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Research Report

Enhancing Trial Delivery in Parkinson's Disease: Qualitative Insights from PD STAT

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Abstract.

Background: Recruitment and retention of participants in clinical trials for Parkinson's disease (PD) is challenging. A qualitative study embedded in the PD STAT multi-centre randomised controlled trial of simvastatin for neuroprotection in PD explored the motivators, barriers and challenges of participants, care partners and research staff.

Objective: To outline a set of considerations informing a patient-centred approach to trial recruitment, retention, and delivery.

Method: We performed semi-structured interviews and focus groups with a subset of trial participants and their care partners. Quantitative and qualitative data were obtained through surveys circulated among the 235 participants across 23 UK sites at the beginning, middle and end of the 2-year trial. We also interviewed and surveyed research staff at trial closure.

Results: Twenty-seven people with PD, 6 care partners and 9 researchers participated in interviews and focus groups. A total of 463 trial participant survey datasets were obtained across three timepoints, and 53 staff survey datasets at trial closure. Trial participants discussed the physical and psychological challenges they faced, especially in the context of OFF state assessments, relationships, and communication with research staff. Care partners shared their insights into OFF state challenges, and the value of being heard by research teams. Research staff echoed many concerns with suggestions on flexible, person-centred approaches to maximising convenience, comfort, and privacy.

Conclusion: These considerations, in favour of person-centred research protocols informed by the variable needs of participants, care partners and staff, could be developed into a set of recommendations for future trials.

Keywords: Parkinson's disease, clinical trial, participation, recruitment, retention, OFF assessment, consent, patient-centred, qualitative, PPI

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative condition comprising a range of motor symptoms, including the classic triad of tremor,

rigidity and bradykinesia, as well as postural instability [1] and a range of autonomic and neuropsychiatric deficits [2, 3] which may often precede and follow diagnosis. The impact of PD on quality of life, social and occupational function is significant for the individual, their family and care partners, and society as a whole. PD currently affects approximately 6 million individuals globally [4], a number which has been conservatively projected to double by 2040 [5].

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Signs and symptoms may affect individuals not only in the seventh decade of life but also those younger than 50, can vary dramatically between patients, and progress at variable rates over time. This diverse clinical picture reflects etiopathological heterogeneity, implicating diverse, interacting culprits at the level of cellular dysfunction, genetic underpinning and environmental triggers [6]. Thus, in addition to better symptomatic treatments, personalised neuroprotective strategies with a view to effectively slowing or halting its inexorable progress throughout brain and body are vitally needed. Currently, disease modification represents an area of huge unmet need in PD [7], as randomized, double blinded, placebo controlled clinical trials (RCT), which still represent the evidential gold standard [8], put novel or repurposed compounds to the test.

In PD, the challenge in an RCT is to demonstrate clinical improvement indicative of impact on the disease process, unconfounded by symptomatic benefit, in a significant number of participants within the trial cohort, which may also inevitably include some who do not benefit presumably because the therapeutic is ill-matched to their pathologic driver. Over the past decade, trial designs have become increasingly complex and involve multiple assessments over prolonged time periods [9], some of which are carried out following transient dopaminergic withdrawal. In this relative 'OFF' state, clinical assessment aims to capture the nature and extent of motor, cognitive and neuropsychiatric deficit [10] unmasked by the symptomatic relief offered by daily medication regimes. In recognition of the aforementioned clinical heterogeneity, trial inclusion criteria have also become more rigorous in a bid to isolate those who are likely to respond using phenotypic, genotypic, and biochemical criteria. Once appropriate participants are identified, they are recruited by clinicians or clinical research staff [11] into the trial, but their retention until its completion depends on their ability to withstand the practical, physical, and psychological challenges posed by continued trial participation. Ongoing care partner support is vital for trial retention, reflecting their significant interpersonal, psychosocial and practical contribution to everyday activities, medication compliance and even help with trial procedures, questionnaires, and transport [12]. Inevitably, and as the science progresses, stringent protocols and strenuous procedures among other factors have led to participant enrolment falling as much as 21% and trial retention plummeting by a third, leading to costly delays [13]. Moreover, studies

in other clinical research areas have shown that the perspectives and experience of research staff are valuable in elucidating how protocols are enacted on the ground and how practice may have diverged from these [14]; these studies also explored the procedural challenges faced by staff and strategies they used to balance clinical and research roles [15].

In the current study, we investigated the experiences of participants, care partners, and staff as key players on the ground, uniquely placed to give us real time feedback on our multi-centre trial, PD STAT, a 26-month, double blind, placebo-controlled phase II futility study of simvastatin for disease modification in PD [16]. Based on its favourable safety profile and a compelling set of preclinical data and epidemiological observations [17], PD STAT began recruiting people with PD in 2016, in order to investigate its neuroprotective properties. In parallel, we used qualitative methods to explore the experiences and understand the motivators and reinforcers to participate, and barriers and challenges to continued participation faced over the course of the trial by a subset of participants and their care partners, as well as research staff who were involved in delivering it. Our aim was to use PD STAT as a platform from which to begin to explore how recruitment and retention could be improved in trials for PD, and how to improve the deliverability of such trials in the future.

MATERIALS AND METHODS

Participants

The qualitative study, 'Experience of Trial Participation', was an embedded sub-study in the PD STAT trial. The reader is referred to the full protocol for further information on study design and inclusion criteria [16]. The study was approved by the North East - Newcastle & North Tyneside 2 Research Ethics Committee (15/NE/0324) and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

The study was introduced to trial participants by a research nurse or clinician at the baseline assessment visit. A database of interested volunteers was created, from which participants were selected using a purposive sampling strategy [18] to ensure that the sample drawn from different study sites was of a representative range in terms of age and gender. Participants recruited in the southwest of England (demographic characteristics in Table 1) included 1) 10 eligible individuals of whom 7 were interviewed again at trial

Table 1
Participant demographics

	Eligible trial participants	Ineligible trial participants	Withdrawn trial participants	Carer partners
<i>n</i>	10	9	8	6
Male	5	6	5	4
Female	5	3	3	2
Age range (y)	43–74	59–78	46–66	60–68

closure and 4 participated in a midway focus group, 2) 8 who commenced but subsequently withdrew from the trial, 3) 9 who were found ineligible at screening. Six care partners (CP) participated in a focus group, two of whom (one female, one male) withheld their age. In addition, a pen and paper survey was circulated among all randomised participants across 23 research sites at baseline, 12 and 26 months: these were completed by 169/235, 152/205, and 142/182 participants at each respective timepoint.

The research team overall comprised 97 clinical research practitioners and 30 principal investigators/clinicians. A purposefully sampled subgroup was identified among these with different roles within the study (clinician principal/sub-investigators, clinical research practitioners, blinded raters, and study coordinators) with the aim of identifying 5 research staff members from sites with good retention and 5 from sites with the lowest retention rates. Nine agreed to be interviewed. All research staff were invited to complete a survey at the end of the trial and 53 participated.

Procedure

The semi-structured interviews with trial participants, each lasting between 15 min to 1 h, took place at approximately one month into the 26-month PD-STAT trial and within one month of its conclusion, at participants' homes. The two focus groups lasting approximately 1.5 h, one with patients and one with care partners, took place midway through the trial at 12 months. The former took place at the Peninsula Clinical Trials Unit, Plymouth, UK and the latter at the Merlin Multiple Sclerosis Therapy Centre, Cornwall, UK. Participant information sheets (PIS) were sent to all participants prior to interview/focus groups. Signed informed consent was obtained.

