

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The needs of patients with parkinsonism and their caregivers: a protocol for the PRIME-UK cross-sectional study
AUTHORS	Tenison, Emma; Lithander, Fiona; Smith, Matthew; Brazier, Danielle; Ben-Shlomo, Yoav; Henderson, Emily

VERSION 1 – REVIEW

REVIEWER	Memon, Adeel A The University of Alabama at Birmingham, Department of Neurology
REVIEW RETURNED	04-Nov-2021

GENERAL COMMENTS	<p>Tenison and colleagues presented the protocol for the PRIME-UK cross-sectional study. It is a well-written article, which aims to collect data through the questionnaire to address the heterogeneity of health needs for people with Parkinsonism. I think it is a critical study to carry out; however, I am worried that this is not the best way to describe the overall symptomatology and phenomenology of PwP quantitatively (mentioned in line 13, page 6). Instead of using a questionnaire, if the authors aim to describe the overall burden of the disease quantitatively (including phenomenology), then maybe collecting the data via devices would be a better strategy. For example, one can use a smartwatch to capture data like ECG (to look for heart rate variability to assess autonomic dysfunction), sleep pattern, the activity level in a day, etc. Likewise, one can use a video recording on a smartphone to determine the gait, tremor, bradykinesia, etc. However, I understand that we cannot acquire all the data digitally like depression, caregiver stress, frailty, bowel function, etc. So, maybe using a hybrid approach would be the best way to get the high impact/valuable data that could be used to address the heterogeneity semiquantitatively.</p>
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REVIEWER	Petersen, Maria The Faroese Hospital System, Department of Occupational Medicine and Public Health
REVIEW RETURNED	10-Nov-2021

GENERAL COMMENTS	<p>This is a detailed and transparent study protocol with the aim of describing 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.</p> <p>I have a few comments. It is not clear from the protocol how you will deal with risk of not getting all questionnaires answered and</p>
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	<p>secondly in the same field, the protocol does not address or discuss limitation or pitfalls. One could imagine that because of the comprehensive questionnaire booklet, a number of participants will not complete all questionnaires – how you will handle lack of completed questionnaires? Have you had considerations about how many questionnaires to employ? Any discussion of the number of questionnaires. It seems comprehensive but without assessment of how long it takes to complete, it's difficult to assess.</p> <p>Minor comments:</p> <p>Abstract. Why calling it a condition rather than disease? You write personal consultee. However, it is not very clear for the reader who this individual is. Could you use another title?</p> <p>p4. L. 40-42. Why can a caregiver take part regardless of the PwP? And what about the opposite situation?</p> <p>p. 5. L. 48. How do you identify and contact informal caregivers?</p> <p>p. 6. L-5 How do you assess and gain evidence that can suggest lack of capacity to consent?</p> <p>P6. L 6. What is meant by capacity assessment is triggered? How will that be triggered? And will you make a new phone call to assess their mental capacity.</p> <p>p6. l.8. personal consultee. I suggest explaining more or rephrase to next-in kind. Also, how do you identify personal consultee.</p> <p>P6. L. 27. Please include assessed time to answer the questionnaire, i.e. how long do you assess the questionnaires will take to complete. And how are they being returned?</p> <p>P10. Line 55. I acknowledge that difficult to assess participation but is there no former experience with this group or similar groups to give an better assessment?</p> <p>p. 11. You touch upon methods to deal with missing data. Maybe be more specific...</p>
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REVIEWER	Russell, Grant Monash University, School of Primary Health Care
REVIEW RETURNED	11-Nov-2021

GENERAL COMMENTS	<p>Thank you for the opportunity to review this manuscript: The needs of patients with parkinsonism and their caregivers: a protocol for the PRIME-UK cross-sectional study for BMJ Open. The study is set in the catchment area of the Royal United Hospital Bath NHS Trust and includes patients suffering from Parkinson's Disease and their primary informal care givers. The dates of the study are for 12 – 24 months from September 2020, and it appears to be a protocol for an ongoing study (data collection is likely to have commenced prior to submission). In keeping with your requests for reviews of protocols my comments relate to clarifications to the rationale or details relating to the methods. I can confirm that there are no results or conclusions presented, no major flaws in the study (apart from concerns about the length of the questionnaire and</p>
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associated participant burden, and uncertainties about the recruitment rate influence on the sample size)

Over all the paper was well constructed, flowed well and was easy to read. I do, however have some areas of concern, that, if addressed would improve the work. I feel that the authors should be well able to address these concerns and would be happy to review further iterations.

Areas Of Clarification

Introduction:

While the acronym PwP has been used in the Parkinson's community it is not commonly or widely understood and I would suggest that it is spelt out appropriately and/or substituted where relevant. PD is appropriate in this context.

