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Research Report

An International Multi-Stakeholder Delphi Survey Study on the Design of Disease Modifying Parkinson's Disease Trials

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Abstract.
Background: Design of disease modification (DM) trials for Parkinson's disease (PD) is challenging. Successful delivery requires a shared understanding of priorities and practicalities.
Objective: To seek stakeholder consensus on phase 3 trials' overall goals and structure, inclusion criteria, outcome measures, and trial delivery and understand where perspectives differ.
Methods: An international expert panel comprising people with Parkinson's (PwP), care partners (CP), clinical scientists, representatives from industry, funders and regulators participated in a survey-based Delphi study. Survey items were informed by a scoping review of DM trials and PwP input. Respondents scored item agreement over 3 rounds. Scores and reasoning were summarized by participant group each round until consensus, defined as $\geq 70\%$ of at least 3 participant groups falling within the same 3-point region of a 9-point Likert scale.
Results: 92/121 individuals from 13 countries (46/69 PwP, 13/18 CP, 20/20 clinical scientists, representatives from 8/8 companies, 4/5 funders, and 1/1 regulator) completed the study. Consensus was reached on 14/31 survey items: 5/8 overall goals and structure, 1/8 Eligibility criteria, 7/13 outcome measures, and 1/2 trial delivery items. Extent of stakeholder endorsement for 428 reasons for scores was collated across items.
Conclusions: This is the first systematic multi-stakeholder consultation generating a unique repository of perspectives on pivotal aspects of DM trial design including those of PwP and CP. The panel endorsed outcomes that holistically measure PD and the importance of inclusive trials with hybrid delivery models. Areas of disagreement will inform mitigating strategies of researchers to ensure successful delivery of future trials.

Keywords: Parkinson's disease, disease modification, clinical trial, Delphi survey

INTRODUCTION

The incidence and prevalence of Parkinson's disease (PD) are increasing, adding significantly to the global burden of neurological disorders [1, 2] creating

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an urgent, unmet need to identify disease modifying therapies (DMTs). In 2021, DMT trials represented 41.5% of 142 active clinical trials in PD [3]. Historically, despite DMTs showing efficacy in phase 2, phase 3 trials have been negative [4–13].

DMT trials for PD pose unique challenges [14]: there are no accepted biomarkers of progression [15]; PD is heterogeneous with phenotypic and genetic subtypes exhibiting different rates of progression [16–18]; and effective symptomatic therapies potentially confound routinely used clinical outcome measures. These factors have contributed to diverse approaches to DMT clinical trial design with regard to participant selection, trial duration, and outcome measures [19–21].

Considering patient and care partner priorities is vital to the design and conduct of trials to ensure effective recruitment and retention, both being major factors in the success and cost of trials [22–24]. As many as 45% of trials do not reach their pre-specified recruitment target [25]. Involving people with Parkinson's (PwP) and their care partners in the design of trials is critical to ensure trials answer patient relevant questions and measure meaningful outcomes in ways that are acceptable to participants. Thus, the interaction of researchers conducting clinical trials with potential trial participants (including those with no previous trial experience) as well as the carepartners that support their participation in trials is vitally important.

This Delphi study facilitated international multistakeholder interaction with a view to seeking consensus on the design of PD trials that test protective treatments aiming to slow, halt, or reverse the progression of PD in a phase-3 setting. Acknowledging that DMT trials can be carried out in many different ways, we aimed to determine aspects of overall goals, eligibility criteria, outcome measures, and trial delivery, importantly including the voice of PwP and their care partners. We present a Delphi methodology that allowed the collection and unbiased presentation of stakeholder reasoning to support informed choice.

MATERIALS AND METHODS

Survey development

A Delphi questionnaire was developed based on a rapid scoping review of DMT trials in PD and PwP input. The survey was piloted on PwP and care partners and iteratively adjusted to ensure questions were suitable for lay participants. Further adjustment to question text was made after the first Delphi round where comments indicated misinterpretation by participants.

The questionnaire contained 31 items covering four domains: trial goals and structure; inclusion criteria; outcome measures; and delivery.

Question text and information displayed to participants as well as the questionnaire piloting process can be found in Supplementary Material 1.

Ethics

The study protocol was approved by the University of Plymouth Faculty of Health Research Ethics and Integrity Committee (Ref. 19/20-1307).

Delphi Panel composition and recruitment

We aimed to recruit 100 international expert panelists representing stakeholders involved in PD DMT clinical trials with the following recruitment targets and eligibility criteria:

- 20 Clinical scientists
  - First or last author or named chief investigator on a publication/registry entry of a trial for a DMT in PD; or a clinical scientist identified as having extensive knowledge in DMT trials.
- 10 Pharmaceutical industry representatives (1 per organization)
  - From companies with a pipeline of DMTs for PD.
- 5 Funding agency representatives (charities) (1 per organization)
  - From an organization that actively supports clinical PD research.
- 40 PwP
  - Diagnosis of PD and the ability to give informed consent.
- 20 Care partners
  - Main carer of a PwP and the ability to give informed consent.
- 3 Regulator representatives (1 per organization)
  - Relevant knowledge of PD trials.