The discussion began with confirmation that participants were aware of the aims of the study before discussing their evolving experience of living with PD since diagnosis in order to contextualise their

future responses and establish rapport. Open-ended questions were employed to explore 1) reasons for participation in this trial, 2) their experience during PD STAT including challenges, 3) how the trial impacted on everyday life, and 4) their suggestions for future trials (interview guides in Supplementary Materials). In total, patient interviews and the focus group yielded 15.8 h and 64.6 min of audio recorded data respectively. The care partner focus group yielded 79.6 min of audio recorded data.

The surveys sent by post to all participants comprised questions and statements with prompts regarding extent of agreement, which were later quantitatively analysed, as well as free text box responses which were submitted to framework analysis. At baseline, the survey items focused on 1) how written information about the trial and the consent process had been received and understood, 2) factors that influenced the decision to join the trial, 3) feedback on different aspects of study visits, including concern regarding future OFF state assessments, and 4) further suggestions for the future study visits. At 12 months, the survey items focused on aspects of communication with the study team, ongoing experience in the trial and suggestions for improvement. At 26 months, we surveyed communication with the study team as well as the home-based OFF state assessments.

In the semi-structured interviews conducted with research staff, consent and interviews were performed over the telephone. Staff were encouraged to share their thoughts on 1) their experience of the trial including logistics, 2) challenges they faced, 3) how retention could be improved in future trials, and 4) design improvements for future studies. These interviews yielded 6.4 h of audio recorded data. The survey circulated electronically focused on a range of themes including site logistics related to study visit organisation, thoughts on retention methodologies to be built into the protocol and areas of improvement.

Analysis

The audio recording data were anonymised, coded, and individually transcribed *in extenso* and *verbatim*. They were subjected to iterative qualitative analysis with the aim of generating a set of themes that reflected the varied experiences associated with participating in and running a RCT. The overall aim was to extract from the data a range of perspectives, attitudes, and experiences, preserving the individuality of each participant and their unique experience of the trial, rather than arriving at consensus. Arriving

at consensus among our patients and carers would risk obliterating the heterogeneity of impairment and hence need which lies at the core of the condition, characterises the PD STAT patient sample and the current qualitative study. The aim of our work overall was to encourage trialists to consider the breadth of that need and its variability. We sought to understand where agendas may overlap and where there may diverge. Thus, the data for each participant group were analysed separately using a framework analysis approach [19, 20], which comprised several stages that occurred iteratively. Familiarisation with the data was initially achieved by a continuous process of recursively reading through the transcripts and listening to the recorded interviews. The raw data were segmented into frequently used phrases, sentences and paragraphs that were mapped out onto identifiable codes for each participant. Each concept map was examined for emerging relationships between data and conceptual patterns through word clusters, to produce a thematic framework. Codes representing issues and concepts evolved into sub themes and themes and categorized to facilitate the interpretation of the varied meanings that emerged. In this essentially interpretive process through the continuous interaction between data and analysis, the evolving themes shaped one another iteratively as new ones emerged and were considered within their broader context and in relation to existing ones. They were identified both deductively through the open questions that served to structure the interviews and survey items, and inductively through intense coding. Analysis continued until no new themes emerged and saturation was reached. The analysis was cross validated by three authors (JG, AAK, CC).

Numerical questionnaire data were summarised using descriptive statistics. Free text responses were transferred to separate documents divided into baseline, 12 months, and 26 months responses. The analysis used this timeline to establish context. These data were analysed along with those from the interview and focus group using the framework approach.

RESULTS

The qualitative themes identified in the interviews and focus groups are presented alongside those that emerged in the surveys separately for each group (PD patients, care partners and research staff, in Tables 2, 3, and 4 respectively). Where appropriate these are supplemented with quantitative observations as the survey data allowed. Overall, several issues identified

Table 2

Themes and subthemes identified in patient narratives through semi-structured interviews, focus groups and qualitative feedback in surveys

Themes	Subthemes
Motivators	Altruism Disappointment and sense of failure at ineligibility related to altruism Benefit to Self
Trial experience and Reinforcers	Well informed Psychosocial benefits Positive relationships with research staff
Challenges and barriers to participation	Off state assessments <ul style="list-style-type: none"> ● Unexpected physical compromise ● Psychological impact ● Logistics and travel to study centres ● Reason for withdrawal ● Need to be better informed in advance Medication <ul style="list-style-type: none"> ● Side effects ● Handling and swallowing problems
Trial organisation	Communication and information sharing Scope for improvement in communications Timely reimbursement Advance planning of study visits

Table 3

Themes and subthemes identified in the care partner focus group

Themes	Subthemes
Trial experience	Good rapport with staff Sometimes overlooked Expertise as daily observers Practical involvement in care and trial participation
Challenges	Off state assessments <ul style="list-style-type: none"> ● Practical challenges ● Emotional burden ● Prolonged recovery ● Need for better support during trial
Trial organisation	Smooth Availability and support by research team

in the patient and care partner narratives were echoed by staff.

PD patients

The main motivators for trial participation emerged consistently across interviews, focus groups and qualitative comments in the survey. In line with previous findings, this included altruism in both those who participated and those found ineligible, who also expressed a sense of disappointment or failure. Personal benefit also emerged as a motive, both for the in-depth assessment that trial participation affords and the study drug itself, which can be positively

Table 4

Themes and subthemes identified in the research staff semi-structured interviews and surveys

Themes	Subthemes
Trial experience	Good communication with central team
	Good organisation
	Benefits of long study visits and continued interaction
	Multiple roles
	Feelings of connection to participants
Motivators	Pride in work
	Competitiveness around targets
Challenges and demotivators	Logistics related to environment inside and outside centres
	Research management and inflexible Trust policies
	Inability to offer home visits
	Internal conflict related to OFF state assessments
	Target driven research and paperwork
What works for patients	Flexible person-centric strategies around home visits
	Early OFF state assessments
	Transport
	Refreshments
	Supporting independence
	Benefits of remote trial management
	End of study information card
Factors affecting retention	Unexpected impairment during OFF state assessments
	Drug side effects
Suggestions for improved trial delivery	Options of home visits or virtual visits including for OFF state assessments
	Dynamic protocols
	Better communication between sites and within teams
	Research team continuity
	Benefits of research staff embedded in clinical teams
	Manage care partner relationships

reinforced by clinicians. Participants felt well informed when recruited into the study. This was mirrored in the survey data at baseline: across the 11 items probing satisfaction and understanding with information shared, agreement ranged from 91% to 98%. Others who were subsequently ineligible expressed the need for more information. In addition, it was suggested that a database of 'expert' participants could aid recruitment. The experience of participating in the trial itself was described as positive owing to the ongoing relationship with the research teams, and their time investment. Being treated with respect and dignity for some participants stood in contrast to experiences in their lives more broadly.

They don't talk to you like you've got an illness, they talk to you like you're a normal person (Patient interview 1 162)

Positive relationships with the trial staff were also reaffirmed in the survey and final interview.

The psychosocial benefits of trial participation were highlighted by many and are particularly important in the context of isolation due to mobility issues and its social implications.

