The Cost-Effectiveness of specialized Nursing Interventions for people with Parkinson's Disease: the NICE-PD study protocol for a randomized controlled clinical trial

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Abstract

Background Current guidelines recommend that every person with Parkinson's disease (PD) should have access to Parkinson's Disease Nurse Specialist (PDNS) care. However, there is little scientific evidence on the cost-effectiveness of PDNS care. This hampers wider implementation, creates unequal access to care and possibly leads to avoidable disability and costs. Therefore, we aim to study the (cost-)effectiveness of specialized nursing care provided by a PDNS compared to usual care (without PDNS) for people with PD in all disease stages. To gain more insight into the deployed interventions and their effects, a pre-planned subgroup analysis will be performed based on disease duration (diagnosis <5, 5-10, or >10 years ago). Methods We will perform an 18-month, single-blind, randomized controlled clinical trial in eight community hospitals in the Netherlands. A total of 240 people with PD that have not been treated by a PDNS over the past two years will be included, independent of disease severity or duration. In each hospital, 30 patients will randomly be allocated in a 1:1 ratio to either care by a PDNS (who works according to a recent guideline on PDNS care) or usual care. We will use two co-primary outcomes: quality of life (measured with the Parkinson's Disease Questionnaire-39) and motor symptoms (measured with the MDS-UPDRS part III). Secondary outcomes include non-motor symptoms, health-related quality of life, experienced quality of care, self-management, medication adherence, caregiver burden and coping skills. Data will be collected after 12 months and 18 months by a blinded researcher. A healthcare utilization and productivity loss questionnaire will be completed every 3 months. Discussion The results of this trial will have an immediate impact on the current care of people with PD. We hypothesize that, by offering more patients access to PDNS care, quality of life will increase. We also expect healthcare costs to remain equal, as increases in direct medical costs (funding additional nurses) will be offset by a reduced number of consultations with the general practitioner and neurologist. If these outcomes are reached, wide implementation of PDNS care is warranted. Trial registration ClinicalTrials.gov: NCT03830190. Registered February 5, 2019 – Retrospectively registered, https://clinicaltrials.gov/ct2/show/NCT03830190.

Background

Parkinson's Disease (PD) is a complex, progressive neurodegenerative disorder. Despite optimal medical management, e.g. with dopaminergic medication or deep brain stimulation (DBS) [1], most persons with PD increasingly experience progressive disabilities that influence the quality of life of both patients and their caregivers [2,3]. PD is characterized by a wide range of motor- and non-motor symptoms, including bradykinesia, tremor, rigidity, gait disturbances, psychiatric symptoms, autonomic and cognitive dysfunction [4]. Many of these symptoms (i.e. freezing of gait, postural instability and a wide range of non-motor symptoms) are poorly controlled by medication [5]. The complexity of the disease in combination with limited treatment options creates tremendous challenges for the management of PD [6] and in coping with the disease for patients and their caregivers [7,8].

In primary care, improved collaboration between doctors and nurses may lead to more integrated and consequently better-quality care. Indeed, there is increasing evidence that care delivered by trained nurses

may generate similar or possibly better health outcomes for a wide range of disorders [9]. For the specific situation of PD, the Parkinson's Disease Nurse Specialist (PDNS) might fulfill a pivotal role in the multidisciplinary team. The PDNS was introduced in 1989 in the United Kingdom to bridge the gap between medical management and the unique personal needs of patients [10]. To obtain greater uniformity in care delivery and to facilitate the efficacy of nursing care in PD, the Dutch Guideline 'Nursing care in Parkinson's disease' was published in 2015 [11]. The main roles of the PDNS are clearly described in this guideline, including (1) providing information, education and instruction; (2) supporting the patient and caregiver in the promotion of self-management; (3) supporting psychosocial care questions; (4) prevention; (5) specialized diagnostic strategies and therapeutic nursing interventions; and (6) multidisciplinary collaboration.

Based on expert opinion from healthcare professionals, the Dutch guideline recommends that every person with PD could benefit from PDNS care, including those in early-stage disease where delivery of information, education about medication compliance and support in self-management are crucial. So far, only three studies have evaluated PDNS care, with inconsistent results. Overall, the findings suggested that PDNS care may improve patient wellbeing, physical functioning and general health status and reduce anxiety and depression [12,13,14], but definite conclusions cannot be drawn. Moreover, there is little evidence to show that quality of life actually improves with PDNS care. Finally, to date no studies have evaluated the cost-effectiveness of PDNS care [9].