Page 5 Line 37 Hoehn and Yahr stage should be clarified for those non familiar with the staging system.

Page 5 line 45-57: This is an important paragraph in justifying the study. It would be helpful if the authors could spell out the proportion of patients likely to have been excluded from these larger studies. It is important context. Given the importance of the methods with respect to patients attending movement disorder clinics, it would be valuable to know any data as to what proportion of patients across the community living with PD attend such clinics. Page 6 Line 17 needs a reference to the statement (it may be ref 13, but if so it would be good to reword by linking the concepts in the second and third sentences.)

Methods

Page 7 Line 9 Please clarify if this is (as is alluded below) a movement disorder specialist working in the movement disorder service. It is unclear as to what profession the specialist would have. Are they medically qualified?

Page 7 Line 21 It would be clearer if the authors could provide more detail on exclusion criteria #3

Page 7: Clarification of the status of Non English speakers would be valuable. As written there is no mention whatsoever of translation, availability in other languages etc.

Page 7 Line 47-56: There is insufficient detail on the recruitment process. We need to know who writes the letter, who makes the follow up calls to non respondents and when.

Page 8 line 3-19 While the process of ascertaining capacity is documented, I found it difficult to understand. Some subheadings or sign posts may help.

Page 8 line 26-43 - this section is repetitive and could be tightened up to increase clarity.

Table 1: this is a very useful table. I believe that the number of questionnaire items per instrument should be included.

Page 11 Line 52-56: The authors suggest that the sample size is calculated with reference to the PDQ-39. I have concerns however about their assumption that the response rate will be between 40 and 70%. Some reassurance as to whether this is achievable with respect to the likely numbers of people with PD in the catchment area. For example a recent US study generated a response rate of 21% (see <https://www.nature.com/articles/s41531-020-00152-9>) This is comparable to a range of other studies. A 20% response rate would really compromise the purported precision.

Page 13 Line 12-19: I feel that there is limited detail on the statistical analysis. I would have appreciated an a priori hypothesis

	<p>and more detail on methods used to examine subgroups and interactions, control for confounding, handling missing data and to account for issues in the sampling strategy</p> <p>Limitations</p> <p>There are a number of limitations to this study that I feel should be alluded to in the paper. The only reason not to include them would be if this was part of the policy of the journal to confine such a discussion to an outcome paper.</p>
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REVIEWER	Marsili, Luca University of Cincinnati, Neurology and Rehabilitation Medicine
REVIEW RETURNED	11-Nov-2021

GENERAL COMMENTS	<p>I read with interest the study protocol to assess the broad range of health needs for people with parkinsonism (PwP) and their carers concerning their stage, comorbidities, and sociodemographic characteristics. The study design is clear and well-defined. I do have only a few comments:</p> <ul style="list-style-type: none"> - I was wondering if the study protocol is designed to include also the possibility of doing tele-visits. Telemedicine will play a more critical role in the next future, and having this possibility embedded in study protocols will become the standard. Please, add a comment on that aspect. It would also be interesting to have web platforms and apps that patients could use to download material for the study (as consent forms or scales). This aspect will help in the broader diffusion of the questionnaires, allowing to reach more participants (if compared to the conventional approach with forms mailed via traditional mail) - Is this going to be a population-based study? Please, clarify. Regarding the issue of being more inclusive in the enrollment, maybe the authors could briefly mention other ongoing studies (e.g., the PPMI, Luxembourg, PPP, and CCBP) to see similarities and differences and their strategies to enroll participants without limitations. - Regarding patients and caregiver participation, is there any payment (even symbolic or through gift cards) for them? It could be a way to acknowledge their contribution and efforts. - Regarding the questionnaire booklets, are you planning to collect data on daytime sleepiness, ADL/iADL, and RBD? What about other demographical information: family history of neurodegenerative diseases; traumatic brain injuries; surgery; cancer; exposure to other toxics or caffeine intake; recreational drugs. Are you planning to collect this data? Please, argue. - Regarding the patient and public involvement statement, do you have a website that participants could see/visit (and maybe log in with their credentials)? Also, how are you planning to share updates of the study (e.g., enrollment plan, achievements, goals..) with them? Are you planning to create a newsletter? Please, argue.
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REVIEWER	Irons, J. Yoon University of Derby, Health and Social Care Research Centre
REVIEW RETURNED	12-Nov-2021

