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The minimum clinically important difference (MCID) for a falls intervention in Parkinson's: A delphi study

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ABSTRACT

Background: Falls are common in Parkinson's disease so any intervention that reduced falls risk would be of value. One potential intervention is the use of cholinesterase inhibitor (ChEi) drugs.
Objective: To establish the minimum clinically important difference (MCID) for fall rates to inform the effect estimate for sample size calculations of future clinical trials.
Methods: We performed a Delphi study assembling a panel of experts in Parkinson's disease from academic and clinical medicine in order to reach a consensus of opinion. Responses from a panel were summarised and resent to the group, until consensus was reached.
Results: 780 clinicians, who had been caring for people with Parkinson's for an average of 14 years, were contacted via three routes. The median (Interquartile range (IQR)) MCID after round 1 was 25% (IQR 20–30%) which equates to the prevention of 5 (IQR 4–6) falls per year. Increasing consensus after round two confirmed the MCID of 25%, narrowing the (IQ) range to 20%–25%. This was unchanged when the panel were shown the number of participants that would need to be recruited to a clinical trial in order to achieve this difference.
Conclusions: We have established that an expert panel of PD specialists consider that an intervention that demonstrated a 25% (IQR 20–25%) relative reduction in falls rate would be clinically meaningful. This estimate can be used to help determine the sample size for any future clinical trial.

1. Introduction

Falls are a frequent and serious complication of Parkinson's disease (PD). Prospective studies report that 60% of people with PD have at least one fall per year and 39% fall recurrently [1]; median survival in patients with PD who have recurrent falls is 6 years [2]. Even in those who have not previously fallen, 21% will fall in the next 3 months. Consequences of falls include fractures and injury [3], fear of future falls [4], hospital admission [5], and increased caregiver burden [6], with falls cited as one of the worst aspects of the disease.

There is an urgent and unmet need to identify strategies to reduce the risk of falls and the potentially devastating sequelae in this high-risk population. Two strategies to tackle falls in PD are physical therapy [7–11] and the use of cholinesterase inhibitor (ChEi) drugs. Three randomised controlled trials of ChEi have demonstrated statistically significant differences in falls [12–14]. However, it is yet unknown as to whether these changes equate to a clinically important difference.

A statistically important difference is mainly determined by the number of people measured [15] and may not equate to a clinically important difference, even with an effective intervention (see Ref. [15] for a review of methods to determine cut-points for continuous scales). Clinicians must therefore determine whether a reported statistically significant difference would translate to a meaningful clinical benefit. This benefit, termed the clinically important difference, is a change that patients and/or clinicians would deem to be important to health or quality of life [16]. The lowest threshold value of this measure is the minimum clinical important difference (MCID), defined as “the smallest change or difference in an outcome measure that is perceived as beneficial and would lead to a change in the patient's medical management, assuming an absence of excessive side effects and costs” [17,18]. As this value is subjective, the estimate of this will vary between individuals rendering it necessary to reach a consensus opinion.

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We used a Delphi survey to determine the MCID for the number of falls that would need to be reduced in a hypothetical trial to be clinically meaningful. A Delphi survey consists of an iterative, multistep process in order to reach a consensus. Responses from a panel of experts are summarised and re-sent to the group recurrently until consensus is reached [19]. A key feature of this widely used methodology is the anonymity that is maintained between participants throughout the structured feedback process [20]. Currently there is no accepted MCID for reducing falls risk in patients with PD. The aim of this paper was to perform a Delphi survey of experts in the field of PD in order to establish the MCID for the potential intervention of ChEi therapy, which can then be used to design future clinical.

2. Methods

2.1. Participants

We sought to identify experts in PD who practised in academic and/or clinical settings. We defined an expert as a) a clinician with a specialist interest (defined as performing ≥1 specialist Movement Disorder clinic/week and attending ≥ 1 recognised Continuing Professional Development (CPD) activity (meeting/conference/course) in PD per year and/or b) an academic who holds a tenured or honorary university post who has published at least 1 peer-reviewed journal article in the last three years in the field of falls and PD. Potential participants were approached via three routes: Clinicians with an interest in Movement Disorders were contacted via two UK mailing lists (the British Geriatrics Society Movement Disorders Section (BGS-MDS) and the Association of British Neurologists (ABN)). A systematic review of the literature was undertaken using the MESH headings 'Falls' and 'Parkinson disease', limited to the last 2 years. From this, the corresponding author was emailed. If no email address was listed on the paper, their institution website was checked. Alternatively, the first or last author was contacted if no contact details were obtainable. All experts remained blinded to the identity of other experts. Completion of the online survey was piloted by physicians who did not have an explicit interest in PD.