Presumably because the scientific evidence is inconclusive, many centers currently lack the nursing capacity and financial resources to offer PDNS care to all patients. This situation creates an undesirable inequality in access to care and presumably leads to avoidable disability and costs (e.g. from early admissions to nursing homes or crisis admissions to the hospital). Therefore, we aim to study the cost-effectiveness of specialized nursing care provided by a PDNS as compared to no PDNS care for people with PD. We hypothesize that offering PDNS care will lead to higher quality of life [15,16]. We also expect healthcare costs to remain equal, because any increases in direct medical costs (to fund the extra nurse staffing) will be offset by a reduced number of (telephone) consultations with the primary care physician and neurologist. When this hypothesis is confirmed, wide implementation of PDNS care, for patients with PD in all disease stages, is warranted. Conversely, negative findings would necessitate a critical reappraisal of the role of PDNS care as it is defined and delivered in its current form.

Methods

Study design

The NICE-PD study protocol will here be reported according to the SPIRIT 2013 Statement [17]. Additional file 1 details the IPPCollapse-II SPIRIT checklist. The study is an 18-month, single-blind randomized controlled clinical trial that will be performed in eight community hospitals in the Netherlands. The participating centers can be found in *Table 1*. A total of 240 people with PD will be included (120 in each group), equally distributed over the participating hospitals. We have selected hospitals where, due to lack

of sufficient PDNS staff, only a proportion of PD patients currently have access to PDNS care. This provides us with a unique opportunity to identify patients who at present have no access to PDNS care, and to randomize them within hospitals (at the patient level) between PDNS care and no nursing intervention. We have summarized the study design in *Figure 1*. The enrolment and assessments during the study period are shown in *Figure 2*.

Eligible patients will be allocated randomly to either PDNS care or usual care in a 1:1 ratio, using a computer-generated list of random numbers. An independent researcher (who will not perform study assessments) will perform the randomization in an online data management system. Subsequently, this researcher will contact the PDNS to inform them about which participants are randomized to the intervention group. The other participants will receive a letter or an e-mail stating that they have been assigned to the control group. To ascertain an equal representation of patients, we will stratify for gender and disease duration (according to pre-defined subgroups, i.e. disease duration <5 years, 5-10 years and >10 years). The PDNS intervention will follow the Dutch 'Guideline Nursing care in PD' [11] (see the section on 'intervention'). A blinded researcher will perform the clinical assessments at baseline (t0), after 12 months (t1) and after 18 months (t2). Patients and caregivers will also be asked to complete a set of questionnaires at t0, t1 and t2. Finally, every three months patients and their caregivers will complete a questionnaire about healthcare utilization, costs and productivity loss. Care providers (e.g. neurologists) will not be blinded for the assigned interventions. We do not foresee any reason why unblinding of participants would be necessary.

Inclusion and exclusion criteria

The inclusion and exclusion criteria for patients are kept purposefully broad, in order to represent the full diversity of the PD spectrum and thus generate results that apply to real clinical practice. All patients with PD regardless of disease severity or disease duration, male and female, aged 18 years or older at the time of PD diagnosis are eligible. We will only exclude patients that:

- do not have sufficient knowledge of the Dutch language to complete questionnaires;
- received care from a PDNS in the past two years;
- have a score of <18 on the Mini-Mental State Examination (MMSE[18]) and <12 on the

Frontal Assessment Battery (FAB[19]).

- have a type of atypical parkinsonism caused by medication (e.g. neuroleptics), a metabolic disorder (e.g. Wilson's disease), encephalitis or a neurodegenerative disorder (e.g.

multiple system atrophy, progressive supranuclear palsy, corticobasal syndrome).

- are residing in a nursing home or another type of residential care facility (because the PDNS is not operational there).

- have any other medical or psychiatric disorder that, in the opinion of the researcher, may compromise participation in the study.

Recruitment

Patients will be approached within each hospital using one of three scenarios.

- The involved neurologists in the hospitals identify eligible patients from their electronic patient file and inform these patients about the study in their clinic (when the patient is coming in for a consultation). If the patient agrees to be approached by a researcher, they will be provided with the patient information letter.
- The neurologists identify eligible patients using their electronic patient file and subsequently approach them by directly sending out a letter including a short description of the study and a form in which patients can indicate if they want to receive any further information about the study or not. Only if patients actively indicate that they wish to be approached, the researcher will contact them by telephone and send the information letter to the patient.
- The research team organizes an information meeting for patients in the participating center (where also the PDNS and neurologist are present). Here, the patient information letter will be handed out directly. Importantly, patients will be given sufficient time to consider their participation. If they are interested, they will be contacted by the research team at least two weeks after the information session.