GENERAL COMMENTS	<p>Thank you for inviting me to provide peer-review on this study protocol. Overall, it is a well-written article. I wish the research team success with the proposed study. It seems to be a worthwhile and useful project. I'd like to make some comments and point out a couple of minor issues.</p>
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	<ol style="list-style-type: none"> 1. Page 5 Line 37 – 40: Increasing age, ... and declining function ARE associated... 2. Page 13 Line 18-20: dealing with missing data. The authors stated, “we will use multiple imputation methods and other methods...”. Would it be possible to elaborate on the ‘other methods’? 3. Page 13 Line 36/37: “we further emphasized...” Br Eng spelling would be emphasised. 4. Has the research team planned to record how many ‘personal consultees’ have filled out the questionnaires? Just a comment. Would the personal consultees know about sexual function of PWP? For example. I appreciate that this study has received Ethical approval. 5. Page15 Ref #2. Year is missing 6. I appreciate that the authors provided PPI statement. I’m slightly concerned that there are a lot of questionnaires for participants and their caregivers to fill out. I wonder whether the research team has discussed the ‘burden’ issues with the PIAG and if yes, how they are going to address that. 7. Are there any incentives for participants? 8. I wonder whether the authors can also report their study registration details.
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VERSION 1 – AUTHOR RESPONSE

Reviewer comment	Authors’ response	Location of change
Reviewer 1		
It is a well-written article, which aims to collect data through the questionnaire to address the heterogeneity of health needs for people with Parkinsonism. I think it is a critical study to carry out.	We thank Reviewer 1 for acknowledging that this is a critical study.	N/A
I am worried that this is not the best way to describe the overall symptomatology and phenomenology of PwP quantitatively (mentioned in line 13, page 6). Instead of using a questionnaire, if the authors aim to describe the overall burden of the disease quantitatively (including phenomenology), then maybe collecting the data via devices would be a better strategy. For example, one can use a smartwatch to capture data like ECG (to look for heart rate variability to assess autonomic dysfunction), sleep pattern, the activity level in a day, etc. Likewise, one can use a video recording on a smartphone to determine the gait, tremor, bradykinesia, etc. However, I	The study was designed to be delivered entirely in people’s homes without any study visits. We are conscious that technology is advancing that may facilitate capture of non-motor and motor measures using digital apps and devices and the inclusion of these more objective measures would be of value. We chose, however, to use validated, conventional paper measures because this was more acceptable to this more frail and less-technologically literate population but we are certainly looking to explore a hybrid technology and conventional approach in future studies. There were also financial constraints that precluded this approach. We have added a comment about the potential future benefits of triangulating these self-	Limitations section

<p>understand that we cannot acquire all the data digitally like depression, caregiver stress, frailty, bowel function, etc. So, maybe using a hybrid approach would be the best way to get the high impact/valuable data that could be used to address the heterogeneity semiquantitatively.</p>	<p>reported measures within the newly added limitations section.</p>	
<p>Reviewer 2</p>		
<p>This is a detailed and transparent study protocol with the aim of describing 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.</p>	<p>We thank reviewer 2 for recognising that the study protocol is detailed and transparent.</p>	<p>N/A</p>
<p>It is not clear from the protocol how you will deal with risk of not getting all questionnaires answered and secondly in the same field, the protocol does not address or discuss limitation or pitfalls. One could imagine that because of the comprehensive questionnaire booklet, a number of participants will not complete all questionnaires – how you will handle lack of completed questionnaires?</p>	<p>Thank you for raising this important point. We have a procedure in place to mitigate against missing data and have now added the following paragraph to the section on 'methods of assessment':</p> <p><i>“If questionnaire booklets have not been received by the research team within 2 weeks of them being posted to participants, the research team will telephone the participant to answer any queries and to offer support. If the participant returns a questionnaire with one or more questions left blank or incorrectly completed (e.g. multiple options are selected for a question which requires only one answer), the participant will be contacted by telephone and asked if they are willing to clarify their answers.”</i></p> <p>We have added a section on potential limitations of the study, in addition to the existing article summary which highlights some potential limitations.</p>	<p>Methods of assessment and limitations sections</p>
<p>Have you had considerations about how many questionnaires to employ? Any discussion of the number of questionnaires. It seems comprehensive</p>	<p>This study aims to undertake detailed and holistic phenotyping of people with parkinsonism in a geographical area and it is</p>	<p>Methods of assessment</p>