PwP and their care partners were recruited via UK and international Parkinson's charities, Facebook

Parkinson's research interest groups and care partner forums. PwPs were purposively selected to create an international panel equally balanced for clinical trial experience. We ensured that trial experienced

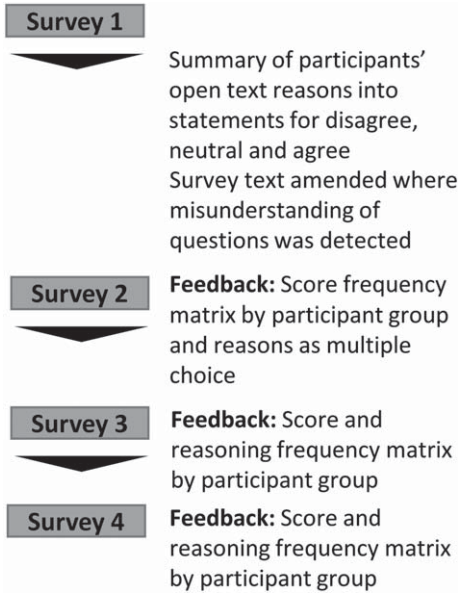

Fig. 1. Study overview. A summary of survey edits and type of feedback supplied to participant within each survey.

and trial naïve subgroups included equal proportions of age (40–50, 50–60, 70+), gender and disease duration (<5 years,>5 years). We aimed to recruit between 40 and 80 PwP to ensure appropriate representation of purposive sampling categories.

Clinical trial registry entries and publication databases were systematically searched for PD DMT trials to identify professional panelists that met eligibility criteria. Additional professional panelists were identified through targeted internet searching, including membership of professional bodies and consortia.

Delphi study

Figure 1 summarizes the Delphi study which consisted of four online surveys built and disseminated through the Jisc online surveys platform.

Non-respondents were sent weekly completion reminders and received a text message or call once before survey closure.

Participants were asked to rate agreement with statements on a 9-point Likert scale from 1 (strongly disagree) to 9 (strongly agree) or indicate that they did not know how to answer. Participants were encouraged to share reasoning for their choices (survey 1 only), suggest further survey topics (survey 1 only) and overall feedback.

For each survey statement, participants were provided with the percentage of votes per participant group falling into the categories 1–3 (disagree), 4–6 (neutral), and 7–9 (agree) (See example in Supplementary Material 1) from preceding surveys as well as their own previous score. Feedback on participants' reasoning was prepared and presented as follows: two reviewers (MLZ and CBC) independently summarized participant reasons into summary statements. Conceptual overlap of statements was assessed and a maximum of 20 statements/question categorized into agree, neutral and disagree. From survey 2, participants were encouraged to select up to five statements most reflecting reasons for their rating or to suggest additional reasons. This was optional to reduce participant burden.

From survey 3 onwards, participant feedback included percentage of votes per participant group for summary statements (Supplementary Material 1).

A fourth survey was conducted for items where the question text or information was changed resulting from survey 1 feedback. Thus, each finalized item underwent a maximum of 3 rounds or until consensus was reached.

Consensus definition

Consensus for an item was reached when $\geq 70\%$ of panelists' ratings of at least 3 groups fell within the same 3-point region (that is 1–3, 4–6, or 7–9) [26, 27].

Analysis

IBM SPSS statistics 25 software was used for all statistical analyses. Where there were three or less participants in a group, percentages and reasoning were not provided in the feedback to participants to protect participant anonymity as well as ensuring individual views did not disproportionately affect other participants' votes. This was clearly communicated to participants.

Data sharing

Qualified external researchers can request access to anonymized participant-level survey responses, respecting patient informed consent, from the corresponding author on reasonable request, and on execution of an appropriate data sharing agreement.