Training and coaching of Parkinson's disease nurse specialists

Before the start of the study, we will organize a single training session with all participating PDNSs (one from each center). The goal of this meeting is to acquire commitment for the study and uniformity in workflow by reviewing the 'Guideline Nursing care in PD', to explain the study specifics and to discuss practical issues related to the study intervention. In addition, PDNSs will be closely coached in order to optimize the intervention and adherence to the guideline. Every month an experienced PD nurse from the Radboudumc will have an individual intervision session with each PD nurse, mainly to discuss difficult cases and to optimize the intervention and its uniformity. Finally, we will organize a video meeting every three months with all PDNSs to maintain commitment, support each other, discuss difficulties related to the study and to give each other advice [20,21].

Importantly, for the purpose of this study, we will implement an increase in nursing staff capacity for participating nurses. This will allow us to study the real impact of current usual care, which would not be achieved by adding a new set of specifically trained research nurses to the existing PDNS staff. The PDNSs are all graduated nurses (education level according to the European Qualifications Framework 6

or 7) with a certificate in Parkinson's Nursing. Furthermore, they have achieved a standard of competences as described in the Guideline on PDNS care [11].

The PDNS intervention

The PDNS intervention will be performed according to the Dutch 'Guideline Nursing care in PD' published in 2015 [11]. The intervention is not standardized, but tailored to the patients' and caregivers' needs. This includes the following:

- Assessment of individual care needs of people with PD and their caregivers. At the start of the study, the PDNS performs a specific nursing assessment related to the medical, physical, psychological and social domains.
- Development of a patient-centered treatment plan that supports the patient and caregiver in self-management. The PDNS composes a multidisciplinary plan, based on the results of the individual assessment, and as prioritized by the patient and caregiver (shared decision making). The treatment plan is developed according to the national self-management framework [22].
- Specific nursing interventions. The intervention varies across disease stages and is tailored to the specific problems and needs of individual patients and their caregivers. The Guideline on PDNS care describes general- and specific nursing interventions. General interventions consist of providing information and education, disease management (e.g. considering advanced treatment options such as DBS) and monitoring (e.g. of caregiver burden). Specific nursing interventions are described for the following areas: mental functions, fatigue, sleep, urogenital functions, sexuality, medication adherence, orthostatic hypotension, caregiver burden, coping, mobility, self-management and dietary issues (*table 2* provides examples of such interventions).
- Collaboration with other healthcare professionals. The PDNS stimulates and supports multidisciplinary collaboration between healthcare professionals based on the individual patient-centered treatment plan. The PDNS also plays a pivotal role in the timely referral to other healthcare professionals.

The PDNS will maintain a pre-defined electronic study report according to a structured format for each PD patient, documenting the individual care needs, present symptoms, performed interventions and (changes in) the individual care plan. This report will be started at the initial assessment and updated at every follow-up contact with the patient, e.g. at the outpatient clinic, during a telephone consultation or at a home visit. This data will be purposefully collected for a possible process analysis at the end of the study.

Patients will have regular contact with their PDNS about the progress and realization of the personal goals, both during face-to-face contacts and by telephone, and sometimes during additional home visits. The frequency and type of contact will be optimized for each patient depending on disease stage and individual patient needs. The Guideline on PDNS care advises that each patient has a minimum of one

contact with the PDNS each year [11]. Currently in the Netherlands, patients are seen on average twice a year by their PDNS, with an additional two interim telephone consultations per year.

The control group will receive ongoing usual care which is medically comparable to the intervention group, but without a nursing intervention. This involves regular consultations with a neurologist in their own community hospital (typically 2-4 times per year, depending on patient preferences and health status). In addition, control patients will have no restrictions considering any other medical treatments (e.g. by a psychologist or social worker). Importantly, many key elements of care (including in particular the treating neurologist) remain comparable between the two arms because of the randomization at the patient level within hospitals.

Clinical assessment and outcome measures

At baseline, t1 and t2 all patients will visit their own hospital for the study assessments which are performed by a blinded researcher (PDQ-39, MDS-UPDRS and TUG). The patients and their caregivers will also complete home questionnaires. In addition, every three months, patients will receive a questionnaire at home regarding healthcare utilization, costs and productivity loss over the past three months. Caregivers will complete a cost questionnaire including healthcare utilization, costs and productivity loss specifically related to caregiver burden. To improve adherence, patients and caregivers can choose whether they prefer to fill out digital or paper-based questionnaires. Participants will be contacted by telephone when they do not complete the questionnaires within four weeks. All the outcomes, including secondary outcome measures, can be found in *Table 3*.