The challenge most prominently identified in the qualitative data was the OFF state assessment; also, 32% of survey respondents reported anxiety and concern at baseline about this assessment and its logistics, which remained an issue in subsequent surveys at 12 and 26 months. The rationale and timings of the OFF state assessments were documented in the PIS, with the caveat that the experience would likely be different for each participant. However, some participants requested greater preparation for these challenging assessments, especially those who had been on dopaminergic regimes for several years and were consequently unable to predict the physical and psychological compromise. Some cited travelling to hospital for these assessments as uncomfortable and difficult, and others elaborated on the unexpected confrontation with the extent of their disease progression. Critically, a number of participants explained that they withdrew from the trial due to their adverse OFF experience and the prospect of future assessments. This significant minority is mirrored in the study attrition rates associated with intolerable OFF state (19/235), accounting for 19/51 (37%) of participants who withdrew at different timepoints between recruitment and the 26-month visit.

I wasn't prepared for how unpleasant... and I think it's a double whammy with Parkinson's in that when the symptoms are pronounced, my dopamine level is low as well, not only am I physically uncomfortable, my brain and mood is less tolerant... it's just too much and I chickened out at that point (Withdrawn 6 54)

Participants also commented on the embarrassment of attending clinics in the OFF state and particularly undertaking assessments (e.g., the 10m timed walk) in a public space. Nonetheless, among the 142 participants who completed the trial and 26-month survey, 138 (97%) stated they would consider taking part in a future trial requiring OFF state assessments. Of the 4 individuals who indicated that they would not, 2 said they would reverse their position if the assessment were undertaken at home. Participants requested a more flexible, person-centred approach to engaging with individual difficulties and impairment experienced during these visits as the logistics

of accessing the study sites were cited as challenging, especially by those who were frail. The survey data reinforced the request to consider that the needs of some participants may be greater than others', and that specific advice and care should be tailored to meet these regarding travel, along with the options of home visits and overnight accommodation to support trial retention.

The second challenge concerned the study drug and placebo preparation. Comments pertained to adverse effects, described in the PIS and reported in the media, an issue which is specific to PD STAT given the notoriety of statins in association with myalgia, but is worth considering and mitigating in relation to other studies employing repurposed drugs. Participants told us of their experiences with side effects—either leading to withdrawal or rendering ongoing participation more challenging. The process for recording adverse events, a daily diary, was also perceived as burdensome by some. The withdrawn participants' narratives highlighted that this can lead to a sense of failure or even letting down the research team, which must also be carefully managed. Another piece of actionable feedback from our participants concerned the size and form of the dispensed tablets and their containers which some found difficult to swallow and handle. Such considerations are essential when designing trials for neurological conditions involving participants with motor and swallowing difficulties.

Trial organisation comments pertained to communication, reimbursement, and advance planning of study visits. Overall, communication with local research teams was deemed satisfactory. At 12 months, 96% reported regular contact by the research team, and 79% indicated that they felt up to date with the trial as it evolved. Rapport and ongoing relationships between participants and research staff facilitated information exchange regarding the particulars of each visit. However, some respondents felt that higher level information sharing about the overall progress of the trial through the newsletter or study website could be improved, and some participants were not aware of the website until the end of the trial. In addition, some participants clearly explained that information and communication are appreciated beyond the end of the study, regarding the overall trial results and their treatment allocation. Other aspects of trial organisation which could have been improved concerned timely travel compensation, which was variable across sites. Travel expenses was not raised as a major issue, although

it was suggested that the equity of reimbursement for car fuel needs review. A final important piece of feedback concerned study visit coordination. Some participants, particularly those in employment, told us that advance notice of appointment times could be improved, in order to request time off work, and to factor in recovery after dopaminergic withdrawal.

Care partners

Our work with care partners highlighted different dimensions to the experience of the trial. Overall, they expressed their satisfaction at being involved in the focus group and would have welcomed further opportunities to meet as a group to share their experiences. Some expressed frustration at feeling overlooked by health professionals despite their significant role in supporting their partner and, importantly, observations of their condition and symptoms in everyday life. Care partners explained their integral supporting role in trial participation and procedures, such as assisting the trial participant with taking the study medications or completing questionnaires. In addition, their insights and observations of the effects of study medications may also be usefully probed during the trial itself. There was consensus that the trial ran smoothly and there was good rapport with the research teams. Many appreciated that the OFF state appointments were often scheduled early in the day so that trial participants could resume their dopaminergic regime as soon as possible.

Mirroring an important challenge voiced by patients, the care partners' experience of witnessing their partner in the OFF state was cited as emotionally distressing and practically challenging.

Awful, it absolutely was, because I mean he can barely get out of bed in the morning, and at least on three occasions one had to get to (location). So even just to get him down the stairs and get him dressed, and then into a taxi and out the other end... He hated it, I hated it. (Care partner 2)

This individual's experience captures aspects of the often unspoken reality of life and/or care partners of people with PD. On this occasion, they elaborated on their position of being inadequately supported by the research team who apparently failed to anticipate this. Although the option of telephoning the team for support was available, this involved leaving voice-mail with no certainty of when help would become available. This was not 'direct help when you need it'. The prolonged recovery phase after the OFF state

462 assessment was also discussed. There was general
463 agreement that it took days rather than hours for
464 patients to return to their baseline, which was evi-
465 dently unanticipated.

466 *Research staff*

467 Research staff shared satisfaction with their
468 involvement in PD STAT and trial organisation,
469 thanks also to good communication with the central
470 research team. They took pride in their work and were
471 motivated by competitiveness. Staff, like patients,
472 valued the time they could spend with participants
473 and appreciated how this improved the quality of the
474 data they were able to obtain. Across the board, they
475 commended participants' zeal, and extended their
476 research role to encompass additional medical and
477 psychosocial support.

478 *There was plenty of time to talk about how they*
479 *were feeling and what their concerns were about*
480 *the situation. So, I think that was the most valu-*
481 *able thing for them really, to have someone to*
482 *speak to just from a social perspective (Staff inter-*
483 *view 431)*

484 At the end of this 2-year trial, some conveyed dis-
485 appointment and even a sense of loss of connections
486 with participants.

487 Logistical issues pertaining to the configuration of
488 the research environment were a frequent source of
489 frustration across different sites. At some centres,
490 there was no designated research room to accom-
491 modate the assessments and 10 m walk test, which
492 were resumed in different rooms or even public areas.
493 Furthermore, travel arrangements for home visits
494 were frequently described as a source of difficulty,
495 due to impractical workplace policies, variable or
496 no access to pool cars, difficulties with claiming
497 travel expenses, car insurance issues if using pri-
498 vate vehicles and poor public transport connections.
499 Notwithstanding practical issues, staff reported ten-
500 sion between good patient care and the constraints
501 and demands imposed by the protocol and local
502 logistics. In line with feedback from patients and
503 care partners, staff also found OFF state assessments
504 challenging. These assessments generated significant
505 dissonance for them; the compassion and duty of
506 care long ingrained in healthcare professionals may
507 not naturally align with delivering a protocol that
508 includes the physically trying experience of dopamin-
509 ergic withdrawal in a person with PD.