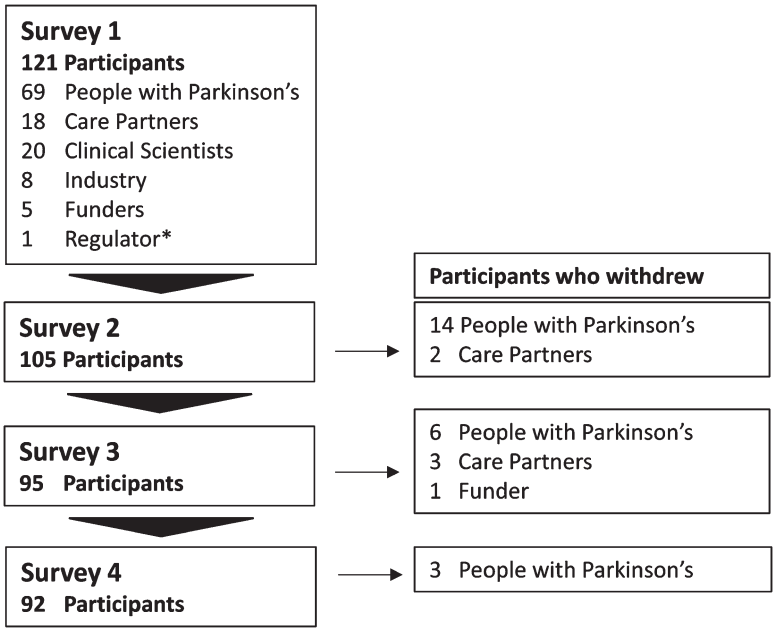

Fig. 2. Study participation. The number of participants and those who withdrew by participant group over 4 surveys.

RESULTS

Delphi participants

121 participants from 13 different countries participated in survey 1 including 69 PwP, 18 care partners, 20 clinical scientists, a representative from 8 pharmaceutical companies, 5 funders, and 1 regulatory agency (Fig. 2). Industry representatives were in diverse roles within their organizations with a median of 7.5 years (5.5 IQR) of experience in DMT trials for PD. Their job titles included: Chief Scientific Officer, Clinical Programme Director, Vice President, Medical Advisor, Global Medical Affairs Manager, Lead Medical Specialist, and Pharmaceutical Physician. Details of participant demographics are shown in Table 1.

The regulatory representative participated in an advisory capacity only: scores did not contribute towards consensus and are not included in this publication. Participants were informed throughout that regulator scores did not represent the official views, rather the personal opinion and experience of the contributor.

Analysis of withdrawals and attrition bias

Thirty participants withdrew over the course of the study, including 23 PwP, 5 care partners, and 1 funder (Fig. 2). Unsolicited reasons for withdrawal included the repetitive nature and difficulty of the questionnaire, time taken to complete the survey, bereavement and a worsening of participants' PD over the course of the study.

There were no major differences in participant demographics between the first and last survey for PwP or care partners (Table 1). Understanding of questions may have contributed to attrition and there was no statistical evidence of attrition bias (Supplementary Material 2) [26, 28].

Feedback engagement

Every question across all participants was counted as an opportunity to leave feedback, creating 9682 opportunities throughout the study. Feedback was provided on 93.7% of occasions.

Delphi Consensus

For each domain (trial goals and structure, eligibility criteria, outcome measures, trial delivery) details of score distributions across participant groups are given in Table 2 and details of reasoning for scores can be found in Supplementary Material 3. In total, 14 out of 31 (45%) items reached consensus (1 in survey 1, 8 in survey 2, 3 in survey 3, and 1 in survey 4) with core recommendations highlighted in Fig. 3. A total of 428 reasons for scores with extent of stakeholder

Table 1
Participant characteristics

	People with Parkinson's		Care partner		Clinical Scientists	Industry	Funders	
	Survey 1 ($n=69$)	Survey 4 ($n=46$)	Survey 1 ($n=18$)	Survey 4 ($n=13$)	Survey 1 ($n=20$)	Survey 1 ($n=8$)	Survey 1 ($n=5$)	Survey 4 ($n=4$)
	Median (IQR) or N (% per participant group)							
Age	65 (13)	63 (11)	68 (6.5)	68 (5)	50 (14.25)	43 (18.25)	54 (8)	56 (7.25)
≤5 y disease duration	37 (53.6%)	27 (58.7%)	–	–	–	–	–	–
Male	45 (65.2%)	32 (69.6%)	2 (11.1%)	1 (7.7%)	15 (75%)	6 (75%)	2 (40%)	2 (50%)
Female	24 (34.8%)	14 (30.4%)	16 (88.9%)	12 (92.3%)	5 (25%)	2 (25%)	3 (60%)	2 (50%)
Have clinical trial experience	32 (46.4%)	24 (52.2%)	8 (44.4%)	6 (46.1%)	–	–	–	–
Years of experience with DMT trials	–	–	–	–	8.5 (12)	7.5 (5.5)	–	–
Non-UK	21 (30.4%)	12 (26.1%)	2 (11.1%)	2 (15.4%)	8 (40%)	5 (62.5%)	3 (60%)	2 (50%)
Ethnicity not declared	3 (4.3%)	0	0	0	–	–	–	–
White	64 (92.7%)	45 (97.8%)	18 (100%)	13 (100%)	–	–	–	–
Help provided by care partner								
None	–	–	2 (11.1%)	2 (15.4%)	–	–	–	–
Little	–	–	12 (66.7%)	7 (53.8%)	–	–	–	–
Lots	–	–	3 (16.7%)	3 (23.1%)	–	–	–	–
Constant	–	–	1 (5.5%)	1 (7.7%)	–	–	–	–
Highest level of experience								
Principal Investigator	–	–	–	–	8 (40%)	–	–	–
Chief Investigator	–	–	–	–	8 (40%)	–	–	–
First or last author	–	–	–	–	1 (5%)	–	–	–
Other	–	–	–	–	3 (15%)	–	–	–

endorsement was collated across items. These can be found in Supplementary Material 3.