<p>but without assessment of how long it takes to complete, it's difficult to assess.</p>	<p>therefore necessary for us to include questionnaires on a broad range of topics.</p> <p>We have now included the approximate completion times for each of the 3 questionnaire booklets within the section 'methods of assessment', based on published literature, where available.</p> <p>We recognise the burden of completing long questionnaires. Study participants do not have to complete the questionnaires on one single occasion but instead can complete the questionnaires over a period of several days with or without the help of a caregiver. They can also be supported with this process via telephone by the study team if required. We have extended the second sentence of the section on methods of assessment to read <i>"Where able, participants will self-complete the questionnaires and can do this over a number of days"</i>.</p>	
<p>Why calling it a condition rather than disease? (abstract)</p>	<p>We have amended this to disease.</p>	<p>Abstract, 1st line</p>
<p>You write personal consultee. However, it is not very clear for the reader who this individual is. Could you use another title? (abstract)</p>	<p>The term personal consultee is the legal term used in guidance published by the U.K. Department of Health (https://www.manchester.gov.uk/download/downloads/id/12218/guidance_on_nominating_a_consultee_for_research_involving_adults_who_lack_capacity_to_consent.pdf) so we have retained this terminology. We have now added further explanation within the main text about the term personal consultee: <i>"...usually a close family member or friend who knows the potential participant in a personal capacity..."</i> to ensure that the meaning is clear to an international readership.</p>	<p>Identification and involvement of a personal consultee</p>
<p>p4. L. 40-42. Why can a caregiver take part regardless of the PwP? And what about the opposite situation?</p>	<p>An important focus of this study is to explore caregiver wellbeing and experience. We therefore do not wish to preclude informal caregivers from taking part where the person they support has opted not to participate. From an ethical point of view, it is also important to respect caregiver autonomy, though it is likely that a caregiver will respect the views of the person with parkinsonism if</p>	<p>Study design and population</p>

	<p>they feel strongly that they should not take part.</p> <p>Likewise, a person with parkinsonism can take part regardless of whether they have an informal caregiver and, if they do, whether this person has agreed to take part. A line has been added to the study design and population to clarify this point.</p> <p><i>“A person with parkinsonism may take part in the study regardless of whether they have an informal caregiver and, if they do, whether this person wishes to take part. Likewise, a caregiver may participate regardless of whether the person with parkinsonism, for whom they care, wishes to take part.”</i></p>	
p. 5. L. 48. How do you identify and contact informal caregivers?	A paragraph explaining this identification process has been added within the sampling and recruitment procedures section under the subheading “Identification of caregivers.”	Identification of caregivers
p. 6. L-5 How do you assess and gain evidence that can suggest lack of capacity to consent?	In the section ‘adults lacking capacity to consent to participation in research’ we state that this will be in accordance with the U.K. Mental Capacity Act 2005 2 stage test. We have added the reference to the MCA 2005 Code of Practice in case readers wish to read more about this process. We have also added further details about the situations which may prompt assessment of capacity as well as the steps taken to help a potential participant to make a capacitous decision where possible.	Adults lacking capacity to consent to participation in research
P6. L 6. What is meant by capacity assessment is triggered? How will that be triggered? And will you make a new phone call to assess their mental capacity.	<p>We have discussed the situations which may prompt capacity assessment within the section ‘adults lacking capacity to consent to participation in research’</p> <p><i>“Situations which will prompt capacity assessment include return of incomplete or partially completed consent forms; an individual (such as care home staff or a patient’s 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.”</i></p>	Adults lacking capacity to consent to participation in research

	<p>In this same paragraph, we have added the following sentence which clarifies that the capacity assessment may be conducted within the same phone call or on an alternative occasion, depending on what would optimise the patient's ability to take part in decision-making.</p> <p><i>"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)."</i></p>	
<p>p6. l.8. personal consultee. I suggest explaining more or rephrase to next-in kind. Also, how do you identify personal consultee.</p>	<p>Thank you for raising this. We have added a new subheading ("Identification and involvement of a personal consultee") within which we explain how these individuals are identified.</p>	<p>Identification and involvement of a personal consultee</p>
<p>P6. L. 27. Please include assessed time to answer the questionnaire, i.e. how long do you assess the questionnaires will take to complete. And how are they being returned?</p>	<p>The estimated time to complete each of the 3 questionnaires has now been added to the 2nd paragraph of 'methods of assessment'.</p> <p>A few words have been added to the first sentence of this section to clarify that questionnaires are returned by post: <i>"...and will be asked to return this to the research team in the pre-paid envelope provided."</i></p>	<p>Methods of assessment</p>
<p>P10. Line 55. I acknowledge that difficult to assess participation but is there no former experience with this group or similar groups to give a better assessment?</p>	<p>The UK-based postal survey which we cite within the sample size section achieved a response rate of 58.2%, which we have now noted within this section.</p> <p>However, we appreciate that the response rate achieved by Jenkinson et al. is higher than is sometimes achieved in this population and note Reviewer 3's comment about a recent US study (see https://www.nature.com/articles/s41531-020-00152-9) which generated a 21% response rate.</p> <p>In the current study, we are taking particular steps to reduce barriers to participation and to proactively prompt and support people to take</p>	<p>Sample size</p>