2.2. Survey

An online survey was emailed to the experts with a follow-up reminder to non-responders. An introductory email provided information about the study and included a link to the online questionnaire. Panellists were asked to respond within 2 weeks of receipt of the email. The survey obtained some descriptive data about the participants and provided them with the background information including a fall rate ascertained from a robust systematic literature review [1]. The range in values of fall rate may result from patient characteristics in study samples, with high rates reported in those with cognitive impairment [21,22], the methods used for fall ascertainment and the classification of single versus recurrent faller [1]. Furthermore, it is recognised that a small proportion of patients will fall extremely frequently [10,13].

The Prevention of Falls Network Europe (ProFaNE) consensus statement advocates the collection of data on falls, fall-related injuries, physical activity, psychological consequences, and generic health-related quality of life (HRQoL) in fall injury prevention trials [23]. Falls were selected as the outcome measure in this study as they represent the index event that leads to the other potential sequelae such as fractures, hospitalisation and decline in health-related quality of life. Fall reduction is a meaningful outcome at both a population and individual level.

Having had a previous fall is a useful predictor of future falls when used alone [24] or in combination with other risk factors [25]. In the most comprehensive review to date [1] recurrent fallers were defined as having had more than one fall in a reported time period which was then adjusted to reflect a 12 month period. A wide range of recurrent fall rates were reported across the studies from 4.7 to 67.6 falls per year (mean 20.8). We therefore used this average to anchor the study in order to apply the proposed treatment effects to a population. Clinicians making a decision on preventive treatment for falls in an individual patient with PD would not necessarily know in advance whether their patient is likely to have an annual fall rate at the lower or higher end, therefore using the mean value as an anchor also replicates pragmatic clinical decision-making.

Participants were asked "In people with PD who have fallen, the average rate of recurrent falls is 20.8 falls per year (range 4.7–67.6). Please assume that a) the patient has no contraindication to cholinesterase inhibitor treatment and b) that a phase III trial has shown that cholinesterase inhibitor treatment results in a statistically significant reduction in fall rate. What is the MINIMUM treatment effect you would need to see before you would routinely consider using a cholinesterase inhibitor for people with PD who have previously fallen? To consider cholinesterase inhibitor therapy for falls prevention it would have to decrease fall rate by at least … (choose one only):"

The following options were presented both as a relative and absolute reduction in risk covering the range of between 2 and 50% or 1 to 10 falls prevented per year. For example, relative reduction of 25% = 5 falls prevented over 1 year = fall rate change from 20.8 to 15.6 falls/year (see data in Supplementary data 1a for all the options.)

Those that completed the first round were invited to participate in a second round. At this point, respondents were shown a figure demonstrating the median and range of all the responses and a reminder of their round 1 response so that they could decide to stay with their first response or alter this in the light of the responses from other participants. The second round contained an additional question that also listed the number of potential trial participants that would be required for each effect size alongside the MCID question (see data in Supplementary data 1b). This was done to see if participants altered their opinion given the pragmatic issues around recruiting PD patients into RCTs. This question was presented at the end of the survey so it could not influence participants' responses to the MCID question. A priori, we anticipated that 2 to 3 rounds would be necessary to achieve consensus. A copy of the MCID question is shown in Supplementary data 1. The survey was hosted on REDCap software. Ethical approval was granted from the University of Bristol ethics committee on 4th July 2016.

All analysis was carried using the Stata software version 15.1 (Stata Corporation, College Station, TX, USA). We reported results using descriptive statistics such as number of responses (percentages), means (SD) or median and (25%–75% IQR), as appropriate. The MCID was summarised using the median due to the skewness of the data, which was assessed visually. We used the emails of responders to determine who had not responded and hence required a reminder. Missing data were possible but we did not use any imputation methods as the number of missing data items was small.

3. Results

A total of 780 clinicians were contacted via the three routes (n = 57 paper authors; n = 408 BGS MDS mailing list; n = 315 ABN mailing list), a CONSORT flow diagram of recruitment is shown in Fig. 1. One hundred and fifteen people responded to the round 1 invitation, of these; 13 did not want to take part. Of the 102 who were interested in participating, 35 did not give consent (so did not proceed to answer the remaining questions), 2 did not provide an email address for the follow-up survey to be sent and 2 did not respond to the MCID question, therefore 63 participant's responses were analysed (8%). 54 participants responded to round 2 (86% of round 1).