510 *If you've got someone who's got Parkinson's,*
511 *who's progressing with a disease over two years,*
512 *you're asking a lot of them to go OFF anyway,*
513 *even if they've got minor symptoms, and some of*
514 *these people had quite major symptoms. And that*
515 *was a problem from our perspective because ulti-*
516 *mately our patient care is our priority, not the*
517 *study, so patients have to be safe. (Staff interview*
518 *145)*

519 This was compounded by inflexible local policies
520 around home visits or on occasion the inability to
521 offer refreshments and adequately reimburse travel,
522 causing professional embarrassment. Here, we iden-
523 tify consequences both in terms of moral injury to
524 staff, and inclusivity impacting on trial data:

525 *because otherwise you end up with the better off*
526 *middle-class more capable patient, and it does*
527 *introduce, if you're not careful, an element of*
528 *bias into your inclusion and exclusion criteria if*
529 *you're limited because of travel or finances. (Staff*
530 *interview 139)*

531 Cumbersome paperwork and target driven recruit-
532 ment associated with delivering a multicentre study
533 were also discussed. Over the course of the recruit-
534 ment period, different sites adjusted their local targets
535 downward to meet them, with foreseeable negative
536 repercussions.

537 Staff shared their willingness and person-centred
538 strategies to flexibly accommodate individual par-
539 ticipants according to their needs, by opting for
540 early OFF assessment appointment times so that
541 medication could be resumed as soon as possible,
542 flexibility in rescheduling or extending appointments,
543 and arranging patient transport. Supporting trial par-
544 ticipants in these ways was important for those who
545 did not have a care partner or who chose to attend our
546 research centres alone; for them, trial participation
547 represented a means of asserting their independence.
548 Additionally, considering that PD STAT continued
549 throughout the COVID-19 pandemic in the UK,
550 remote trial delivery methods were implemented.
551 Although for some participants the use of video con-
552 ferencing was difficult or impossible due to technical
553 problems, staff noted that remote assessments may
554 have put others at ease, possibly due to social dis-
555 tancing afforded by video consultation and feeling
556 more relaxed in their home setting. Staff felt this
557 facilitated social interaction and may have reduced
558 participants' tremor which was ascribed to reduced
559 anxiety (although a sensitivity analysis comparing

remote with face to face assessments revealed no significant differences). Staff also commented positively on the end of study information card which explained whom participants could contact for study findings and unblinding their drug allocation.

Mirroring the patient narratives, staff identified the OFF state assessments and medication-related challenges especially in the context of declining health over the 2-year trial as significant factors affecting retention. Suggestions for improvement included home visits for OFF state assessments as part of the protocol, supported financially and through local policy, to avoid bias that could introduce confounds in participant selection:

Supporting home visits from an early stage and consulting with staff management to encourage it - this would help the staff doing the home visits as well as the participants. Being aware maybe of unconscious bias by some sites of excluding patients with a greater disability whose retention was helped by home visits. The difficulty is that 'off period' visits are useful but very draining on patients (Staff survey)

Staff asked for more dynamic protocols with built-in flexibility to accommodate a range of needs and abilities, adapted to medication regime, including digital technology and video conferencing to assess participants at home where possible. Alternatively, overnight stays in hospital or nearby hotel accommodation were also suggested for those whose disability would otherwise preclude OFF state visits. Although staff appreciated the PD STAT newsletters, they suggested that bolstering interaction with patients and improving their awareness of how the study was progressing across different centres could be beneficial for both recruitment and retention. They readily identified the essential contribution of solid working relationships with participants, and the value of research nurses embedded within the routine care clinical teams. The composition of the research teams and continuity within these was identified as important. Inclusion of a PD nurse specialist can be a reassuring way of touching base with any concerns or new issues patients may be dealing with. In general, continuity within research teams and interactions with familiar healthcare professionals in the context of research can generate opportunistic health benefits, in terms of picking up on common minor ailments or educating participants on their condition, reducing inter-rater variability and improving data quality. Within teams, the ability to communicate

shared goals and shared investment also contributes to retention. Some staff shared with us their belief that if care partners did not fully approve of participation, this would affect recruitment and retention. For these reasons, establishing fluent relationships with them was suggested as a parallel aim although in some situations, awareness of the care partner's influence on a participant may even raise safeguarding issues.

DISCUSSION

This qualitative study on the experiences of patients, care partners and research staff in PD STAT aimed to understand the motivators, reinforcers, and barriers to participation, as well as challenges faced by each involved party, how these impacted on trial delivery and how this could be improved. Through interviews, focus groups and surveys, we gleaned insights into the highs and lows, what worked, what didn't and what might, as the individuals participating in and working on this trial progressed through its assessments over the course of 26 months. To our knowledge, this study is the first of its kind in the field of PD research to concurrently address the trial experience as it evolved.

Embedded and implicit throughout the narratives analysed in this study were suggestions and requests on how a future trial could improve on the current one, which can only be elicited through qualitative methodology. They allow us to anticipate some of the challenges that we and others designing and delivering clinical trials may face, and to outline a set of salient considerations which could serve to support future work on a consensus approach among a wider range of stakeholders.

Enhancing trial recruitment

Participant recruitment remains a thorny issue in PD trials, with 85% of trials delayed by recruitment difficulties and 30% failing to recruit a single subject [21]. We considered it necessary to tap into what motivates both people with PD as well as the care partners who support them through the trial process and found this was both altruism and personal gain. This sets up a range of expectations. Perceived benefit in terms of clinical care, improved disease awareness, early identification of issues and timely intervention, were key enablers of recruitment and retention identified by participants and staff alike. Health outcomes for patients enrolled in clinical trials can be superior to those treated outside of the trial context

659 [22–24] and similar gains may be seen for patients
660 treated in hospitals with high research participation
661 (e.g., [25]). The causal pathway likely reflects numer-
662 ous factors underlying empowered engagement with
663 healthcare and responsible self-management, which
664 in turn lead to both research participation and over-
665 all better health outcomes. Nonetheless, at least part
666 of these benefits also reflects the time for extended,
667 free-flowing conversations which enable symptom
668 identification and more rapid access to timely and
669 targeted care. Notwithstanding the utility and signifi-
670 cant advantages of telemedicine in the management
671 of PD [26–28] and the feasibility of remote trial
672 delivery methods [29, 30], some of the psychosocial
673 benefits associated with in-person contact may
674 be lost in the remote context, and this is of concern
675 to patients [31]. Clinical research nurses embedded
676 within clinical teams [32] can help capitalise on
677 existing relationships formed during routine clinical
678 care and improve inclusivity by promoting partici-
679 pation. Bringing the trial to the patient increases the
680 likelihood that candidates well matched in terms of
681 inclusion and exclusion criteria are identified and
682 optimally recruited. Moreover, tapping into pride and
683 a sense of friendly competition between sites may
684 serve to bolster recruitment efforts, and could be
685 further supported by monthly newsletters including
686 leader boards, success stories and tips for recruitment
687 from both participants and staff.

688 One of the principal themes that emerged from
689 the narratives of both trial participants and staff per-
690 tained to dynamic patient-centred protocols which
691 accommodate the challenges and limitations individ-
692 ual participants may face. PD trials tend to mostly
693 target and recruit older participants, and protocols
694 are often designed based on assumptions around
695 lifestyles traditionally associated with retirement. We
696 urge trialists to consider that many of these assump-
697 tions rule out participation for otherwise eligible
698 participants who may still be in employment, may
699 have caring duties themselves, or have young onset
700 PD [33, 34] and hence are in full time employment
701 often with parallel family commitments.