	part, so we anticipate that we will achieve a response rate of over 40%. We have edited the sentence about the response rate to read <i>“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.”</i>	
p. 11. You touch upon methods to deal with missing data. Maybe be more specific...	We have expanded this section which now reads as follows: <i>“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 analysis with the imputed results.”</i>	Statistical analysis
Reviewer 3		
In keeping with your requests for reviews of protocols my comments relate to clarifications to the rationale or details relating to the methods. I can confirm that there are no results or conclusions presented, no major flaws in the study (apart from concerns about the length of the questionnaire and associated participant burden, and uncertainties about the recruitment rate influence on the sample size)	Thank you for your positive comments about this study. We recognise the burden of completing long questionnaires. Study participants do not have to complete the questionnaires on one single occasion but instead can complete the questionnaires over a period of several days with or without the help of a caregiver. They can also be supported with this process via telephone by the study team if required. This has been documented in the manuscript. The concern about recruitment rate/sample size is addressed below.	N/A
Over all the paper was well constructed, flowed well and was easy to read. I do, however have some areas of concern, that, if addressed would improve the work. I feel that the authors should be well able to address these concerns and would be happy to review further iterations.	We are grateful to Reviewer 2 for recognising that the paper is well-constructed.	N/A

<p>While the acronym PwP has been used in the Parkinson's community it is not commonly or widely understood and I would suggest that it is spelt out appropriately and/or substituted where relevant. PD is appropriate in this context.</p>	<p>This acronym has been substituted with either "people with PD" or "people with parkinsonism", depending on the context.</p>	<p>Throughout</p>
<p>Page 5 Line 37 Hoehn and Yahr stage should be clarified for those non familiar with the staging system.</p>	<p>This has been changed to 'functional disability'.</p>	<p>Introduction, 3rd paragraph</p>
<p>Page 5 line 45-57: This is an important paragraph in justifying the study. It would be helpful if the authors could spell out the proportion of patients likely to have been excluded from these larger studies. It is important context.</p>	<p>Patients are likely to have been excluded from these studies both for explicit reasons (e.g. because the study excluded people above a certain age cut off) and implicitly (because aspects of the study design led to barriers to participation, for example, study information only being provided in writing meaning that the information was not accessible to potential participants with visual impairment).</p> <p>We have examined these studies' results and it is challenging, if not impossible, to estimate the numbers excluded for either reason. Authors often do not report a flowchart presenting numbers excluded at each stage of the eligibility screening process and may also not report the response rate achieved from those who were eligible/invited.</p>	
<p>Given the importance of the methods with respect to patients attending movement disorder clinics, it would be valuable to know any data as to what proportion of patients across the community living with PD attend such clinics.</p>	<p>U.K. guidelines advocate that the diagnosis of Parkinson's and related conditions should be made by a movement disorder specialist. As such the vast majority of patients with suspected disease are referred to movement disorder services.</p> <p>It is however possible that we will not have captured people with suspected parkinsonism who are in the process of being referred to a movement disorder clinic nor those who are lost to follow-up or who have chosen not to engage with specialist services. To address this issue, we additionally screened lists of patients coded as having parkinsonism during an inpatient admission.</p>	<p>Sampling and recruitment procedures</p>

	<p>The first paragraph of the sampling and recruitment procedures section now reads as follows:</p> <p><i>“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”.</i></p>	
<p>Page 6 Line 17 needs a reference to the statement (it may be ref 13, but if so it would be good to reword by linking the concepts in the second and third sentences.)</p>	<p>We thank Reviewer 3 for drawing our attention to this omission. We have added a reference (Chaudhuri KR, Odin P, Antonini A, Martinez-Martin P. Parkinson’s disease: the non-motor issues. <i>Parkinsonism Relat Disord.</i> 2011;17(10):717-23) to line 17 of the last paragraph of the introduction. We realise that reference 13 had been duplicated at the end of the following sentence (“However, more global aspects...”) in error, whereas it should only be included with lines 3-4. This sentence reflects our evaluation of the literature and hence no reference is available.</p>	<p>Final paragraph of introduction</p>
<p>Page 7 Line 9 Please clarify if this is (as is alluded below) a movement disorder specialist working in the movement disorder service. It is unclear as to what profession the specialist would have. Are they medically qualified?</p>	<p>We have added <i>“made by a movement disorder specialist (a physician sub-specialising in neurology or geriatric medicine)”</i> to clarify this eligibility criteria.</p>	<p>Inclusion criteria</p>
<p>Page 7 Line 21 It would be clearer if the authors could provide more detail on exclusion criteria #3</p>	<p>We have added an example to this exclusion criterion: <i>“e.g. individuals in the last days/weeks of life”</i></p>	<p>Exclusion criteria</p>
<p>Page 7: Clarification of the status of Non English speakers would be valuable. As written there is no mention whatsoever of translation, availability in other languages etc.</p>	<p>We have added <i>“identify if there are any requirements for translation”</i> to the section on sampling and recruitment to indicate that an important function of the telephone calls is to identify participants for whom English is not their first language. Telephone translation services can be used if required.</p>	<p>Sampling and recruitment procedures</p>