The demographics of the respondents are shown in Table 1. The majority were based in Europe and had been caring for people with PD for an average of 14 years. The majority were frequent prescribers of ChEi. The two most commonly cited limitations to ChEi use were concerns regarding side effects and efficacy.

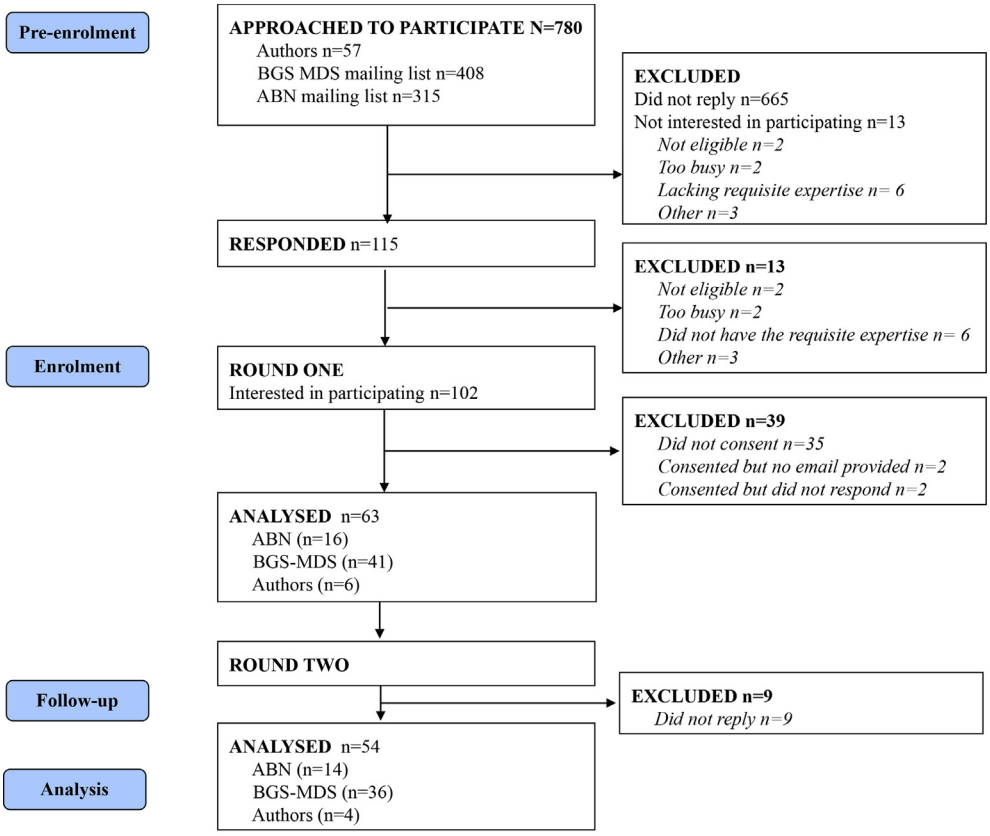

Fig. 1. Flow diagram of study.

Table 1
Demographic characteristics of respondents in Round 1 and Round 2.

	Round 1 N = 63	Round 2 N = 54
	n (%)	n (%)
Role		
Academic Geriatrician with clinical responsibility	3 (5)	3 (6)
Academic Neurologist with clinical responsibility	9 (14)	7 (13)
Academic with no patient responsibility	1 (2)	1 (2)
Clinician (Geriatrician)	26 (41)	21 (39)
Clinician (Neurologist)	13 (21)	11 (20)
Other	4 (11)	4 (7)
Missing	7 (11)	7 (13)
Continent		
Europe	53 (84)	45 (83)
North and South America	3 (5)	2 (4)
Australia	3 (5)	3 (6)
Missing	4 (6)	4 (7)
Mean (SD) years managing Parkinson's disease	14 (9.3)	14 (9.7)
Frequency of ChEi prescribing		
Frequently	32 (51)	23 (43)
Moderately	18 (29)	18 (33)
Rarely	5 (8)	5 (9)
Not applicable (do not treat people with Parkinson's)	8 (13)	8 (15)
Reasons cited as limitations to ChEi prescribing		
Efficacy	24/63 (37)	20/54 (37)
Side effects	37/63 (59)	30/54 (56)
Patient compliance	18/63 (29)	12/54 (22)
Confidence and familiarity with the drug	7/63 (11)	6/54 (11)
Cost effectiveness	4/63 (6)	4/54 (7)
Other	9/63 (14)	8/54 (15)

SD = Standard deviation; ChEi = cholinesterase inhibitor.