702 *Enhancing retention: Managing OFF state* 703 *assessments and study drug challenges*

704 We focus closely on OFF state assessments. Across
705 the board, our patients, care partners and staff whose
706 voice this article amplifies, cited these as the greatest
707 challenge due to the physical and cognitive com-
708 promise they entail [35]. For patients, these were

709 psychologically confronting and physically onerous,
710 accounting for over a third of drop outs. Notably,
711 some PD participants and care partners felt that
712 commensurate advance warning and support from
713 the research team was lacking. It is necessary to
714 address this communication gap. While participants
715 were informed in writing on procedural aspects of
716 OFF assessments and the variability of dopaminergic
717 withdrawal, some found this was more severe than
718 predicted, or felt they had been led to expect, and
719 some found this intolerable. It is difficult to parse
720 *ex post facto* on a case-by-case basis the extent to
721 which this could have been avoided through better
722 communication. Identifying this communication gap
723 is significant and qualitative methodology is a useful
724 means to this end [36]. We learned that understanding
725 why OFF state assessments were required contributed
726 to patients persevering with them, highlighting the
727 importance of shared understanding of what the trial
728 is trying to achieve as a means of enhancing reten-
729 tion. Our drop-out rates were in line with other studies
730 (22.5% over 26 months) [37] but we note that high
731 drop-out rates pose ethical concerns more generally
732 as to whether participant decision making and con-
733 sent have been effectively supported at the outset and
734 throughout the trial [38]. The vast majority of peo-
735 ple with moderate PD will be well acquainted with
736 the detrimental effects of delayed dosing, and missed
737 doses would represent a rare event over the years of
738 living with the condition, but the ethical imperative
739 to inform them in a more concrete way about the OFF
740 state is clear. This pertains to all ongoing and future
741 trials targeting disease modification given our current
742 methods which rely heavily on these assessments.

743 At minimum, we can infer that those written
744 descriptions were inadequate for a significant minor-
745 ity of participants. Digital multimedia approaches to
746 consent have already been tested and shown to confer
747 benefits over and above paper-based information in
748 other areas of medicine (see [39, 40]). Could video
749 recordings and verbal testimonies of a few consented
750 trial participants in their OFF state convey the nec-
751 essary information for consent with greater fidelity?
752 This would better serve future participants in making
753 a sustainable decision to participate in a trial. More-
754 over, a platform of virtual peer support in the form
755 of a database of ‘expert participants’ available to dis-
756 cuss different aspects of the trial as was suggested
757 here, could meet the needs of participants in ways
758 that otherwise available and forthcoming research
759 teams cannot. More work is needed on how best to
760 inform and prepare participants about intrinsically

761 challenging aspects of trials. It will also be necessary
 762 to anticipate ethical problems posed by multime-
 763 dia approaches to informed consent and investigate
 764 their impact on the magnitude of nocebo and placebo
 765 effects.

766 Staff narratives helped us identify issues surround-
 767 ing the impact of logistics on the deliverability of our
 768 publicly funded trial which focused on the accessibil-
 769 ity of study visits, a salient problem in the context of
 770 OFF state assessments, with the potential to introduce
 771 selection bias. Local organisational policies linked
 772 to insurance and work patterns meant that staff at
 773 different sites were not always able to carry out
 774 home visits which would have prevented trial with-
 775 drawal for some participants. PD STAT aimed for
 776 geographical inclusivity, enabling coverage of large
 777 areas of the UK across its 23 sites. To enhance reten-
 778 tion, site policies and processes should be aligned
 779 with protocol provisions, convenience maximised
 780 by full re-imbursement of travel expenses, use of
 781 pre-paid taxis, early morning visits, overnight stays,
 782 convenient on-site parking and meet and greet with
 783 wheelchair. For participants, for whom social embar-
 784 rassment can be a key contributor to quality of life
 785 [41], dedicated assessment space away from public
 786 areas would be much valued. Privacy considerations
 787 also pertain to the home environment.

788 The use of digital technologies instead of in-
 789 person clinic visits could also serve well. However,
 790 until we gain full traction on remote trial delivery
 791 methodology and develop competence and confi-
 792 dence in its implementation, we recommend that
 793 mitigation strategies including home visits, espe-
 794 cially for OFF state assessments, be built into trial
 795 protocols and routinely offered, anticipated through
 796 appropriate budgeting and adequately supported by
 797 funders. Digital enablers of inclusivity such as video
 798 conferencing to carry out remote assessments was
 799 primarily driven by the COVID-19 pandemic, but
 800 future protocols could include it, both to facilitate
 801 study delivery where validated processes exist, and
 802 to build the evidence base to support future method-
 803 ological implementation. One of the many challenges
 804 that we will face in implementing these will be to
 805 discover how the benefits afforded by in-person trial
 806 participation can be reproduced in digital remote
 807 pathways.

808 Finally, adverse experiences with the trial drug
 809 which, real or perceived, all therapies carry, are
 810 significant. Patients and research teams need to be
 811 fully informed about these during the consent pro-
 812 cess, with explicit plans in protocols to mitigate

813 them as appropriate. While for some therapies the
 814 side effects will be well known and may lead to a
 815 nocebo effect, for others especially in early phase
 816 studies, the documentation of adverse events will
 817 form an important part of the trial findings. Adverse
 818 event diaries were implemented in PD STAT but
 819 the limited feedback we received on these indicated
 820 that participants found these too repetitive. Smart-
 821 phone app technologies which might require just
 822 a few minutes daily to complete could be prefer-
 823 able. In PD, tremor, weakness, poor manual dexterity
 824 and swallowing difficulties may be further exacer-
 825 bated by arthritis or other comorbidities as a function
 826 of increasing age, which is a major risk factor for
 827 developing the condition. In PD STAT, we obtained
 828 feedback on dummy versions of the capsules from
 829 a Patient and Public Involvement (PPI) group who
 830 helped us select the over-encapsulated preparation
 831 used in the trial, yet some participants still ran into
 832 difficulties. Could dummy dosing to check accept-
 833 ability of the intervention/drug preparation as part
 834 of the screening or informed consent process be addi-
 835 tionally implemented? Registering this feedback and
 836 adapting future trials also sends a powerful message
 837 to trial participants and represents a true instantiation
 838 of the patient-clinician-researcher partnership.

839 *Other factors affecting trial retention: the roles* 840 *of care partners and research staff*

841 The role of care partners who support people with
 842 PD with every day activities, personal safety and
 843 medication compliance is often under-recognised and
 844 generates its own corollary set of needs [42], research
 845 into which is important and would be welcomed
 846 [43, 44]. In clinical trials, care partners represent an
 847 untapped resource as observers of their partner's PD;
 848 their input and views affect whether a participant
 849 completes the trial [12]. In this study, care part-
 850 ners indicated that patients may misrepresent their
 851 symptoms during consultations and assessments; at
 852 minimum this 'change blindness' is an inevitable
 853 consequence of retrospection and introspection. Clin-
 854 ically, the importance of collateral information from
 855 care partners of people with PD on activities of daily
 856 living [45], everyday language difficulties [46] and
 857 psychiatric symptoms [47] is recognised. Nonethe-
 858 less, some shared with us that they sometimes felt
 859 overlooked or inadequately supported, indicating an
 860 area for improvement. Although in dementia trials
 861 for example, patient self-report is routinely validated
 862 by a care partner interview, we are not aware of any

863 such validation in PD studies. These are necessary.
864 It is likely that care partners will be supporting the
865 person with PD with study participation and proce-
866 dures, so it is important that they also understand
867 the study requirements, particularly potential side
868 effects, as they can support the participant through
869 that and assist retention. Moreover, any new ther-
870 apy (if adopted into care) will also impact on care
871 partners, adding to pill burden and potential for
872 adverse events. Since care partners play a key role
873 in managing compliance to therapy, the impact of
874 any new therapy on them is also relevant [eg, see,
875 48]. Notwithstanding this, feedback from staff sug-
876 gested that care partner involvement may also need
877 to be counteracted with a view to protecting a par-
878 ticipant's autonomy and best interests. Concerning
879 such additional safeguarding dimensions and the
880 thresholds for action warranted by the subtle or obvi-
881 ous cues which research staff may detect, how are
882 superordinate healthcare guidelines implemented in
883 protocols? It is unclear whether and what training
884 is available to help staff navigate these sensitive
885 interactions.