<p>Page 7 Line 47-56: There is insufficient detail on the recruitment process. We need to know who writes the letter, who makes the follow up calls to non respondents and when.</p>	<p>We have added “<i>by the study team on behalf of their Parkinson’s clinician</i>” to the 2nd paragraph of the ‘sampling and recruitment procedures’ section.</p> <p>Regarding the timing of follow up calls, we have added “... <i>after they have had at least 1 week to consider the information</i>” and have clarified that these calls are made by the study team.</p> <p>We have also added a paragraph to the section on ‘methods of assessment’ to clarify the process for follow up calls to participants who have consented but not returned a questionnaire.</p>	<p>Sampling and recruitment procedures; methods of assessment</p>
<p>Page 8 line 3-19 While the process of ascertaining capacity is documented, I found it difficult to understand. Some subheadings or sign posts may help.</p>	<p>Thank you for this valid comment. We have separated the process of assessing capacity and then identifying/involving a personal consultee into 2 separate sub-headings and added some additional information about the process in response to comments from Reviewer 2.</p>	<p>Adults lacking capacity to consent; identification and involvement of a personal consultee</p>
<p>Page 8 line 26-43 - this section is repetitive and could be tightened up to increase clarity.</p>	<p>Thank you for this valid point. The second paragraph of the section on ‘methods of assessment’ has been revised. Some repetition is necessary to ensure there is no ambiguity about who completes each of the three questionnaire booklets.</p>	<p>Methods of assessment</p>
<p>Table 1: this is a very useful table. I believe that the number of questionnaire items per instrument should be included.</p>	<p>Thank you for this valuable suggestion. We have added an additional column to state the number of items for each questionnaire.</p>	<p>Table 1</p>
<p>Page 11 Line 52-56: The authors suggest that the sample size is calculated with reference to the PDQ-39. I have concerns however about their assumption that the response rate will be between 40 and 70%. Some reassurance as to whether this is achievable with respect to the likely numbers of people with PD in the catchment area. For example a recent</p>	<p>We acknowledge the concerns around the likely response rate. In this study, we are purposefully taking steps to mitigate the challenges of achieving a good response to a postal survey, in particular by conducting one or more follow up telephone calls to potential participants who do not respond to the postal invitation. This is important not only to boost the initial response rate but to ensure that individuals who are typically under-</p>	<p>Sample size</p>

<p>US study generated a response rate of 21% (see https://www.nature.com/articles/s41531-020-00152-9) This is comparable to a range of other studies. A 20% response rate would really compromise the purported precision.</p>	<p>represented in research are supported and facilitated to take part wherever possible. We anticipate that this proactive approach to recruitment is likely to translate into a better response rate than is typically seen in postal/online studies. We have edited the sentence about the response rate to read <i>“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.”</i></p>	
<p>Page 13 Line 12-19: I feel that there is limited detail on the statistical analysis. I would have appreciated an a priori hypothesis and more detail on methods used to examine subgroups and interactions, control for confounding, handling missing data and to account for issues in the sampling strategy</p>	<p>We have expanded the ‘statistical analysis’ section to include further detail on handling missing data and on subgroup analyses.</p>	<p>Statistical analysis</p>
<p>There are a number of limitations to this study that I feel should be alluded to in the paper. The only reason not to include them would be if this was part of the policy of the journal to confine such a discussion to an outcome paper.</p>	<p>We have added a section entitled ‘limitations’.</p>	<p>Limitations</p>
<p>Reviewer 4</p>		
<p>I read with interest the study protocol to assess the broad range of health needs for people with parkinsonism (PwP) and their carers concerning their stage, comorbidities, and sociodemographic characteristics. The study design is clear and well-defined.</p>	<p>We are grateful to Reviewer 4 for describing the study design as clear and well defined.</p>	<p>N/A</p>
<p>I was wondering if the study protocol is designed to include also the possibility of doing tele-visits. Telemedicine will play a more critical role in the next future, and having this possibility embedded in study protocols will become the standard. Please, add a comment on that aspect. It would also be interesting to have web platforms and apps that patients could use to</p>	<p>Our ethics approval included the possibility of electronic consent and online questionnaire completion, although in practice we have so far used written consent and completion has been by post or facilitated by telephone. We thank the reviewer for this useful point. In future phases of our work, and where study visits are required, we will include the option for visits to be conducted virtually.</p>	<p>N/A</p>