Similar to previous large randomized controlled trials in the field of PD [23,24], we will use two co-primary outcomes: quality of life and motor symptoms [25]. For measuring quality of life, we will use the PDQ-39, which is the most widely used quality of life scale in PD and frequently used as outcome measure, e.g. in trials on DBS [26] and multidisciplinary care [27]. Our second co-primary outcome measure is the severity of motor symptoms measured by the MDS-UPDRS part III. The MDS-UPDRS is a frequently used clinical rating scale and has been shown to be sensitive to change in clinical status [28]. Both scales have been previously validated and are reliable and valid methods to either measure quality of life [29] or motor symptoms [30] in people with PD.

Data collection and management

Patients will be given a unique personal identification code not containing any information that refers back to the individual. The key-file, connecting personal identification codes to the individual patient, will be stored on a secure Radboudumc data server. Only the research team has access to this key. The key-file will be stored on a different server from the acquired study data for five years, allowing the research team to contact patients after they have finished the study. After five years, the key-file will be destroyed.

Data from all paper-based Case Report Forms (CRFs) completed by the researcher (PDQ-39, MDS-UPDRS and TUG) will be entered manually into an online certified data management system (Castor EDC). Online CRFs (the remaining questionnaires) will automatically be recorded in Castor. When patients or caregivers are not able to complete questionnaires online, they also have the opportunity to do this on paper. We will send out the questionnaires by post and patients can return the completed questionnaires using a self-addressed envelope. These questionnaires will be entered manually into Castor. Both online and paper-based CRFs only contain the personal identification code.

Clinical notes taken by the PDNS in the online study report will also not contain any information that refers back to the individual. PDNSs are instructed to make notes according to a pre-defined structured format, without mentioning personal information that traces back to an individual patient. The study report will be completed in Castor.

Adverse events

All serious adverse events (SAEs) will be collected and followed up by the investigators and documented in the electronic CRFs. Each SAE will be reported by the respective PDNS to the study team (DR) and the SAE will be notified to the local ethics committee as soon as the researcher has knowledge of the SAE, but no later than 24 hours after the researcher has become aware of the event. Other adverse events will not actively be inquired for during the study, because of the low risk associated with the trial. When a participant spontaneously reports an adverse event, it will be registered in the electronic CRF.

Sample size analysis

We performed a sample size calculation based on the PDQ-39 score. Based on observations in one of our previous studies in a similar population of PD patients where we evaluated multidisciplinary care [27], we found a mean improvement in PDQ-39 score in the intervention group of -2.5 (SD: 5.8) points and a mean deterioration in PDQ-39 score in the control group of +1.4 (SD: 8.6). We calculated the sample size based on a mean difference between groups of 3.9, with a standard deviation of 8.6 (the highest SD reported). Using a significance level of alpha=0.025 (instead of 0.05 because of two primary endpoints; PDQ-39 and MDS-UPDRS part III) and a power of 80%, a sample of 93 patients in each group would be needed. Considering an attrition rate of 20%, 117 patients are needed per group. We have rounded this up to 120 patients per group, which means a total of 240 patients. We expect this to be feasible, because following a baseline inventory, all centers indicated to be able to include at least 30 patients.

Data analysis

The economic evaluation investigates, alongside the clinical trial, the value for money of full implementation of the PDNS into PD care from a societal and healthcare perspective. We will take all relevant costs into account. The cost-effectiveness timeframe adheres to the clinical study protocol and

evaluates cost-effectiveness up to 18 months after randomization. Cost will be measured using a healthcare utilization questionnaire (e.g. including medical consultations, hospital admissions, medication, travel costs, etc.) and a questionnaire measuring productivity loss while working of both patients and caregivers. Per item of healthcare consumption, standard cost-prices will be determined using the guideline for performing economic evaluations [31]. If standardized prices are not available, full cost prices will be determined using activity-based costing. Costs will be analyzed using a mixed model approach or a general linear model approach with a gamma distribution using a log link to account for possible skewness of the cost data.

We will use a PD-specific quality of life measure (PDQ-39) and a generic health-related quality of life scale (EQ5D) to evaluate the quality of the health status of patients. The potential difference in Quality-Adjusted Life Years (QALYs) measured with the EQ5D will be analyzed with a regression approach. We will use a linear mixed model with repeated measurements to test for differences in quality of life (measured with the PDQ-39) between both groups. The same analysis will be used to measure differences between groups in the secondary outcome measures. We will include study center as a random effect and fixed effects for group, time and the interaction between group and time. Each of the outcomes will be included as dependent variable. Statistical analyses will be performed based on the intention-to-treat principle.

