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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 |
|---|---|---|---|---|
| *n* | 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 quantitively 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 in the patient and care partner narratives were echoed by staff.

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 |
| | • Unexpected physical compromise |
| | • Psychological impact |
| | • Logistics and travel to study centres |
| | • Reason for withdrawal |
| | • Need to be better informed in advance |
| | Medication |
| | • 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 |
| | • Practical challenges |
| | • Emotional burden |
| | • Prolonged recovery |
| | • Need for better support during trial |
| Trial organisation | Smooth |
| | Availability and support by research team |

### *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 voicemail 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

assessment was also discussed. There was general agreement that it took days rather than hours for patients to return to their baseline, which was evidently unanticipated.

*Research staff*

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

> *There was plenty of time to talk about how they were feeling and what their concerns were about the situation. So, I think that was the most valuable thing for them really, to have someone to speak to just from a social perspective* (Staff interview 431)

At the end of this 2-year trial, some conveyed disappointment and even a sense of loss of connections with participants.

Logistical issues pertaining to the configuration of the research environment were a frequent source of frustration across different sites. At some centres, there was no designated research room to accommodate the assessments and 10 m walk test, which were resumed in different rooms or even public areas. Furthermore, travel arrangements for home visits were frequently described as a source of difficulty, due to impractical workplace policies, variable or no access to pool cars, difficulties with claiming travel expenses, car insurance issues if using private vehicles and poor public transport connections. Notwithstanding practical issues, staff reported tension between good patient care and the constraints and demands imposed by the protocol and local logistics. In line with feedback from patients and care partners, staff also found OFF state assessments challenging. These assessments generated significant dissonance for them; the compassion and duty of care long ingrained in healthcare professionals may not naturally align with delivering a protocol that includes the physically trying experience of dopaminergic withdrawal in a person with PD.

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

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

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

Cumbersome paperwork and target driven recruitment associated with delivering a multicentre study were also discussed. Over the course of the recruitment period, different sites adjusted their local targets downward to meet them, with foreseeable negative repercussions.

Staff shared their willingness and person-centred strategies to flexibly accommodate individual participants according to their needs, by opting for early OFF assessment appointment times so that medication could be resumed as soon as possible, flexibility in rescheduling or extending appointments, and arranging patient transport. Supporting trial participants in these ways was important for those who did not have a care partner or who chose to attend our research centres alone; for them, trial participation represented a means of asserting their independence. Additionally, considering that PD STAT continued throughout the COVID-19 pandemic in the UK, remote trial delivery methods were implemented. Although for some participants the use of video conferencing was difficult or impossible due to technical problems, staff noted that remote assessments may have put others at ease, possibly due to social distancing afforded by video consultation and feeling more relaxed in their home setting. Staff felt this facilitated social interaction and may have reduced participants' tremor which was ascribed to reduced 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

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

One of the principal themes that emerged from the narratives of both trial participants and staff pertained to dynamic patient-centred protocols which accommodate the challenges and limitations individual participants may face. PD trials tend to mostly target and recruit older participants, and protocols are often designed based on assumptions around lifestyles traditionally associated with retirement. We urge trialists to consider that many of these assumptions rule out participation for otherwise eligible participants who may still be in employment, may have caring duties themselves, or have young onset PD [33, 34] and hence are in full time employment often with parallel family commitments.

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

We focus closely on OFF state assessments. Across the board, our patients, care partners and staff whose voice this article amplifies, cited these as the greatest challenge due to the physical and cognitive compromise they entail [35]. For patients, these were psychologically confronting and physically onerous, accounting for over a third of drop outs. Notably, some PD participants and care partners felt that commensurate advance warning and support from the research team was lacking. It is necessary to address this communication gap. While participants were informed in writing on procedural aspects of OFF assessments and the variability of dopaminergic withdrawal, some found this was more severe than predicted, or felt they had been led to expect, and some found this intolerable. It is difficult to parse *ex post facto* on a case-by-case basis the extent to which this could have been avoided through better communication. Identifying this communication gap is significant and qualitative methodology is a useful means to this end [36]. We learned that understanding why OFF state assessments were required contributed to patients persevering with them, highlighting the importance of shared understanding of what the trial is trying to achieve as a means of enhancing retention. Our drop-out rates were in line with other studies (22.5% over 26 months) [37] but we note that high drop-out rates pose ethical concerns more generally as to whether participant decision making and consent have been effectively supported at the outset and throughout the trial [38]. The vast majority of people with moderate PD will be well acquainted with the detrimental effects of delayed dosing, and missed doses would represent a rare event over the years of living with the condition, but the ethical imperative to inform them in a more concrete way about the OFF state is clear. This pertains to all ongoing and future trials targeting disease modification given our current methods which rely heavily on these assessments.

At minimum, we can infer that those written descriptions were inadequate for a significant minority of participants. Digital multimedia approaches to consent have already been tested and shown to confer benefits over and above paper-based information in other areas of medicine (see [39, 40]). Could video recordings and verbal testimonies of a few consented trial participants in their OFF state convey the necessary information for consent with greater fidelity? This would better serve future participants in making a sustainable decision to participate in a trial. Moreover, a platform of virtual peer support in the form of a database of 'expert participants' available to discuss different aspects of the trial as was suggested here, could meet the needs of participants in ways that otherwise available and forthcoming research teams cannot. More work is needed on how best to inform and prepare participants about intrinsically

challenging aspects of trials. It will also be necessary to anticipate ethical problems posed by multimedia approaches to informed consent and investigate their impact on the magnitude of nocebo and placebo effects.