<p>download material for the study (as consent forms or scales). This aspect will help in the broader diffusion of the questionnaires, allowing to reach more participants (if compared to the conventional approach with forms mailed via traditional mail)</p>		
<p>Is this going to be a population-based study? Please, clarify.</p>	<p>This study is a cross-sectional study recruiting individuals from a specific geographical region who have parkinsonism. Importantly, we are sampling from a district general hospital, rather than from a specialist or tertiary centre. Whilst this is not truly population-based, because we may miss people with parkinsonism who are undiagnosed or who have not been referred to secondary care, given this study is based in a free health care system with good access, it is equivalent to a population-based study.</p>	
<p>Regarding the issue of being more inclusive in the enrollment, maybe the authors could briefly mention other ongoing studies (e.g., the PPMI, Luxembourg, PPP, and CCBP) to see similarities and differences and their strategies to enroll participants without limitations.</p>	<p>A detailed description of these biomarker development cohorts is beyond the scope of this protocol paper but we agree that it is encouraging that these studies generally have broad inclusion criteria. We have added a sentence to the penultimate paragraph of the Introduction to highlight the CCBP: <i>“It is, however, encouraging to note that some ongoing biomarker development cohorts are taking an inclusive approach towards recruitment, including the Cincinnati Biomarker Program which is enrolling participants with any form of parkinsonism or dementia, at any disease stage, though participant burden may implicitly exclude some participants.”</i></p>	<p>Introduction, 4th paragraph</p>
<p>Regarding patients and caregiver participation, is there any payment (even symbolic or through gift cards) for them? It could be a way to acknowledge their contribution and efforts.</p>	<p>Participants do not receive any payment or incentive. We have added the following line to the 'sampling and recruitment procedures' section to clarify this: <i>“Research participants do not receive any remuneration or incentive for taking part, but all postal costs are covered.”</i></p>	<p>Sampling and recruitment procedures</p>
<p>Regarding the questionnaire booklets, are you planning to collect data on daytime sleepiness, ADL/iADL, and RBD? What about other demographical information: family history of neurodegenerative diseases; traumatic brain injuries; surgery; cancer; exposure</p>	<p>We have not included the additional information listed (e.g. caffeine intake, exposure to toxins) since this study is not aiming to explore aetiological factors in the development of parkinsonism.</p>	<p>N/A</p>

<p>to other toxics or caffeine intake; recreational drugs. Are you planning to collect this data? Please, argue.</p>	<p>The Non-motor symptom questionnaire (NMSQ), within the questionnaire booklet for patient participants with capacity to consent to research, contains a question about daytime somnolence (Q22- “finding it difficult to stay awake during activities such as working, driving or eating”). The NMSQ also includes a question about “talking or moving about in your sleep as if you are ‘acting’ out a dream” which relates to REM sleep behaviour disorder.</p> <p>Although the Parkinson’s Disease Questionnaire-39 (PDQ-39) is a health-related quality of life scale, it contains 6 items relating to activities of daily living (such as washing, dressing, cutting up food). To minimize burden on participants, whilst seeking to take a broad and holistic perspective on the experience and needs of people with parkinsonism, we have not included separate questionnaires to assess sleep or activities of daily living within the booklet for participants with parkinsonism with capacity to consent to research.</p> <p>The questionnaire booklet completed by a representative (on behalf of a participant with parkinsonism who lacks capacity to consent to research) includes the Bristol Activities of Daily Living Scale in order to describe this in greater detail for participants who are likely to have the highest care needs.</p>	
<p>Regarding the patient and public involvement statement, do you have a website that participants could see/visit (and maybe log in with their credentials)? Also, how are you planning to share updates of the study (e.g., enrollment plan, achievements, goals..) with them? Are you planning to create a newsletter? Please, argue.</p>	<p>Participants can visit the study website (https://primeparkinson.blogs.bristol.ac.uk/)</p> <p>It is stated within the ‘ethics and dissemination’ section: “When we share the results of key findings, we will upload a lay summary to the PRIME-Parkinson website.”</p>	<p>N/A</p>
<p>Reviewer 5</p>		