Overall goals of the trial (Domain 1)

Participants reached consensus that a trial aiming to investigate DMTs should try to identify treatment responsive subtypes, gather evidence that supports the drug working to slow disease progression, be placebo controlled and have multiple treatment arms, as well as being used to validate new digital outcome measures (Fig. 3).

There was no consensus on the two questions pertaining to trial length (Table 2, Domain 1, D1Q3, whether trials should collect the best information possible even if this takes up to five years; D1Q4, whether trials should be as short as possible even if there is a risk of providing partial information).

Items where consensus was reached but within-group consensus within at least one participant group lay below 60% are described below:

In contrast to the remaining panel only 40% of funders agreed that trials should be aiming to gather evidence that supports the drug working to slow disease progression.

Inclusion criteria (Domain 2)

The Delphi panel reached consensus on one out of 8 inclusion criteria disagreeing with the statement that the trial should only include patients who do not yet require PD medication (Fig. 3) with 78% of PwP, 80% of clinical scientists and 75% of funders disagreeing with a restriction of trials to drug naïve PwP.

No consensus was reached on whether trials should be as inclusive as possible, have an upper age limit, have a lower age limit, only include those with a disease duration of less than 5 years, include those experiencing wearing off, not include those with cognitive impairment, not include those who have had brain surgery for their PD (Table 2, Domain 2).

Although the panel did not reach consensus on any other inclusion criteria, the majority of PwP were in favor of inclusivity on all items with the exception of eligibility restrictions based on participants having undergone brain surgery for their PD (Table 2, Domain 2).

Items where consensus was reached but within-group consensus within at least one participant group lay below 60% are described below:

In contrast to the rest of the panel, only 50% of industry respondents disagreed with the statement that the trial should only include those who are not yet on any medications for their PD.

Outcome measures (Domain 3)

Consensus was achieved on the importance of considering seven of 13 items proposed within the survey for phase 3 outcome assessment: OFF-state motor assessments, quality of life, activities of daily living, delaying the development of new symptoms, passive digital measures, patient completed questionnaires, and utilizing more than one measure (Fig. 3).

No consensus was achieved regarding ON-state motor assessments, motor symptoms, non-motor symptoms, duration of good quality ON time, digital measures requiring completion of regular tasks or questionnaire scales administered by the research team (Table 2, Domain 3).

Items where consensus was reached but within-group consensus within at least one participant group lay below 60% are described below:

care partners (46%) and funders (50%) were supportive OFF-state motor assessments (Table 2, D3Q1); clinical scientists were least supportive of activities of daily living (ADL) measures (55%) (Table 2, D3Q6); passive digital monitoring was highly supported by professional participant groups (75%, 100%, 100% of clinical scientist, industry and funder respondents respectively), while PwP and care partners were less supportive (57% and 54% of votes respectively) (Table 2, D3Q10); Patient completed questionnaires were viewed as important measures by 75% of respondents within all professional participant groups whilst PwP and care partners were less supportive with 39% and 46% rating within the agreement region of the scale respectively (Table 2, D3Q12).

Passive digital monitoring was highly supported by professional participant groups, with PwP and care partners being less supportive (Table 2).

Patient completed questionnaires were viewed as important measures by 75% of professional participants. PwP and care partners were less supportive with 39% and 46% rating within the agreement region of the scale respectively (Table 2).

Trial Delivery (Domain 4)

More than 70% of all participant groups agreed that the trial should provide the option of home