Staff narratives helped us identify issues surrounding the impact of logistics on the deliverability of our publicly funded trial which focused on the accessibility of study visits, a salient problem in the context of OFF state assessments, with the potential to introduce selection bias. Local organisational policies linked to insurance and work patterns meant that staff at different sites were not always able to carry out home visits which would have prevented trial withdrawal for some participants. PD STAT aimed for geographical inclusivity, enabling coverage of large areas of the UK across its 23 sites. To enhance retention, site policies and processes should be aligned with protocol provisions, convenience maximised by full re-imbursement of travel expenses, use of pre-paid taxis, early morning visits, overnight stays, convenient on-site parking and meet and greet with wheelchair. For participants, for whom social embarrassment can be a key contributor to quality of life [41], dedicated assessment space away from public areas would be much valued. Privacy considerations also pertain to the home environment.

The use of digital technologies instead of in-person clinic visits could also serve well. However, until we gain full traction on remote trial delivery methodology and develop competence and confidence in its implementation, we recommend that mitigation strategies including home visits, especially for OFF state assessments, be built into trial protocols and routinely offered, anticipated through appropriate budgeting and adequately supported by funders. Digital enablers of inclusivity such as video conferencing to carry out remote assessments was primarily driven by the COVID-19 pandemic, but future protocols could include it, both to facilitate study delivery where validated processes exist, and to build the evidence base to support future methodological implementation. One of the many challenges that we will face in implementing these will be to discover how the benefits afforded by in-person trial participation can be reproduced in digital remote pathways.

Finally, adverse experiences with the trial drug which, real or perceived, all therapies carry, are significant. Patients and research teams need to be fully informed about these during the consent process, with explicit plans in protocols to mitigate them as appropriate. While for some therapies the side effects will be well known and may lead to a nocebo effect, for others especially in early phase studies, the documentation of adverse events will form an important part of the trial findings. Adverse event diaries were implemented in PD STAT but the limited feedback we received on these indicated that participants found these too repetitive. Smartphone app technologies which might require just a few minutes daily to complete could be preferable. In PD, tremor, weakness, poor manual dexterity and swallowing difficulties may be further exacerbated by arthritis or other comorbidities as a function of increasing age, which is a major risk factor for developing the condition. In PD STAT, we obtained feedback on dummy versions of the capsules from a Patient and Public Involvement (PPI) group who helped us select the over-encapsulated preparation used in the trial, yet some participants still ran into difficulties. Could dummy dosing to check acceptability of the intervention/drug preparation as part of the screening or informed consent process be additionally implemented? Registering this feedback and adapting future trials also sends a powerful message to trial participants and represents a true instantiation of the patient-clinician-researcher partnership.

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

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

such validation in PD studies. These are necessary. It is likely that care partners will be supporting the person with PD with study participation and procedures, so it is important that they also understand the study requirements, particularly potential side effects, as they can support the participant through that and assist retention. Moreover, any new therapy (if adopted into care) will also impact on care partners, adding to pill burden and potential for adverse events. Since care partners play a key role in managing compliance to therapy, the impact of any new therapy on them is also relevant [eg, see, 48]. Notwithstanding this, feedback from staff suggested that care partner involvement may also need to be counteracted with a view to protecting a participant's autonomy and best interests. Concerning such additional safeguarding dimensions and the thresholds for action warranted by the subtle or obvious cues which research staff may detect, how are superordinate healthcare guidelines implemented in protocols? It is unclear whether and what training is available to help staff navigate these sensitive interactions.

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

### *Communication and management of study closure*

All participants in this qualitative study valued regular communications regarding trial progress, both at the site as well as the superordinate trial level. In PD STAT we relied heavily on newsletters but did not fully exploit the study website, used mostly for recruitment. Personalised and accurate post-trial communication is valued by participants, with a telephone call being preferred to a press release [55] as is sensitively handling information on placebo allocation [56]. In PD STAT, we sent out individual letters with the trial results the day before the official press release. We also organised a shared post-study results dissemination event for participants, care partners and study delivery teams; this had been planned to be a series of events held in person at different locations within the UK but were converted into a single on-line virtual event due to COVID-19 restrictions.

Our findings here are in line with the recent impactful Innovations in Clinical Trial Design and Delivery for the Under-served (INCLUDE) guidelines [57]. Enabling participation in clinical trials for people with PD is necessary, particularly those who are older and with more co-morbidities. Moreover, ethnic minority group enrolment in clinical trials for PD is very low [58] and women are also less likely to enrol [59]; both groups have been historically underrepresented in clinical trials. The INCLUDE guidelines aim to reduce barriers and challenges to trial participation and improve engagement with research for under-served groups. They are aimed at all stakeholders as well as funders, whose decisions must take into account the fact that recruiting and retaining those who are hard to recruit and retain, such as people on low income and with dependants, will inevitably cost more. Ensuring diversity and inclusivity in clinical trials is both ethically imperative and scientifically essential [60].

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

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## CONFLICT OF INTEREST

The authors have no conflict of interest to report.

## SUPPLEMENTARY MATERIAL

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