<p>Thank you for inviting me to provide peer-review on this study protocol. Overall, it is a well-written article. I wish the research team success with the proposed study. It seems to be a worthwhile and useful project.</p>	<p>We thank the reviewer for these comments.</p>	<p>N/A</p>
<p>Page 5 Line 37 – 40: Increasing age, ... and declining function ARE associated</p>	<p>Thank you for drawing our attention to this typographical error which we have now corrected.</p>	<p>Introduction, 3rd paragraph</p>
<p>... Page 13 Line 18-20: dealing with missing data. The authors stated, “we will use multiple imputation methods and other methods...”. Would it be possible to elaborate on the ‘other methods’?</p>	<p>We have expanded this section which now reads as follows: <i>“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.”</i></p>	<p>Statistical analysis</p>
<p>Page 13 Line 36/37: “we further emphasized...” Br Eng spelling would be emphasised.</p>	<p>Thank you. This has been corrected to ‘emphasised’</p>	<p>PPI statement, point 2</p>
<p>Has the research team planned to record how many ‘personal consultees’ have filled out the questionnaires? Just a comment.</p>	<p>A personal consultee is only sought for participants with parkinsonism who are found to lack capacity to make a decision about involvement in the research. In this case, a bespoke questionnaire, designed for completion by a representative (close friend or relative of the person with parkinsonism) is posted to the individual acting as representative. We are therefore recording how many full patient questionnaire booklets are sent out and completed and how many adapted patient questionnaire booklets (for representative completion) are sent out and completed. These data will be presented when the results are published.</p>	<p>N/A</p>
<p>Would the personal consultees know about sexual function of PWP? For example. I appreciate that this study has received Ethical approval.</p>	<p>The Scopa-Aut questionnaire, which includes questions on sexual function, is not included in the questionnaire booklet for completion by representatives who complete questionnaires on behalf of a person with parkinsonism who lacks capacity to consent to the study.</p>	<p>N/A</p>

	The questionnaire booklet for completion by a representative has been specifically compiled to be suitable for proxy completion and, as far as possible, includes questionnaires validated for use in this way.	
Page15 Ref #2. Year is missing	Thank you; this has been added.	Reference 2
I appreciate that the authors provided PPI statement. I'm slightly concerned that there are a lot of questionnaires for participants and their caregivers to fill out. I wonder whether the research team has discussed the 'burden' issues with the PIAG and if yes, how they are going to address that.	<p>This study aims to undertake detailed and holistic phenotyping of people with parkinsonism in a geographical area and it is therefore necessary for us to include questionnaires on a broad range of topics.</p> <p>We have now included the approximate completion times for each of the 3 questionnaire booklets within the section 'methods of assessment', based on published literature, where available.</p> <p>We recognise that the assessments are in-depth. We advocate that study participants can complete the questionnaires in more than one sitting, with or without the help of a caregiver to avoid the effects of fatigue etc. They can also be supported with this process via telephone by the study team if required.</p> <p>Anecdotally, in our experience, the length of the questionnaires does not have much influence on those who are keen to participate but, for those who are ambivalent, it may of course be more of a factor in their decision.</p>	Methods of assessment
Are there any incentives for participants?	Participants do not receive any payment or incentive. We have added the following line to the 'sampling and recruitment procedures' section to clarify this: <i>"Research participants do not receive any remuneration or incentive for taking part, but all postal costs are covered."</i>	Sampling and recruitment procedures

I wonder whether the authors can also report their study registration details.	The study is registered with the ISRCTN (ISRCTN11452969 https://doi.org/10.1186/ISRCTN11452969)	Ethics and dissemination
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VERSION 2 – REVIEW

REVIEWER	Memon, Adeel A The University of Alabama at Birmingham, Department of Neurology
REVIEW RETURNED	27-Mar-2022

GENERAL COMMENTS	Thanks for addressing all the comments and concerns.
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REVIEWER	Petersen, Maria The Faroese Hospital System, Department of Occupational Medicine and Public Health
REVIEW RETURNED	07-Apr-2022

GENERAL COMMENTS	My comments and concerns have been addressed by the authors and manuscript revised accordingly. I have no further comments.
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REVIEWER	Russell, Grant Monash University, School of Primary Health Care
REVIEW RETURNED	01-Apr-2022

GENERAL COMMENTS	Thank you for your comprehensive response to my and the other reviewer's evaluation of the manuscript. I feel that all my questions have been addressed. I have no further concerns.
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REVIEWER	Marsili, Luca University of Cincinnati, Neurology and Rehabilitation Medicine
REVIEW RETURNED	28-Mar-2022

GENERAL COMMENTS	I commend the authors for their work. They addressed all my points. I do not have any further comments.
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REVIEWER	Irons, J. Yoon University of Derby, Health and Social Care Research Centre
REVIEW RETURNED	04-Apr-2022

GENERAL COMMENTS	Many thanks for addressing fully the issues that 5 reviewers have raised. The manuscript reads really well. Well wishes to the author team with the study.
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