Table 2
Summary of item scores across 4 survey domains

Survey Item The trial should…	Consensus round (Survey #)	Scores	% Votes per Participant Group				
			PwP	Care partners	Clinical Scientists	Industry	Funder
Domain 1 - The overall goals and structure of the trial (Five out of eight items reached consensus)							
D1Q1. Try to find out if the drug is working to slow disease progression rather than treating the symptoms of Parkinson's	Round 1 (2)	Agree (7-9)	70	69	75	75	40
D1Q2. Try to find out for which types of Parkinson's the drug might work best	Round 1 (1)	Agree (7-9)	83	78	75	88	80
D1Q3. Collect the best information possible even if this takes up to 5 years	no consensus (3)	Disagree (1-3)	12	8	0	38	0
		Neutral (4-6)	16	31	20	25	25
		Agree (7-9)	71	54	80	38	50
		Unsure	0	8	0	0	25
D1Q4. Be as short as possible, (perhaps up to 1 year) even if there is a risk of providing partial information.	no consensus (3)	Disagree (1-3)	41	54	90	50	75
		Neutral (4-6)	39	23	10	38	25
		Agree (7-9)	20	23	0	13	0
		Unsure	0	0	0	0	0
D1Q5. Be placebo controlled	Round 1 (2)	Agree (7-9)	74	69	90	88	60
D1Q6. Have a standard of care control arm	no consensus (4)	Disagree (1-3)	24	46	95	88	50
		Neutral (4-6)	26	15	0	13	0
		Agree (7-9)	50	38	0	0	25
		Unsure	0	0	5	0	25
D1Q7. Have multiple treatment arms	Round 2 (2)	Agree (7-9)	85	75	65	63	80
D1Q8. Test new apps and devices to see whether they can improve the way Parkinson's is measured	Round 1 (2)	Agree (7-9)	78	81	60	75	60
Domain 2 – Inclusion criteria (one of eight items reached consensus)							
D2Q1. Be as inclusive as possible	no consensus (3)	Disagree (1-3)	10	0	10	25	25
		Neutral (4-6)	20	23	65	50	0
		Agree (7-9)	69	62	25	25	75
		Unsure	0	15	0	0	0
D2Q2. Have an upper age limit	no consensus (3)	Disagree (1-3)	65	54	50	25	75
		Neutral (4-6)	16	38	30	25	25
		Agree (7-9)	18	8	20	50	0
		Unsure	0	0	0	0	0
D2Q3. Have a lower age limit*	no consensus (3)	Disagree (1-3)	76	69	20	13	25
		Neutral (4-6)	18	31	45	38	50
		Agree (7-9)	6	0	35	50	25
		Unsure	0	0	0	0	0
D2Q4. Only include people who have had Parkinson's for less than 5 years	no consensus (3)	Disagree (1-3)	78	85	30	13	25
		Neutral (4-6)	14	15	55	50	75
		Agree (7-9)	8	0	15	38	0
		Unsure	0	0	0	0	0
D2Q5. Only include people who are not yet on any medications for their Parkinson's	Round 2 (3)	Disagree (1-3)	78	69	80	50	75
D2Q6. Also include people who experience their medication wearing off	no consensus (3)	Disagree (1-3)	4	0	10	38	0
		Neutral (4-6)	20	15	75	50	100
		Agree (7-9)	76	69	15	13	0
		Unsure	0	15	0	0	0
D2Q7. Not include people with thinking and memory problems related to their Parkinson's	no consensus (4)	Disagree (1-3)	65	38	60	13	50
		Neutral (4-6)	24	54	30	13	25
		Agree (7-9)	11	8	10	75	25
		Unsure	0	0	0	0	0
D2Q8. Not include people who have had brain surgery for their Parkinson's (e.g., Deep Brain Stimulation)	no consensus (4)	Disagree (1-3)	46	38	10	13	0
		Neutral (4-6)	22	54	10	0	50
		Agree (7-9)	30	8	80	88	50
		Unsure	2	0	0	0	0
Domain 3 – Outcome measures (Seven out of 13 items reached consensus)							
D3Q1. OFF-state motor assessments†	Round 3 (4)	Agree (7-9)	70	46	85	75	50
D3Q2. ON-state motor assessments	no consensus (4)	Disagree (1-3)	9	8	5	13	0
		Neutral (4-6)	33	38	75	63	100
		Agree (7-9)	57	54	20	25	0
		Unsure	2	0	0	0	0
D3Q3. Motor symptoms	no consensus (4)	Disagree (1-3)	2	0	10	13	25
		Neutral (4-6)	43	38	60	13	50
		Agree (7-9)	52	62	30	75	25
		Unsure	2	0	0	0	0
D3Q4. Non-motor symptoms	no consensus (4)	Disagree (1-3)	2	0	0	25	0
		Neutral (4-6)	46	54	75	38	100
		Agree (7-9)	50	46	25	38	0
		Unsure	2	0	0	0	0

Table 2
(*Continued*)