886 An important motivation for this piece of work
887 stemmed from an appreciation of the benefits
888 of motivated and supported research teams, and
889 the instrumental role of well-trained staff. Some
890 researchers reported tension around equipoise [49],
891 when asking patients to withdraw from medication in
892 view of its physical and cognitive repercussions. The
893 emotional toll associated with clinical trials for those
894 delivering them on the ground and the complexity
895 of balancing between clinical and research roles [50]
896 is salient currently, in view of the workforce crisis
897 facing the National Health Service [51, 52] and high
898 levels of burnout [53]. Moreover, emotional tension
899 and ethical challenges may arise for staff at trial clo-
900 sure, at the ending of established relationships as our
901 staff shared with us, and when a potentially benefi-
902 cial treatment may need to be withdrawn [54]. In the
903 realm of both symptom control and disease modifi-
904 cation for PD, such scenaria are easy to predict, and
905 should be mitigated appropriately.

906 *Communication and management of study* 907 *closure*

908 All participants in this qualitative study valued reg-
909 ular communications regarding trial progress, both
910 at the site as well as the superordinate trial level.
911 In PD STAT we relied heavily on newsletters but
912 did not fully exploit the study website, used mostly

913 for recruitment. Personalised and accurate post-trial
914 communication is valued by participants, with a tele-
915 phone call being preferred to a press release [55]
916 as is sensitively handling information on placebo
917 allocation [56]. In PD STAT, we sent out individ-
918 ual letters with the trial results the day before the
919 official press release. We also organised a shared post-
920 study results dissemination event for participants,
921 care partners and study delivery teams; this had been
922 planned to be a series of events held in person at dif-
923 ferent locations within the UK but were converted
924 into a single on-line virtual event due to COVID-19
925 restrictions.

926 Our findings here are in line with the recent impact-
927 ful Innovations in Clinical Trial Design and Delivery
928 for the Under-served (INCLUDE) guidelines [57].
929 Enabling participation in clinical trials for people
930 with PD is necessary, particularly those who are
931 older and with more co-morbidities. Moreover, ethnic
932 minority group enrolment in clinical trials for PD is
933 very low [58] and women are also less likely to enrol
934 [59]; both groups have been historically underrepre-
935 sented in clinical trials. The INCLUDE guidelines
936 aim to reduce barriers and challenges to trial par-
937 ticipation and improve engagement with research for
938 under-served groups. They are aimed at all stakehold-
939 ers as well as funders, whose decisions must take into
940 account the fact that recruiting and retaining those
941 who are hard to recruit and retain, such as people on
942 low income and with dependants, will inevitably cost
943 more. Ensuring diversity and inclusivity in clinical
944 trials is both ethically imperative and scientifically
945 essential [60].

946 A terminal comment pertains to the use of mixed
947 methods and the inclusion of a qualitative compo-
948 nent to RCTs which is rare. This reflects a relative
949 reluctance toward qualitative methods in medical
950 research despite their potential to confer a host of
951 benefits such as facilitating participant recruitment
952 and reinforcing engagement, optimizing the delivery
953 and acceptability of its intervention, and crucially,
954 enabling fluent and sensitive interactions with trial
955 participants whose dynamic needs and motivations
956 can be responded to sooner and more effectively [61,
957 62]. Where they are conducted, their findings are
958 often poorly integrated with those of the trial [63].
959 The current study with its qualitative methodology
960 has brought to light the unique insights, concerns,
961 and strategies of those who participated in and deliv-
962 ered PD STAT. It is hoped that they become lessons
963 learned and bolster the design of better trials in the
964 future.

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

SUPPLEMENTARY MATERIAL

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REFERENCES

- [1] Jankovic J (2008) Parkinson's disease: Clinical features and diagnosis. *J Neurol Neurosurg Psychiatry* **79**, 368-376.
- [2] Chaudhuri KR, Healy DG, Schapira AH (2006) Non-motor symptoms of Parkinson's disease: Diagnosis and management. *Lancet Neurol* **5**, 235-245.
- [3] Kehagia AA, Barker RA, Robbins TW (2010) Neuropsychological and clinical heterogeneity of cognitive impairment and dementia in patients with Parkinson's disease. *Lancet Neurol* **9**, 1200-1213.
- [4] Parkinson's Disease Collaborators GBD (2018) Global, regional, and national burden of Parkinson's disease, 1990-2016: A systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* **17**, 939-953.
- [5] Dorsey ER, Bloem BR (2018) The Parkinson pandemic-a call to action. *JAMA Neurol* **75**, 9-10.
- [6] Espay AJ, Kalia LV, Gan-Or Z, Williams-Gray CH, Bedard PL, Rowe SM, Morgante F, Fasano A, Stecher B, Kauffman MA, Farrer MJ, Coffey CS, Schwarzschild MA, Sherer T, Postuma RB, Strafella AP, Singleton AB, Barker RA, Kieburtz K, Olanow CW, Lozano A, Kordower JH, Cedarbaum JM, Brundin P, Standaert DG, Lang AE (2020) Disease modification and biomarker development in Parkinson disease: Revision or reconstruction? *Neurology* **94**, 481-494.
- [7] Lang AE, Espay AJ (2018) Disease modification in Parkinson's disease: Current approaches, challenges, and future considerations. *Mov Disord* **33**, 660-677.
- [8] Sibbald B, Roland M (1998) Understanding controlled trials. Why are randomised controlled trials important? *BMJ* **316**, 201.
- [9] Athauda D, Foltynie T (2016) Challenges in detecting disease modification in Parkinson's disease clinical trials. *Parkinsonism Relat Disord* **32**, 1-11.
- [10] Chou KL, Stacy M, Simuni T, Miyasaki J, Oertel WH, Sethi K, Fernandez HH, Stocchi F (2018) The spectrum of "off" in Parkinson's disease: What have we learned over 40 years? *Parkinsonism Relat Disord* **51**, 9-16.
- [11] Picillo M, Kou N, Barone P, Fasano A (2015) Recruitment strategies and patient selection in clinical trials for Parkinson's disease: Going viral and keeping science and ethics at the highest standards. *Parkinsonism Relat Disord* **21**, 1041-1048.
- [12] Shim B, Landerman LR, Davis LL (2011) Correlates of care relationship mutuality among carers of people with Alzheimer's and Parkinson's disease. *J Adv Nurs* **67**, 1729-1738.
- [13] Mathur S, Mursaleen L, Stamford J, DeWitte S, Robledo I, Isaacs T (2017) Challenges of improving patient-centred care in Parkinson's disease. *J Parkinsons Dis* **7**, 163-174.
- [14] Lawton J, Jenkins N, Darbyshire JL, Holman RR, Farmer AJ, Hollowell N (2011) Challenges of maintaining research protocol fidelity in a clinical care setting: A qualitative study of the experiences and views of patients and staff participating in a randomized controlled trial. *Trials* **12**, 108.
- [15] Lawton J, Jenkins N, Darbyshire J, Farmer A, Holman R, Hollowell N (2012) Understanding the outcomes of multi-centre clinical trials: A qualitative study of health professional experiences and views. *Soc Sci Med* **74**, 574-581.
- [16] Carroll CB, Webb D, Stevens KN, Vickery J, Eyre V, Ball S, Wyse R, Webber M, Foggo A, Zajicek J, Whone A, Creanor S (2019) Simvastatin as a neuroprotective treatment for Parkinson's disease (PD STAT): Protocol for a double-blind, randomised, placebo-controlled futility study. *BMJ Open* **9**, e029740.
- [17] Carroll CB, Wyse RKH (2017) Simvastatin as a potential disease-modifying therapy for patients with Parkinson's disease: Rationale for clinical trial, and current progress. *J Parkinsons Dis* **7**, 545-568.
- [18] Palinkas LA, Horwitz SM, Green CA, Wisdom JP, Duan N, Hoagwood K (2015) Purposeful sampling for qualitative data collection and analysis in mixed method implementation research. *Adm Policy Ment Health* **42**, 533-544.
- [19] Pope C, Ziebland S, Mays N (2000) Qualitative research in health care. Analysing qualitative data. *BMJ* **320**, 114-116.
- [20] Gale CR, Deary IJ, Wardle J, Zaninotto P, Batty GD (2015) Cognitive ability and personality as predictors of participation in a national colorectal cancer screening programme: The English Longitudinal Study of Ageing. *J Epidemiol Community Health* **69**, 530-535.
- [21] Mathur S (2019) The power of the Parkinson's patient according to Tom Isaacs: A call to action. *Eur J Neurosci* **49**, 304-306.
- [22] Vist GE, Bryant D, Somerville L, Birmingham T, Oxman AD (2008) Outcomes of patients who participate in randomized controlled trials compared to similar patients receiving similar interventions who do not participate. *Cochrane Database Syst Rev*, MR000009.
- [23] Fernandes N, Bryant D, Griffith L, El-Rabbany M, Fernandes NM, Kean C, Marsh J, Mathur S, Moyer R, Reade CJ, Riva JJ, Somerville L, Bhatnagar N (2014) Outcomes for patients with the same disease treated inside and outside of randomized trials: A systematic review and meta-analysis. *CMAJ* **186**, E596-609.
- [24] Nijjar SK, D'Amico MI, Wimalaweera NA, Cooper N, Zamora J, Khan KS (2017) Participation in clinical trials improves outcomes in women's health: A systematic review and meta-analysis. *BJOG* **124**, 863-871.
- [25] Majumdar SR, Roe MT, Peterson ED, Chen AY, Gibler WB, Armstrong PW (2008) Better outcomes for patients treated at hospitals that participate in clinical trials. *Arch Intern Med* **168**, 657-662.

