Cost-effectiveness of specialized nursing interventions for patients with Parkinson's disease

PROTOCOL

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)**
AE	**Adverse Event**
AR	**Adverse Reaction**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CRF(s)	**Case Report Form(s)**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
EU	**European Union**
EudraCT	**European drug regulatory affairs Clinical Trials**
GCP	**Good Clinical Practice**
IB	**Investigator's Brochure**
IC	**Informed Consent**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
METC	**Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)**
PD	**Parkinson's disease**
PDNS	**Parkinson's Disease Nurse Specialist**
(S)AE	**(Serious) Adverse Event**
SPC	**Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
Wbp	**Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)**
WMO	**Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: The Dutch Multidisciplinary Guideline for Parkinson's disease (PD) recommends that each PD patient should have access to Parkinson's Disease Nurse Specialist (PDNS) care. Based on this recommendation, almost all Dutch hospitals now offer PDNS treatment. However, many hospitals lack the nursing capacity to offer care to all patients, creating unequal access to care and presumably avoidable disability and costs. This is at least partly due to lack of scientific evidence on the cost-effectiveness of PDNS care. We hypothesize that, by offering more patients access to PDNS care, quality of life will increase with equal healthcare costs. Increasing direct medical costs (for nurse staffing) will be offset by a reduced number of (telephone) consultations with the general practitioner and neurologist.
Objective: We aim to study the cost-effectiveness of specialized nursing care provided by a PDNS as compared to no PDNS care for patients with PD in all disease stages.
Study design: An 18-month single-blind randomised controlled trial (RCT).
Study population: A total of 240 Dutch patients with PD (and their caregivers), male or female, age 18 years or older at the time of PD diagnosis, who are currently not treated by a PDNS and have not been treated by a PDNS over the past two years. Patients can be included regardless of disease duration or disease severity.
Intervention (if applicable): Eight regional hospitals in the Netherlands will be included, where currently only a proportion of PD patients have access to PDNS care. Thirty patients in each hospital will randomly be allocated in a 1:1 ratio to either PDNS care according to the Dutch Guideline on PDNS care (2015), or no nursing intervention (usual care).
Main study parameters/endpoints: We selected two co-primary outcome measures: quality of life measured by the PDQ-39 and motor symptoms measured by the MDS-UPDRS part III. The secondary outcome measures include, among others, non-motor symptoms, experienced quality of care, health-related quality of life, self-management, medication adherence, caregiver burden and healthcare utilization including costs.
Nature and extent of the burden and risks associated with participation, benefit and group relatedness: The intervention evaluated in this study is non invasive and of very low risk, which therefore causes the risks associated with this study to be negligible. Also the burden associated with participation is limited. Patients will visit the PDNS based on their individual needs and preferences, which may vary from once a month to once every few months. These appointments may also be conducted by telephone. Patients will visit the researcher at baseline (t0), after 12 months (t1) and after 18 months (t2)), and each visit will take approximately one hour. Questionnaires will be filled out at home at t0, t1 and t2, taking one hour each time. Additionally, every three months patients will complete a short online questionnaire about healthcare costs, taking approximately 30 minutes to complete.

1. INTRODUCTION AND RATIONALE

Despite optimal medical management (medication or brain surgery), most patients with Parkinson's disease (PD) experience progressive disability that increasingly influences their quality of life (1-5). Examples of motor symptoms that respond insufficiently to medical management include impairments in speech or balance. Additional disability arises from non-motor symptoms (e.g. cognitive decline, depression), most of which are controlled poorly by medication (1,6). This creates tremendous challenges in advanced disease stages, and even early in the course of PD (7).

There is increasing evidence that non-pharmacological management offers symptomatic relief of symptoms that are otherwise difficult to treat (8). Many healthcare disciplines can be involved in PD care. Physiotherapy has been studied most widely (8,9,10), but this cannot cover all PD-related problems. A more integral, multidisciplinary approach remains needed.

The Parkinson's Disease Nurse Specialist (PDNS) plays an essential role in the multidisciplinary team of people with PD. Here, we will study the cost-effectiveness of treatment by a PDNS, which was introduced to bridge the gap between medical management and the unique personal needs of patients (11). The recent Dutch guideline on PDNS care (2015) clearly describes the roles of a PDNS, including diagnostic strategies (e.g. detection of urinary retention or orthostatic hypotension) and therapeutic interventions (e.g. optimizing medication compliance, or strategies to alleviate orthostatic intervention) (12). Also, the PDNS assists patients and caregivers in their need of support, information, access to services and coordination of care (12).