Survey Item	Consensus round (Survey #)	Scores	% Votes per Participant Group				
			PwP	Care partners	Clinical Scientists	Industry	Funder
D3Q5. Quality of life	Round 1 (2)	Agree (7-9)	87	94	65	88	100
D3Q6. Activities of daily living	Round 1 (2)	Agree (7-9)	67	81	55	75	80
D3Q7. Delaying the development of new symptoms	Round 1 (2)	Agree (7-9)	74	75	70	88	100
D3Q8. Duration of good quality ON time.	no consensus (4)	Disagree (1-3)	2	0	15	25	0
		Neutral (4-6)	26	23	60	50	75
		Agree (7-9)	70	69	25	25	25
		Unsure	2	8	0	0	0
D3Q9. More than one measure	Round 1 (2)	Agree (7-9)	65	88	80	88	60
D3Q10. Passive digital monitoring	Round 2 (3)	Agree (7-9)	57	54	75	100	100
D3Q11. Parkinson's as measured at home by the participant completing regular tasks on smart phones or tablets	no consensus (4)	Disagree (1-3)	7	0	0	0	0
		Neutral (4-6)	41	54	50	25	50
		Agree (7-9)	50	38	50	75	50
		Unsure	2	8	0	0	0
D3Q12. Parkinson's as measured by patient completed questionnaires	Round 2 (3)	Agree (7-9)	39	46	75	75	75
D3Q13. Parkinson's as measured by questionnaire scales that are administered by the research team	no consensus (4)	Disagree (1-3)	11	0	0	0	0
		Neutral (4-6)	37	31	40	13	50
		Agree (7-9)	52	62	60	88	50
		Unsure	0	8	0	0	0
Domain 4 – Trial Delivery (One out of two items reached consensus)							
1. Trial visits should only take place in the research or study clinic.	no consensus (3)	Disagree (1-3)	53	62	85	100	50
		Neutral (4-6)	20	31	5	0	50
		Agree (7-9)	27	0	10	0	0
		Unsure	0	8	0	0	0
2. The trial should provide the option of home-based or video trial visits whenever possible.	Round 1 (1)	Agree (7-9)	75	89	70	75	80

For exact question wording and background information given to participants please refer to Supplementary Material 1, Dark shading indicates the reaching of the within group consensus threshold; * Definition within survey: The trial should have a lower age limit (adults); † Definition within survey: Participants are asked not to take their normal Parkinson's medication temporarily whenever a measurement of their symptoms takes place

based or video trial visits whenever possible (Table 2, D4Q2).

No consensus was reached on trial visits taking place only within the research or study clinic (Table 2, D4Q1).

DISCUSSION

This international Delphi study engaged multiple stakeholders with an interest in DMT trials for PD, capturing stakeholder perspectives, facilitating exchange of viewpoints, and reaching consensus on 14 out of 31 items covering trial goals and structure, eligibility criteria, outcome measures and trial delivery. A succinct but comprehensive summary of arguments for and against aspects of trial design was generated through the process, highlighting synergistic as well as contrasting views of stakeholders (Supplementary Material 3).

An important aspect of this study was the inclusion of both professional and lay participant groups, in particular both trial naïve and experienced PwP and care partners. Trial naïve PwP are an important cohort for future participation in disease modification studies [14, 29] thus their inclusion in discussions pertaining to the conduct of trials is essential, especially considering that many trials fail due to an inability to meet recruitment targets [30].

Non-numerical feedback was a key feature of this study: it enabled lay participants to gain an understanding of advantages and disadvantages of survey items, allowing meaningful participation, and highlighted areas of contention between participant groups. Although this increased participant burden, adherence with provision of feedback across the survey was high (94%) and non-adherence was not associated with attrition.

In contrast to conventional Delphi methodology [26, 31], the anonymous online survey format, consensus definition and feedback representation by participant group, granted each group equal weight, prevented individuals from disproportionately influencing the panel and protected against bias through unequal group attrition [32].

The distribution of items reaching consensus across survey rounds (1 in survey 1, 8 in survey 2, 3 in survey 3, and 1 in survey 4) highlights 3 surveys as optimum number of Delphi rounds.

There were several limitations to the study. As lay panel members, PwP and care partners may not have fully understood all implications of their preferences despite being able to review reasoning and scores

Consensus Items	Key Considerations
Domain 1: Overall Goals and Structure	
The trial should: • Distinguish between disease modification and symptom relief • Identify treatment responsive subtypes • Be placebo controlled • Have multiple treatment arms • Validate new digital measures	• **The necessity for long trials needs to be clearly communicated** Although PwP and researchers/funders were understanding of the need for longer trials, there was persistent tension with the need for efficiency • **The need for a placebo arm should be clearly communicated to PwP** PwP/care partners were the least strongly in favour of placebo, and many supported a standard of care comparator
Domain 2: Eligibility Criteria	
• The trial should not be limited to treatment naïve patients	• **The research community should consider the unmet clinical need of DMTs for advanced disease** PwP and care partners favoured inclusive trials including longer disease duration (>5 years) and more advanced disease (wearing off, cognitive decline) • **The rationale for limiting eligibility should be critically considered and justifiable** There was a tension between PwP/care partners wanting therapies that can be applied in real-world clinics and industry/funders' preference to test therapies in homogeneous patient populations • **The need for a lower age limit needs to be clearly explained to PwP** PwP did not agree with lower age limits
Domain 3: Outcome Measures	
Evidencing phase 3 success should include: • OFF-state motor assessments • Quality of life • Activities of Daily Living • Disease milestones • More than one measure • Passive digital monitoring • Patient completed questionnaires	• **Improvement in non-motor outcomes is particularly important to PwP/care partners** Giving a holistic picture was the most frequently selected reason for all endorsed outcomes • **The use of questionnaires should be critically considered, justifiable and their need clearly communicated to PwP** PwP raised concerns regarding repetition, completion burden and potential lack of insight into own symptoms, whilst care partners were concerned about PwP vision and writing difficulties • **Digital outcomes have potential but require better end-user engagement and validation** PwP were concerned about passive monitoring, eg not holistic, impersonal • **The concerns of care partners should be fully addressed by study teams, particularly in relation to OFF-state assessments** Care partners raised safety concerns
Domain 4: Trial Delivery	
• Home or virtual study visits- should be offered whenever possible	• **Flexible delivery models are critical to improve accessibility of trial participation** Flexibility in trial delivery models was valued by all participants • **Where clinic visits are required, efforts should be made to minimise stress and burden associated with participant travel** This was the most frequent concern raised by PwP