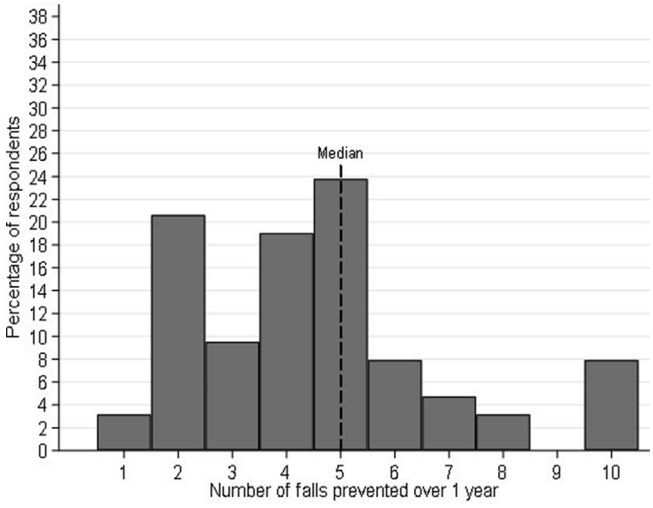

Fig. 2. Round 1 minimal clinically important difference (MCID) in falls rates.

The median (interquartile range (IQR)) MCID after round 1 was 25% (IQR 20–30%) (Fig. 2) which equates to the prevention of 5 (IQR 4–6) falls per year. However, there was, as expected, a wide range with some participants regarding even 1 fall (2% relative reduction) prevented as being meaningful and others requiring a much larger 10 fall (50% relative reduction).

The results of round 2 did not alter the MCID but narrowed the IQR - 25% (IQR 20%–25%) (Fig. 3) which equates to a reduction of 5 falls (IQR4-5) per year. The median point estimate for MCID therefore remained unchanged but the range narrowed between the two rounds, suggesting greater consensus. The consensus MCID remained

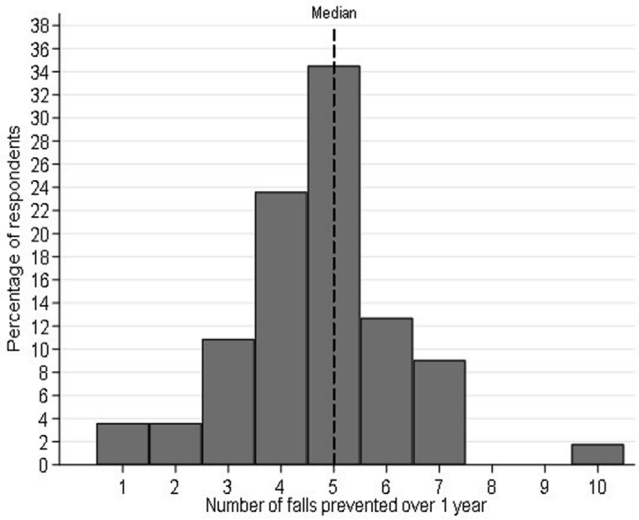

Fig. 3. Round 2 minimal clinically important difference (MCID) in falls rates.

unchanged (IQR 20–30%) when respondents were shown the total number of participants that would need to be recruited to a clinical trial in order to achieve that effect size (Supplementary data 2).

As so few responders were based outside Europe it was not possible to determine whether estimates differed regionally. There was no difference between the median MCID estimated by clinicians versus academics nor geriatricians versus neurologists and no difference for those who had practised for 12 or more years compared with those who have less than 12 years' experience. Side effects and efficacy were the two most commonly cited reasons for non-prescription of ChEis.

4. Discussion

This study determined the MCID for a falls intervention trial, (e.g. a ChEi) to be 25% (IQR 20%–25%) which equated to a reduction of 5 falls (IQR 4–5) per year in our hypothetical population. This would equate to a moderate to large size trial (total sample size required: 734, 367 per group in a 2-group study) given 90% power and 5% two-sided alpha. Having ascertained the MCID, it will be possible to determine in future studies whether the reported point estimate is clinically important, i.e. if the MCID is smaller than the lower limit of the confidence interval [26]. This reduction is smaller than the 45–69% reduction in falls reported in the 3 randomised controlled clinical trials of ChEi treatment that have been performed to date [12–14].