- 1081 [26] Barbour PJ, Arroyo J, High S, Fichera LB, Staska-Pier MM, 1146
 1082 McMahon MK (2016) Telehealth for patients with Parkin- 1147
 1083 son's disease: Delivering efficient and sustainable long-term 1148
 1084 care. *Hosp Pract (1995)* **44**, 92-97. 1149
- 1085 [27] Fincher L, Ward C, Dawkins V, Magee V, Willson P (2009) 1150
 1086 Using telehealth to educate Parkinson's disease patients 1151
 1087 about complicated medication regimens. *J Gerontol Nurs* 1152
 1088 **35**, 16-24. 1153
- 1089 [28] Peacock D, Baumeister P, Monaghan A, Siever J, Yoneda J, 1154
 1090 Wile D (2020) Perception of healthcare access and utility of 1155
 1091 telehealth among Parkinson's disease patients. *Can J Neurol* 1156
 1092 *Sci* **47**, 700-704. 1157
- 1093 [29] van der Kolk NM, de Vries NM, Kessels RPC, Joosten H, 1158
 1094 Zwiderman AH, Post B, Bloem BR (2019) Effectiveness 1159
 1095 of home-based and remotely supervised aerobic exercise in 1160
 1096 Parkinson's disease: A double-blind, randomised controlled 1161
 1097 trial. *Lancet Neurol* **18**, 998-1008. 1162
- 1098 [30] Tarolli CG, Andrzejewski K, Zimmerman GA, Bull M, 1163
 1099 Goldenthal S, Auinger P, O'Brien M, Dorsey ER, Biglan K, 1164
 1100 Simuni T (2020) Feasibility, reliability, and value of remote 1165
 1101 video-based trial visits in Parkinson's disease. *J Parkinsons* 1166
 1102 *Dis* **10**, 1779-1786. 1167
- 1103 [31] Spear KL, Auinger P, Simone R, Dorsey ER, Francis J 1168
 1104 (2019) Patient views on telemedicine for Parkinson disease. 1169
 1105 *J Parkinsons Dis* **9**, 401-404. 1170
- 1106 [32] Faulkner-Gurstein R, Jones HC, McKevitt C (2019) "Like a 1171
 1107 nurse but not a nurse": Clinical Research Practitioners and 1172
 1108 the evolution of the clinical research delivery workforce in 1173
 1109 the NHS. *Health Res Policy Syst* **17**, 59. 1174
- 1110 [33] Willis AW, Schootman M, Kung N, Racette BA (2013) Epi- 1175
 1111 demiology and neuropsychiatric manifestations of Young 1176
 1112 Onset Parkinson's Disease in the United States. *Parkinsons-* 1177
 1113 *ism Relat Disord* **19**, 202-206. 1178
- 1114 [34] Schrag A, Hovris A, Morley D, Quinn N, Jahanshahi 1179
 1115 M (2003) Young- versus older-onset Parkinson's disease: 1180
 1116 Impact of disease and psychosocial consequences. *Mov Dis-* 1181
 1117 *ord* **18**, 1250-1256. 1182
- 1118 [35] Rastgardani T, Armstrong MJ, Gagliardi AR, Grabovsky A, 1183
 1119 Marras C (2020) Experience and impact of OFF periods in 1184
 1120 Parkinson's disease: A survey of physicians, patients, and 1185
 1121 carepartners. *J Parkinsons Dis* **10**, 315-324. 1186
- 1122 [36] Behrendt C, Golz T, Roesler C, Bertz H, Wunsch A (2011) 1187
 1123 What do our patients understand about their trial participa- 1188
 1124 tion? Assessing patients' understanding of their informed 1189
 1125 consent consultation about randomised clinical trials. *J Med* 1190
 1126 *Ethics* **37**, 74-80. 1191
- 1127 [37] Carroll C, Stevens K, Jones B, Campbell S, Jeffery A, 1192
 1128 Chapman R, Webber M, Foggo A, Zajicek J, Whone A, Cre- 1193
 1129 nor S (2020) Simvastatin as a neuroprotective treatment 1194
 1130 for Parkinson's disease (PD STAT): Results of a double- 1195
 1131 blind, randomised, placebo-controlled futility study. *MDS* 1196
 1132 *Virtual Congress 2020, September 12-16, 2020-Late Break-* 1197
 1133 *ing Abstracts*, LBA 1. 1198
- 1134 [38] Gillies K, Entwistle VA (2012) Supporting positive expe- 1199
 1135 riences and sustained participation in clinical trials: 1200
 1136 Looking beyond information provision. *J Med Ethics* **38**, 1201
 1137 751-756. 1202
- 1138 [39] Tait AR, Voepel-Lewis T (2015) Digital multimedia: A new 1203
 1139 approach for informed consent? *JAMA* **313**, 463-464. 1204
- 1140 [40] Bollschweiler E, Aptsch J, Obliers R, Koerfer A, Monig 1205
 1141 SP, Metzger R, Holscher AH (2008) Improving informed 1206
 1142 consent of surgical patients using a multimedia-based pro- 1207
 1143 gram? Results of a prospective randomized multicenter 1208
 1144 study of patients before cholecystectomy. *Ann Surg* **248**, 1209
 1145 205-211. 1210
- [41] Angulo J, Fleury V, Peron JA, Penzenstadler L, Zullino D, 1146
 Krack P (2019) Shame in Parkinson's disease: A review. *J* 1147
Parkinsons Dis **9**, 489-499. 1148
- [42] Martinez-Martin P, Rodriguez-Blazquez C, Forjaz MJ 1149
 (2012) Quality of life and burden in caregivers for patients 1150
 with Parkinson's disease: Concepts, assessment and related 1151
 factors. *Expert Rev Pharmacoecon Outcomes Res* **12**, 1152
 221-230. 1153
- [43] Berger S, Chen T, Eldridge J, Thomas CA, Habermann 1154
 B, Tickle-Degnen L (2019) The self-management balanc- 1155
 ing act of spousal care partners in the case of Parkinson's 1156
 disease. *Disabil Rehabil* **41**, 887-895. 1157
- [44] Hulshoff MJ, Book E, Dahodwala N, Tanner CM, Robertson 1158
 C, Marras C (2021) Current knowledge on the evolution of 1159
 care partner burden, needs, and coping in Parkinson's 1160
 disease. *Mov Disord Clin Pract* **8**, 510-520. 1161
- [45] Benge JF, Balsis S (2016) Informant perceptions of the cause 1162
 of activities of daily living difficulties in Parkinson's disease. 1163
Clin Neuropsychol **30**, 82-94. 1164
- [46] Wolff L, Benge J (2019) Everyday language difficulties in 1165
 Parkinson's disease: Caregiver description and relationship 1166
 with cognition, activities of daily living, and motor disabili- 1167
 ty. *Am J Speech Lang Pathol* **28**, 165-173. 1168
- [47] Hirsch ES, Adler G, Amspoker AB, Williams JR, Marsh L 1169
 (2013) Improving detection of psychiatric disturbances in 1170
 Parkinson's disease: The role of informants. *J Parkinsons* 1171
Dis **3**, 55-60. 1172
- [48] Slade SC, Bruce C, McGinley JL, Bloem BR, Morris ME 1173
 (2020) Patient and care partner views on exercise and 1174
 structured physical activity for people with progressive 1175
 supranuclear palsy. *PLoS One* **15**, e0234265. 1176
- [49] Donovan JL, de Salis I, Toerien M, Paramasivan S, Hamdy 1177
 FC, Blazeby JM (2014) The intellectual challenges and 1178
 emotional consequences of equipoise contributed to the 1179
 fragility of recruitment in six randomized controlled trials. 1180
J Clin Epidemiol **67**, 912-920. 1181
- [50] Lawton J, Kirkham J, White D, Rankin D, Cooper C, Heller 1182
 S (2015) Uncovering the emotional aspects of working on 1183
 a clinical trial: A qualitative study of the experiences and 1184
 views of staff involved in a type 1 diabetes trial. *Trials* 1185
16, 3. 1186
- [51] Appleby J (2019) Nursing workforce crisis in numbers. *BMJ* 1187
367, l6664. 1188
- [52] Iacobucci G (2019) It's the workforce, stupid: Five minutes 1189
 with...Mark Britnell. *BMJ* **367**, l6555. 1190
- [53] Bailey S (2021) Parliamentary report on workforce burnout 1191
 and resilience. *BMJ* **373**, n1603. 1192
- [54] Lawton J, White D, Rankin D, Elliott J, Taylor C, Cooper 1193
 C, Heller S, Hollowell N (2017) Staff experiences of clos- 1194
 ing out a clinical trial involving withdrawal of treatment: 1195
 Qualitative study. *Trials* **18**, 61. 1196
- [55] Dorsey ER, Beck CA, Adams M, Chadwick G, de Blicke 1197
 EA, McCallum C, Briner L, Deuel L, Clarke A, Stew- 1198
 art R, Shoulson I, Huntington Study Group TREND-HD 1199
 Investigators (2008) Communicating clinical trial results to 1200
 research participants. *Arch Neurol* **65**, 1590-1595. 1201
- [56] Di Blasi Z, Crawford F, Bradley C, Kleijnen J (2005) Reac- 1202
 tions to treatment debriefing among the participants of a 1203
 placebo controlled trial. *BMC Health Serv Res* **5**, 30. 1204
- [57] Witham MD, Anderson E, Carroll C, Dark PM, Down K, 1205
 Hall AS, Knee J, Maier RH, Mountain GA, Nestor G, Oliva 1206
 L, Prowse SR, Tortice A, Wason J, Rochester L, INCLUDE 1207
 writing group (2020) Developing a roadmap to improve trial 1208
 delivery for under-served groups: Results from a UK multi- 1209
 stakeholder process. *Trials* **21**, 694. 1210