Fig. 3. Consensus Items and Key Considerations by survey domain.

provided by other participant groups. Thus, the outcomes of this Delphi process may support researchers in considering PwP and care partner as well as other stakeholders' preferences sensitively and serve as a starting point to explore these within the context of their own trial as part of their patient engagement activities to support trial design decisions and communications strategies.

Efforts were made to balance PwP for age, disease duration range and trial experience. Nevertheless, the nature of the study precluded the recruitment of a sample representative of the PwP population. English language requirements and online recruitment and conduct meant that the sample was younger, digitally literate, and not ethnically diverse, and therefore further studies will be needed to explore the translatability of findings to more diverse PwP and care partner groups. Our selection methodology resulted in a median age of 65 (13 IQR) which although younger than incident PD population [33], was slightly older than the average participant age in DMT trials (62 years) [21]. Finally, no information was collected on PwP/Care partners' experience with medical devices or digital outcomes for PD which could have aided in the interpretation of PwP/care partners' views.

There was higher attrition from lay participants than professional groups and some participant group sizes were small, although representation of collected demographics remained similar between rounds and no attrition bias was identified.

We included a question on the necessity of distinguishing DMT versus symptomatic effects in DMT trials although this was implicit in the setup of the study. The question was included because this distinction remains a methodological challenge in DMT trials, and there is increasing discussion over its need. We were interested to understand the perspectives of the different stakeholder groups regarding the importance of making this distinction. Some survey participants felt that the answers to questions covered within the study would depend on the DM agent being trialed or the aim of the study. Although the weight and prioritization of factors influencing trial design decisions will be determined by the therapy being tested and its stage of development, future researchers will be able to draw on this panel's perspectives and

develop strategies to mitigate general concerns raised by stakeholders. The propensity of neutral views is clearly represented and frequency of reasons reflecting a neutral attitude by the panel were captured and displayed for the reader (Supplementary Material 3).

In terms of overall DMT trial aims and design, the panel favored designs that maximize efficiency and learnings such as having multiple treatment arms, trying to identify treatment responsive subtypes, validating new digital outcome measures, evidencing disease modification, and being placebo controlled. No consensus was reached on trial length. Interestingly, all stakeholders understood the necessity for long term trials to measure real, long-term impacts of DMTs on patients and ensure potential benefits are not missed, although only clinical scientists and PwP voted in favor of long trials (Supplementary Material 3, D1Q3). This demonstrates that PwP understand the complexity of their disease warranting the need for longer trials and echoes regulatory guidance which recommends DMT trial durations of between 2–5 years [34]. This highlights the need for stakeholder engagement with funders, industry, and care-partners to address practical challenges of supporting long term trials.

The eligibility section of the survey was the most contentious yielding least consensus. Overall, industry participants favored less inclusive trials reflecting a need to reduce the potential impact of disease heterogeneity on trial findings.

The only point on which the panel agreed concerning eligibility was that the trial should not be restricted to drug naïve patients. This contrasts common practice of restricting recruitment to early, untreated PwP in DMT trials, which is argued to reduce the confounding effect of symptomatic therapy and increase the window for meaningful intervention in pathological pathways [14, 29].

PwP were in favor of inclusivity for almost all eligibility aspects presented in the study, including the inclusion of participants with more advanced disease highlighting an unmet need to address disease modification in this population. Narrow inclusion criteria make positive results less generalizable and are not representative of real world situations which can raise important safety and efficacy concerns [35], especially since participant demographics for PD trials often misalign with the final user population [30]. In addition, variability in PD progression is poorly understood with proposed subtypes often yielding unreproducible results [36, 37] and it is therefore questionable whether attempts at cohort homogenization through eligibility criteria is sufficiently justified especially in a phase 3 setting. The importance of ensuring trial participants are representative of the intended target population is increasingly recognized, has led to national efforts such as the INCLUDE project in the UK and is embedded within regulatory guidance [35, 38]. The FDA specifically urges the critical review of common eligibility criteria to ensure a strong scientific or clinical rationale [39]. Thus, eligibility criteria need to be aligned with the trial aim, with advantages and disadvantages carefully weighed by investigators and decision making clearly communicated with stakeholders, especially the patient community.