As mentioned previously, we hypothesize that both interventions (PDNS care versus no PDNS care) will yield equal costs, while PDNS care is more effective. If this hypothesis is confirmed, then the effect analysis is sufficient to show the efficiency of PDNS care. The design of the economic evaluation follows the principles of a cost-effectiveness analysis and adheres to the Dutch guideline for performing economic evaluations in healthcare [31].

Besides the overall cost-effectiveness evaluation, we will perform a pre-planned subgroup analysis based on disease duration (diagnosis made <5 years, 5-10 years or >10 years ago) to obtain more insight into the nursing interventions used in each disease stage and the effects of PDNS care in these different groups of patients. This subgroup analysis will be performed because, for example, for the more severely affected patients the nursing intervention is expected to become more intensive and possibly more effective, but also more expensive. When different patterns of this kind are found, this should be investigated further in future trials that are powered adequately to address such group differences.

Trial oversight

The chief investigator has the overall responsibility for the conduct of the study. The study group has responsibility for the day-to-day management of the trial and consists of the following people. DLMR, HHL, RHH, MM, NMdV and BRB designed the study. DLMR and NMdV are responsible for day-to-day management of the trial, including the inclusion of participants and communication with participating centers, participants and the ethics committee. TvA, CCSD and HV have a more consultative role and provide substantial feedback to the trial procedures. There will be no independent data monitoring committee, due to the low risk associated with the trial. The results of the study will be sent for

publication to a peer-reviewed medical journal. No professional writers will be involved. In addition, the results will be shared with trial participants via the Dutch Parkinson Association and via ParkinsonNet. We report no restrictions for publication.

Discussion

Here, we present the rationale and design of the NICE-PD study, a large (n=240) randomized controlled clinical trial that aims to evaluate the cost-effectiveness of specialized nursing interventions provided by a PDNS for people with PD. The results of this trial will have an immediate impact on the current care for people with PD, independent of its outcome. When the intervention is shown to be cost-effective, a wider implementation of PDNS care for all patients is warranted. This requires an increase in PD nursing capacity, which means that further efforts towards policy makers and payers must then be initiated to ensure that they will invest in the reimbursement of PDNS care. We expect that investment in extra PDNS capacity will not lead to a net increase in costs, because the number of neurologist consultations may decrease proportionally to the increasing PDNS care. On the other hand, if cost-effectiveness is not shown, current guideline recommendations should be re-evaluated critically and a discussion should be started on how PDNS care delivery should be modified for it to be more effective. One may also argue that PDNS care could be considered successful when quality of life significantly improves with a slight increase in costs. With this outcome, it may be worth to invest in PDNS care to further improve the quality of life of people with PD, and to search for solutions to optimize efficiency and to reduce costs of PDNS care interventions.

We hypothesize that offering PDNS care will lead to higher quality of life with equal healthcare costs. Increasing direct medical costs (for nurse staffing) are expected to be offset by a reduced number of (telephone) consultations with the general practitioner and neurologist. These short-term goals are the focus of the present NICE-PD proposal. In addition to the short-term effects, we also expect long-term benefits, but these are beyond the scope of the present project. Examples of potential long-term benefits include a reduction in the number of nursing home admissions and fewer emergency visits to the hospital, which could potentially lead to a substantial cost reduction.

This is the first randomized controlled clinical trial to evaluate the cost-effectiveness of PDNS care. However, this study is not without challenges. During the study period, each hospital receives extra budget (out of the grant money) to increase their PDNS capacity for providing better care to the patients in the intervention group. However, this reimbursement cannot be continued after the study has ended. It will be a challenge to offer continuity of care for the participating patients, when nursing capacity has to be reduced again after the study because of a reduction in funding. We hope that positive results of the present study will provide a strong impetus for identifying the necessary financial resources to finance sufficient nursing capacity in the long-term. To ascertain this, we will engage in discussions with Dutch payers already at the outset of the study. The second challenge is that the patients in the control group will not have access to PDNS care during the complete study period. However, there are no restrictions to other medical treatments, which means that the control patients are allowed to consult all other available

healthcare providers (e.g. physiotherapists, psychologists and social workers). There are two exceptions though, in which care by a PDNS will only be directed at these specific situations: 1) providing specific information and guidance about advanced therapies (e.g. deep brain stimulation, duodopa infusion); and 2) moral dilemmas in crisis situations (e.g. psychosis). Note that a group of patient researchers who were involved in the design of this NICE-PD study consider it ethically acceptable to deny these patients access to PDNS care during a period of 18 months, since we are not withholding an evidence-based treatment (current evidence is limited). This is because patients were not receiving any PDNS care anyway outside the study and because we can now exploit this situation to gain scientific evidence about the cost-effectiveness of PDNS care. This new knowledge will eventually benefit all PD patients, including those allocated to the control arm of the present trial.

