this single centre. There are approximately 1,200 people with parkinsonism who are within the geographical catchment of the RUH Bath. The likely response rate is unclear but we anticipate we will achieve a response rate of over 40% which would result in 480 completed patient questionnaires.

A previous cross-sectional postal survey, with a response rate of 58.2%, noted a mean Parkinson's Disease Questionnaire-39 (PDQ-39) summary index score of 44.6 (SD 17.6) [67]. With a sample size of 480 we can estimate a mean PDQ-39 score with the following precision of approximately +/- 3.3 points. This 95% confidence interval range is sufficiently precise for descriptive purposes. Further sub-groups e.g., by age group and gender will be less precise.

Statistical analysis

Results will be displayed as descriptive statistics using mean plus standard deviation for normally distributed variables and median plus interquartile range for skewed variables. Multivariable linear and logistic regression models will be used to test simple associations. Our a priori hypotheses are that we will show worse health needs and greater disability with increasing age, disease duration and gender. Other variables of interest include socioeconomic status, geography (urban-rural), and ethnicity (though we have limited numbers of ethnic minorities in this catchment area so will be underpowered). We are specifically interested to test how these factors could potentially interact with each, using goodness of fit or likelihood ratio tests. We will also examine if other covariates such as multi-morbidity could act as potential mediators. For example, men with similar disease duration may have greater disability partially due to a greater burden of cardio-respiratory disease. Since these are exploratory subgroup analyses, we are cognisant of the potential for type 1 error due to multiple testing.

Where possible, we will follow the recommendation of the questionnaires' authors for how to deal with missing questionnaire responses, for example pro rating the score, where appropriate. We will explore which factors predict the missing variables and then use multiple imputation methods, assuming these are "missing at random" to combine the effects over 10 simulated datasets and incorporating uncertainty using Rubin's rules. This will allow us to conduct a sensitivity analysis to compare the complete case with the imputed results.

Limitations

Despite our efforts to reduce barriers to participation, in order to recruit a representative sample of people with parkinsonism, there will inevitably be some non-response bias. We also acknowledge that the region around RUH Bath is not ethnically diverse. Additionally, some recruited participants may not complete and return all questionnaires, although we aim to minimise missing data by following up any queries by telephone. Finally, this study only assesses symptomatology using questionnaire-based measures; there would be benefit to triangulating these self-reported measures with digital measures in the future.

Patient and public involvement statement

This study has been designed and performed in conjunction with the study public involvement advisory group (PIAG), all of whom have PD. The PIAG been critical to the design and content of participant information leaflets and consent forms. Changes made as a result of their valuable contribution include:

- Improved sensitivity around terminology for those who care for someone with PD, acknowledging that they may live with someone who has PD but not see themselves as a carer/caregiver, but may 'provide support'. The term 'caregiver' was preferred over 'carer' and therefore used throughout the study documentation.
- Inclusion of an approximate time to complete the questionnaires in the participant information leaflet and we further emphasised that the questionnaires are intended to be completed at home
- Inclusion of information for plans regarding dissemination of results to participants.

Ethics and dissemination

This protocol was approved by the London - Brighton & Sussex Research Ethics Committee on 27 July 2020 (REC reference 20/LO/0890). It is registered with the ISRCTN (11452969).

All participants will either provide written informed consent or, in the case of patient participants who lack capacity to consent to participation in the study, a consultee will provide advice on their prior wishes and will sign a consultee declaration if they believe the patient would be willing to participate.

If the person with parkinsonism has opted not to participate themselves, it is necessary, so far as possible, for us to collect some basic information about who the caregiver supports. In this case, the person with PD (or their personal consultee if they lack capacity to make decisions about the study) is asked to sign a section on the back of the caregiver consent form if they are happy for their caregiver to provide basic information about them.

Participants can choose to withdraw for any reason at any time during their involvement in the study and will not be followed up after withdrawal from the study. They will be asked their reason for withdrawal but do not have to provide this. Data collected up to the time of withdrawal will be used.

We plan to publish the results of this protocol in an international peer-reviewed journal and at academic national and international meetings and conferences. When we share the results of key findings, we will upload a lay summary to the PRIME-Parkinson website.

Authors' contributions

ET, FEL, YBS and EJH were responsible for the concept of the study and contributed to study development and design. ET, DEB and MDS contributed to patient recruitment. ET drafted the manuscript and all authors provided critical revision and approved the final protocol.

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Data statement

Access to the data will be available through application to the Chief Investigator. Pseudo-anonymised data may be shared with other researchers to enable meta-analyses.

Competing Interests Statement

EJH received funding from the National Institute of Health Technology (NIHR), the Gatsby Foundation and Parkinson's UK; received fees for speaking and consultancy from Profile pharma Medicys and Luye; and received travel support from Bial Abbvie and Ever pharma.

YBS is a recipient of a Radboud Excellence award. He has received research support from the UK Medical Research Council, Wellcome Trust, NIHR, Parkinson's UK, Versus Arthritis, Gatsby Foundation, Dunhill Trust, and received a Radboud Excellence Award.

All other authors declare that they have no competing interests.

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For peer review only

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1	"...a protocol for the PRIME-UK cross-sectional study"
			2	"In this single site cross-sectional study..."
	(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2	Methods and analysis summarises what will be done What was found- N/A	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3	Introduction (paragraphs 1-4)
Objectives	3	State specific objectives, including any prespecified hypotheses	4	Paragraph 5 of introduction
			12	Statistical analysis "Our a priori hypotheses are that we will show..."
Methods				
Study design	4	Present key elements of study design early in the paper	4	Study design and population section
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4	Study design and population
			7	Data collection: "Recruited participants will complete a single questionnaire booklet..."
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up		
		<i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls		
		<i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	5	Inclusion/exclusion criteria

		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed		N/A
		<i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8 5	Methods of assessment and Inclusion criteria
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7 8	Methods of assessment section Table 1
Bias	9	Describe any efforts to address potential sources of bias		
Study size	10	Explain how the study size was arrived at	11/12	Sample size section: “The sample size is pragmatic based on...”

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Statistical analysis
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Statistical analysis
		(b) Describe any methods used to examine subgroups and interactions	12 Statistical analysis, 1 st paragraph
		(c) Explain how missing data were addressed	12 Statistical analysis, 2 nd paragraph
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	This is a cross-sectional where all eligible participants have been invited so sampling weights are not required.
		(e) Describe any sensitivity analyses	Statistical analysis, 2 nd paragraph
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	N/A
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	N/A
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	N/A
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	N/A
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	N/A
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/A
		(b) Report category boundaries when continuous variables were categorized	N/A
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	N/A
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	N/A
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	N/A
Generalisability	21	Discuss the generalisability (external validity) of the study results	N/A
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13 Funding statement

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.