- 1211 [58] Di Luca DG, Sambursky JA, Margolesky J, Cordeiro JG, 1231
1212 Diaz A, Shpiner DS, Moore HP, Singer C, Luca C (2020) 1232
1213 Minority enrollment in Parkinson's disease clinical trials: 1233
1214 Meta-analysis and systematic review of studies evaluating 1234
1215 treatment of neuropsychiatric symptoms. *J Parkinsons Dis* 1235
1216 **10**, 1709-1716. 1236
- 1217 [59] Tossierams A, Araujo R, Pringsheim T, Post B, Darweesh 1237
1218 SKL, IntHout J, Bloem BR (2018) Underrepresentation of 1238
1219 women in Parkinson's disease trials. *Mov Disord* **33**, 1825-
1220 1826.
- 1221 [60] Caplan A, Friesen P (2017) Health disparities and clinical
1222 trial recruitment: Is there a duty to tweet? *PLoS Biol* **15**,
1223 e2002040.
- 1224 [61] Donovan J, Mills N, Smith M, Brindle L, Jacoby A, Peters
1225 T, Frankel S, Neal D, Hamdy F (2002) Quality improve-
1226 ment report: Improving design and conduct of randomised
1227 trials by embedding them in qualitative research: ProtecT
1228 (prostate testing for cancer and treatment) study. Commem-
1229 tary: Presenting unbiased information to patients can be
1230 difficult. *BMJ* **325**, 766-770.
- [62] Moore GF, Audrey S, Barker M, Bond L, Bonell C, Harde-
man W, Moore L, O'Cathain A, Tinati T, Wight D, Baird J
(2015) Process evaluation of complex interventions: Medi-
cal Research Council guidance. *BMJ* **350**, h1258.
- [63] Lewin S, Glenton C, Oxman AD (2009) Use of qualitative
methods alongside randomised controlled trials of complex
healthcare interventions: Methodological study. *BMJ* **339**,
b3496.

Uncorrected Author Proof