With the exception of passive digital measures and OFF-state assessments, the Delphi panel favored outcome measures that give a holistic, clinically relevant picture of PD progression such as quality of life, activities of daily living, delaying the development of new symptoms, showing an effect on more than one measure, and patient completed questionnaire scales. This is appropriate for phase 3 trial outcomes where regulatory guidance for evidencing disease-modification claims requires collected evidence to reflect meaningful and persistent changes in clinical function [34].

However, there are clear challenges as PD is a slowly progressing condition with a heterogeneous disease course and fluctuating symptom severity that can mask small signals as well as the detection of persistent changes. Current initiatives are exploring our understanding of PD experience to develop novel clinical outcome assessments, including milestone-based approaches [40–43].

A patient centric approach is crucial to reduce the burden of study participation, to maximize data quality and completeness. As well as being less supportive of patient completed questionnaires than professional participant groups, patients and care partners both expressed concern regarding the potential of patient and researcher completed questionnaires to increase the physical, emotional and cognitive strain on participants (Supplementary Material 3, D3Q12/D3Q13).

OFF-state motor assessments were also endorsed by the panel as a phase 3 outcome, albeit not until the fourth survey, with both funders and care partners taking a more neutral stance. Care partners in particular raised safety concerns (Supplementary Material 3, D3Q1). A recent qualitative sub-study of the PD-STAT trial, a multi-center trial with 235 participants at baseline, also highlighted OFF assessments as one of the most prominent challenges reported by both

patients and care partners and accounted for 37% of 51 withdrawals from the study [44]. From a regulatory standpoint, an OFF-state motor examination is not an adequate primary outcome for phase 3 trials on its own [34].

Digital outcomes are becoming increasingly important, with the COVID-19 pandemic accelerating their development [45–47]. This Delphi study facilitated the discussion of multiple aspects of digital outcomes and remote methods of trial delivery (D1Q8, D3Q10, D3Q11). Digital measures were viewed to be an important area to develop, having the potential to improve the way PD is measured by capturing more continuous, objective data, reduce trial cost and be easier, time saving solutions for participants (Supplementary Material 3, D3Q10, D3Q11). As with clinical outcome measures, digital outcome development is a vibrant, fast changing field with an increasing need to close the gap between digital innovation and validation of measures to clinical trial standards [46, 48]. Initiatives such as WATCH-PD as well as incorporation of digital measures as exploratory endpoints in trials are important to drive digital outcome development forward [49]. Whilst passive digital measures were endorsed by the panel, no consensus was reached on active measures. Furthermore, patients and care partners in particular held a more neutral position towards digital outcomes and despite the majority voting for positive statements, a wide range of limitations/concerns regarding digital measures were raised with the most frequent being concerns around diminishing emotional support through the trial and the inability of passive measures to capture all aspects of PD. Notably, although not receiving significant traction within the panel, concerns around active measures were centered around user ability, participant burden, compliance and retention while concerns raised by the panel around passive measures focused around data integrity and privacy (Supplementary Material 3, D3Q10, D3Q11). Thus, in addition to careful validation, development and use of digital outcomes requires engagement with user groups ensuring user-friendly, engaging design with appropriate consideration of the provision of participant support.

There was unanimous agreement of the Delphi panel that trial delivery should have a homebased or video trial visit component whenever possible, which would help support geographical inclusivity and retention. Stress and anxiety around travel were the main considerations for PwP rather than the burden of clinic visits themselves (Supplementary Material 3, D4Q1). Travel burden, particularly in the OFF state, has been identified as a significant barrier to participation [44]. Frequency of remote versus in person assessments was not considered within this study and this could have significantly influenced the panel's decision. Research accessibility and flexibility tailored to participants' needs is critically important for retention.

Conclusion

This Delphi study has generated a unique repository of stakeholder perspectives regarding pivotal aspects of DMT trial design in PD, importantly including those of patients and care partners. It provides an understanding of where consensus exists and a basis for further exploration of views where it does not. Despite patient and care partner opinion often not being pivotal in trial design decisions, due to the need for considering rigor and practicalities, reservations need to be addressed with a shared understanding critical to build trust and for patient-centered trial design and delivery.

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CONFLICT OF INTEREST

Prof. Camille B. Carroll is an Editorial Board Member of this journal but was not involved in the peer-review process nor had access to any information regarding its peer-review.

None of the other authors have any conflict of interest to report.

DATA AVAILABILITY

The raw data supporting the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/JPD-230109.

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