Third, because PDNSs are not operational in nursing homes or other types of residential care facility, it may be more difficult to include severely affected patients in this study. We will try to overcome this by stratifying for disease duration and by carefully selecting patients from all disease stages from each center. Finally, because quality of life is a very generic outcome measure, it may be a challenge to find relevant results on this metric. To overcome this challenge, we have chosen to use two co-primary outcome measures. To accommodate this, we have chosen more cautious levels of statistical significance. Moreover, the study was powered for a single outcome (quality of life), but our power is sufficient to also detect a clinically minimally important difference for the co-primary outcome (the MDS-UPDRS). The reason why we expect an improvement in this other primary outcome is because when patients receive more integrated care, motor symptoms may also improve.

In conclusion, this study will generate new insights into the cost-effectiveness of specialized PD nursing interventions for people with PD. If positive results are found, a large shift in the organization of PD care is needed to warrant equal access to PDNS care for every person with PD.

Trial Status

Protocol version 2, date: June 26, 2018. Recruitment has started on January 7, 2019 and is currently ongoing. The expected date for recruitment completion is December 2019.

List Of Abbreviations

CRFs = Case Report Forms
MDS-UPDRS = Movement Disorders Society-sponsored revision of the Unified Parkinson's Disease Rating Scale;
PD = Parkinson's disease;
PDNS = Parkinson's disease nurse specialist;
PDQ-39 = Parkinson's Disease Questionnaire;
SAE = Serious Adverse Event;
TUG = Timed Up and Go.

Declarations

Ethics approval and consent to participate

This study will be conducted in accordance with the Good Clinical Practice (GCP) guidelines promulgated by the International Conference on Harmonization (ICH), the principles of the Declaration of Helsinki and the Medical Research Involving Human Subjects Act (WMO). The NICE-PD study protocol and communication materials have been approved by the local ethics committee (Commissie Mensgebonden Onderzoek Arnhem-Nijmegen; NL65468.091.18). The study is registered in the ClinicalTrials.gov registry (NCT03830190) [32]. The trial results will be reported according to the CONSORT 2010 guidelines [33].

When a patient meets the inclusion criteria, informed consent will be obtained by the research team, explaining the procedures and requirements of the study, how subjects' confidentiality will be maintained and any potential hazards/risks. Each patient will sign such an informed consent form in-person at the baseline visit, before baseline assessment takes place. The researcher will sign the informed consent immediately after the patient has signed it. The researcher provides a copy of the signed informed consent form to each participant and keeps a copy in the participant's study file.

When important changes are made to the study protocol (e.g. changes in eligibility criteria, outcomes or statistical analyses), the Principal Investigator will notify relevant parties about these changes and a copy of the revised protocol will be sent to these parties (e.g. the Ethics Committee, participating centers and the clinical trial registry). Furthermore, the updated protocol will be included in the trial registry.

Consent for publication

Not applicable.

Availability of data and material

On the consent form, participants will be asked whether they agree with the following: 'I know that participating in this trial is voluntary. I also know that at any time I can decide to withdraw from the trial. I do not have to give any reason. The data that is collected until that moment, will be used for the research. A number of people are allowed to view my data. These include the members of the research team, the Ethical Committee, people that verify the safety of the trial (monitor), and the Dutch Healthcare Inspection.'

This trial does not involve collecting biological specimens for storage. The aggregated datasets analyzed during the current study will be available from the corresponding author on a reasonable request.

Competing interests

BRB and MM were supported by a research grant of the Parkinson’s Foundation and the Gatsby Foundation. DLMR, HHL and NMdV were supported by a research grant of ZonMw (The Netherlands Organisation for Health Research and Development) and Zambon. HV, TvA and CCSD declare that they have no competing interests.

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Author contributions

DLMR designed the study, drafted and revised the manuscript. HHL designed the study and revised the manuscript. HV provided substantial feedback to the design of the study and revised the manuscript. TvA provided substantial feedback to the design of the study and revised the manuscript. CCSD provided substantial feedback to the design of the study and revised the manuscript. RHH designed the study and revised the manuscript. MM designed the study and revised the manuscript. BRB designed the study and revised the manuscript. NMdV designed the study, drafted and revised the manuscript. All named authors read and approved the final manuscript. All authors adhered to the authorship guidelines of Trials. No professional writers have been involved.

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Tables

Table 1. The participating community hospitals in the Netherlands.