This is the first study known to the authors that has sought to determine the MCID for reduction falls in PD. The study has several advantages. We sought opinions from established specialists in PD and included clinicians and academics. Using an online tool meant that opinions were expressed anonymously in contrast to a group setting where individuals can exert undue influence over a group [27]. In our study, we achieved adequate consensus with two rounds of the survey with a relatively high retention of participants.

There are several limitations. The majority of experts were approached via UK based mailing lists and therefore the sample included high numbers of clinicians and academics from Europe. Though a Europe-focus was not exclusive, our sample may not therefore be wholly representative of worldwide PD specialists. The proportion of experts who responded was low and therefore may have been biased although there was fair representation from academic and clinical specialists, the majority of whom had responsibility for patient care and prescribed ChEi. Our panel size was larger than that utilised in other Delphi studies that have sought to determine clinically meaningful differences [28,29]. Repeating the exercise with a different panel sample would further inform the extent to which this opinion is generalisable to other experts in the field.

It is anticipated that the MCID that we have determined pertains to the *group* differences ascertained in a randomised controlled trial. Our anchor (the mean recurrent fall rate of 20.8 falls per year) was therefore determined at an overall group level for a *population* of people with PD (see Ref. [30] for a comprehensive worked example). Our choice of the mean fall rate was based on a comprehensive systematic review of recurrent fallers [1]. It could be argued that the average fall rate could have more optimally been derived from the median fall rates from individual papers. An additional limitation is that the consensus has been derived using a scenario that applies to a hypothetical patient falling recurrently 21 times in 12 months and the wider generalizability to those falling more or less frequently is limited.

To apply the MCID at an individual level, group minimal difference can be used in trials as a response criterion to determine the proportion of patients in each arm whose change is greater than the MCID [31]. At an individual level for a person with PD who is falling, a 25% (relative reduction in fall rate will translate differently depending on the individual's absolute risk. This reduction will yield a greater absolute reduction in number of falls in the very frequent faller versus the occasional faller. At this *individual* level a more appropriate question to pose may be 'what reduction in fall rate results in a minimally important improvement in quality of life'. For example, falls that result in significant soft tissue injuries, fractures and hospitalisation may negatively impact patients to a greater extent that simply the number of falls. Therefore, these alternative outcome measures may be of more importance to patients than the reduction in overall fall rate. To determine meaningful differences at the individual level, it is therefore important to capture changes in fall sequelae, including patient quality of life.

In our study, we did not seek to subclassify the aetiology of the fall or the characteristics of the faller. Future trials and meta-analyses should be able to identify whether a given fall intervention performs differently depending on pre-existing fall risk and other factors such as age or gender. Interventions that are effective in those at higher risk of falling have the potential to be more cost-effective. This process is aided by the standardisation of the fall trials outcomes in line with the ProFaNE consensus [23]. We recognise that a smaller difference in improvement in fall rate may be accepted if it led to a clinically meaningful difference in disability related measures and quantifying meaningful differences across fall related domains offers a promising avenue for future study.

We chose to contextualise our scenario with a potential drug intervention (ChEi). We think our findings are likely generalisable to other drugs treatments. Assuming no major differences in serious side effects, the cost-effectiveness of two equally effective treatments will be sensitive to the cost of the therapies. Our findings may not be generalisable to clinical decisions about patients whose fall rates differ markedly from the mean value used in this study. It is less clear if our findings are generalisable to non-pharmacological interventions such as physiotherapy. In principle, there should be no difference but we cannot be sure that clinicians do not hold different expectations from such interventions. Commonly, non-pharmacological interventions are considered to have fewer negative effects therefore clinicians may have a lower threshold for the MCID required for them to consider a non-pharmacological prescription."

This study ascertained the MCID for a falls intervention using a Delphi process to obtain consensus amongst experts. This difference translates to a meaningful clinical benefit, derived from experienced academics and practising clinicians, which researchers should take into account when designing trials of fall interventions in PD. There are future opportunities to perform research to ascertain consensus opinion in patients and caregivers on other outcomes, such as quality of life or reduced caregiver burden, that a falls intervention should be expected to deliver.

Data availability

Access to the source data used in this study will be considered on application to the corresponding author.

Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2018.11.008.

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