Center	Location
BovenIJ Hospital	Amsterdam
Treant Care Group, location Bethesda	Hoogeveen
Elisabeth-TweeSteden Hospital	Tilburg
St. Jans Gasthuis	Weert
Máxima Medical Center	Veldhoven
Rode Kruis Hospital	Beverwijk
Waterland Hospital	Purmerend
Zaans Medical Center	Zaandam

Table 2. Examples of specific nursing interventions according to the Dutch ‘Guideline Nursing care in PD’ [11], that are also reminiscent of the Fundamentals of Care Framework [34] (this list is not exhaustive).

Area	Interventions
Mental functions	Providing information and education Activation and supporting the creation of a day structure Supporting the caregiver
Fatigue	Supporting the intake of food with sufficient caloric value Promoting physical exercise Structuring daily activities
Sleep	Providing sleep hygiene advice (e.g. no alcohol or caffeine before sleep, no watching television or using the computer before sleep) Changing medication in consultation with the neurologist in case of nocturnal ON/OFF fluctuations
Urogenital functions	Advising to drink 1.5-2.0 liters of fluid per day Advising the reduction of fluid intake before sleep Advising the intake of food rich in fibers
Sexuality	Providing information and education Providing specific advice according to the type of sexual dysfunction (e.g. reduced sexual desire, erectile dysfunction)
Medication adherence	Providing information and education about the timing and intake of medication (e.g. with water, not with milk) Stimulating medication adherence
Orthostatic hypotension	Advising to wear support stockings Advising to have sufficient salt- and fluid intake per day Providing advice about postural changes
Caregiver burden	Providing information and education Refer the caregiver for cognitive behavioral therapy Refer the caregiver to a Parkinson-specific support group
Coping	Advising mindfulness training Supporting patients and caregivers to view problems from different perspectives to develop new strategies for solving these problems Refer for cognitive behavioral therapy
Mobility	Applying cognitive movement strategies Applying external cues Stimulating the patient to perform sufficient physical exercise
Self-management	Stimulating the patient to ask questions Providing individual, patient-related information Asking if the provided information matches the patient’s question
Dietary issues	Providing information and education about problems with food absorption, e.g. because of the interaction with protein intake Preventing accidental weight loss Providing advice about oral care

Table 3. Used outcome measures at different time points.

Outcome	Questionnaire	Baseline	12 month follow-up	18 month follow-up	Every 3 months
Co-primary outcome measures					
Quality of life	Parkinson's disease Questionnaire (PDQ-39)[35]	X	X	X	
Motor symptoms	Movement Disorders Society-sponsored revision of the Unified Parkinson's Disease Rating Scale part III (MDS-UPDRS part III)[36]	X	X	X	
Secondary outcome measures (patient-related)					
Longitudinal PD symptoms	Movement Disorders Society-sponsored revision of the Unified Parkinson's Disease Rating Scale part I, II, IV (MDS-UPDRS part I, II, IV)[36]	X	X	X	
Mobility	Timed Up and Go (TUG)[37]	X	X	X	
Non-motor symptoms (anxiety and depression)	Hamilton Anxiety and Depression Scale (HADS)[38]	X	X	X	
Non-motor symptoms (e.g. sleep, incontinence, constipation)	Scales for Outcomes in Parkinson's Disease – Autonomic Questionnaire and Sleep Questionnaire (SCOPA-AUT)[39], (SCOPA-SLEEP)[40]	X	X	X	
Health-related quality of life	EuroQoL5D (EQ5D)[41]	X	X	X	
Experienced quality of care	Consumer Quality Index (CQI)[42]	X	X	X	
Self-management	Patient Activation Measure (PAM13)[43]	X	X	X	
Medication adherence	Morisky Medication Adherence Scale (MMAS)[44]	X	X	X	
Secondary outcome measures (caregiver-related)					
Health-related quality of life	EuroQoL5D (EQ5D)[41]	X	X	X	
Caregiver burden[35]	Zarit Caregiver Burden Index (ZBI)[45]	X	X	X	
Caregiver quality of life	CarerQol-7D[46]	X	X	X	
Skills of proactive coping	Utrechtse Proactieve Coping Competentielijst (UPCC)[47]	X	X	X	
Healthcare utilization, costs and productivity loss					
Medical consumption of the patient	Medical Consumption Questionnaire (MCQ)[48]				X
Productivity loss of the patient	Productivity Cost Questionnaire (PCQ)[49]				X
Medical consumption of the caregiver	Medical Consumption Questionnaire (MCQ)				

related to caregiver burden	specifically adapted for and aimed at caregivers[48]				
Productivity loss of the caregiver related to caregiver burden	Productivity Cost Questionnaire (PCQ) specifically adapted for and aimed at caregivers[49]				X

PD = Parkinson's disease

Figures

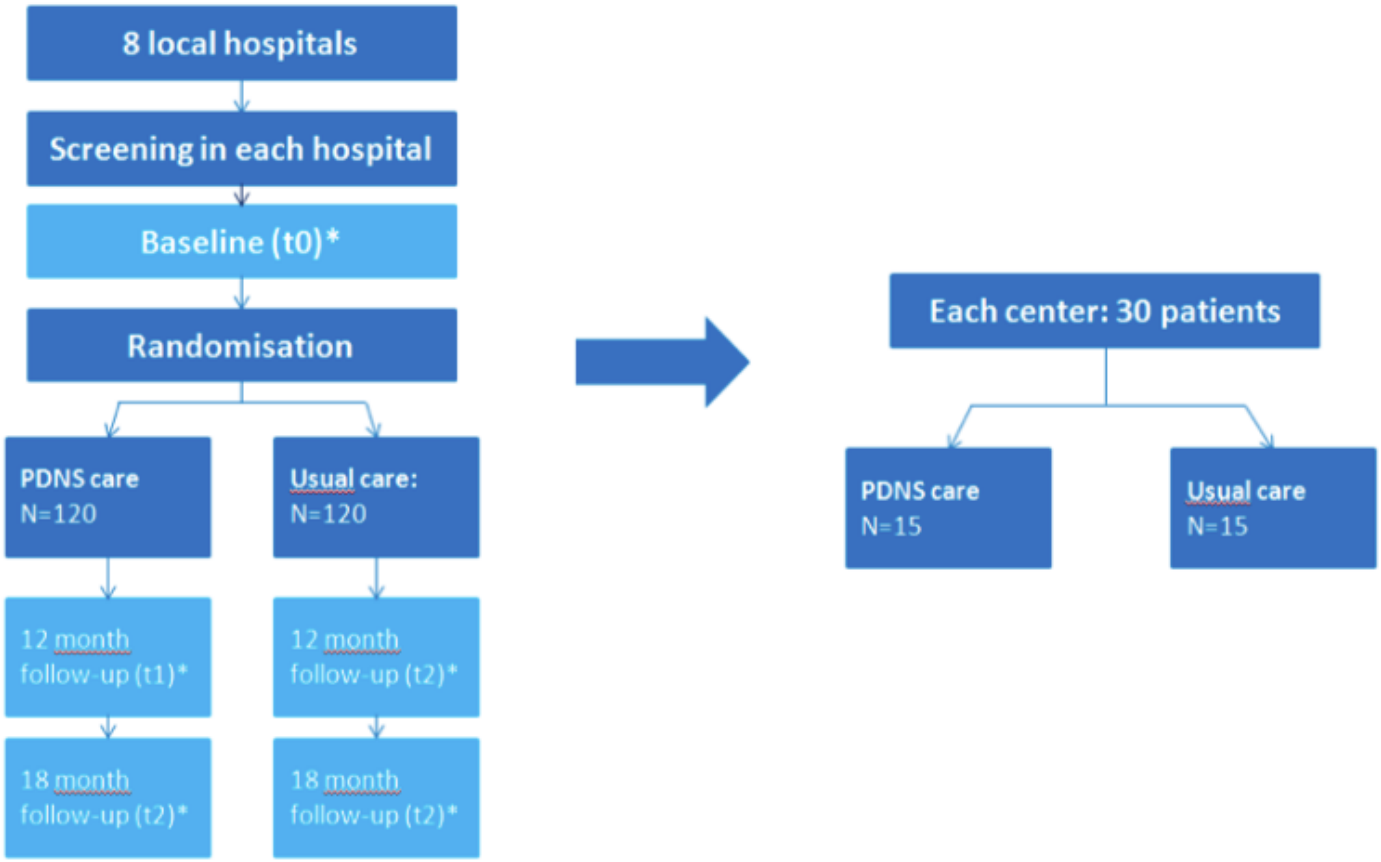

Figure 1

Summary of the study design.

	STUDY PERIOD				
	Enrolment	Allocation	Post-allocation		Close-out
TIMEPOINT**	Month 1-6 (t_0)	Month 1-6	Month 12 (t_1)	Month 18 (t_2)	t_x
ENROLMENT:					
Eligibility screen	X				
Informed consent	X				
Allocation		X			
INTERVENTIONS:					
PDNS care			X	X	
Usual care			X	X	
ASSESSMENTS:					
All co-primary and secondary variables	X				
All co-primary and secondary variables			X	X	X

Figure 2

Example template of recommended content for the schedule of enrolment, interventions, and assessments.

Supplementary Files

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- TrialsRadderAdditionalFile1V2.doc