The Dutch Multidisciplinary Guideline for PD (13) recommends that each PD patient should have access to PDNS care. Based on this recommendation, almost all Dutch hospitals now offer PDNS treatment to their patients. However, many hospitals lack the nursing capacity that is needed to offer PDNS care to all patients, creating an undesirable inequality in access to care. Crucially, this situation offers a unique opportunity to now, for the first time, study the cost-effectiveness of PDNS intervention. Indeed, current evidence indicates that PDNS care may improve patient wellbeing, physical functioning and general health status, and reduce anxiety and depression (14,15,16). Also, scenario analyses (performed to estimate the potential cost-effectiveness of PDNS intervention) showed that PDNS treatment can be cost-effective, provided the patients' quality of life improves (14). However, there is little evidence to show that quality of life actually improves after PDNS intervention.

Because of guideline recommendations (12,13) the PDNS has been implemented widely as an intervention in the Netherlands. However, in current practice there is great heterogeneity in delivery of PDNS care. Specifically, driven by lack of sufficient PDNS staff in most community hospitals, only a proportion of patients (mostly those with advanced disease) presently have access to a PDNS. This is at least partly due to the lack of scientific evidence on the cost-effectiveness of PDNS care. Yet, expert opinion dictates that all PD patients can benefit from PDNS interventions, including those with early-stage disease where e.g. delivery of information, advice about exercise, education about medication compliance, and support in self-management are critical. Consequently, care delivery remains suboptimal, fragmented and ineffective for many patients, presumably leading to unnecessary disability and avoidable costs. The Dutch multidisciplinary guideline therefore calls for an increase in PDNS capacity across the Netherlands, even though the cost-effectiveness of such a widespread implementation of PDNS care is unknown.

This single-blind randomized controlled trial will provide information about the cost-effectiveness of PDNS care. Furthermore, this study will permit more insight into the cost-effectiveness of PDNS care in different subgroups of PD patients, based on disease duration. If the objectives are successfully reached, the chances of further implementation of PDNS care increases substantially, creating equal access to PDNS care for all PD patients.

2. OBJECTIVES

Primary Objective: To study the cost-effectiveness of specialized nursing care provided by a Parkinson Disease Nurse Specialist (PDNS) as compared to no PDNS care for patients with PD in all disease stages.

Secondary Objective(s): To perform a subgroup analysis based on disease duration, in order to gain more insight into the exact interventions used per disease stage and the effects of PDNS care in these different groups of patients:
- Disease duration of <5 years (early, relatively uncomplicated phase)
- Disease duration of 5-10 years (phase of response fluctuations)
- Disease duration of >10 years (complicated phase)

3. STUDY DESIGN

This study is an 18-month Randomized Controlled Trial (RCT), which will be performed in eight community hospitals in the Netherlands. We consider this a monocenter study, because all research activities are carried out by a researcher from the Radboudumc. The neurologists in the community hospitals only deliver patients for inclusion and are not included in the research team. A total of 240 patients will be included, which implies 30 patients in each hospital. We have selected hospitals where, due to lack of sufficient PDNS staff, only a proportion of PD patients currently has access to PDNS care. This gives us a unique opportunity to identify patients who currently have no access to PDNS care, and to randomize them within hospitals, and at the patient level, between PDNS care versus no nursing care.

Eligible patients will be allocated randomly using a computerized sequence, in a 1:1 ratio, to either PDNS care or no nursing intervention (usual care). To ascertain an equal representation of representative patients, we will stratify for gender, age and disease duration (according to the pre-defined subgroups, i.e. <5 years, 5-10 years en >10 years). The PDNS intervention will be carried out according to the Dutch Guideline on PDNS care (2015) (12). A blinded researcher will perform an assessment of PD symptoms (Movement Disorders Society-sponsored revision of the Unified Parkinson's Disease Rating Scale), mobility (Timed up and Go Test) and bradykinesia (Pegboard Test) at three time points: prior to randomization (t0), after 12 months (t1) and after 18 months (t2). Caregivers will be asked whether they also agree to fill out questionnaires. Subsequently, patients and their caregivers will complete online questionnaires (Parkinson's Disease Questionnaire, Hamilton Anxiety and Depression Scale, Scales for Outcomes in PD – Autonomic questionnaire, EuroQoL5D, Consumer Quality Index, Patient Activation Measure, Morisky Medication Adherence Scale, Zarit Caregiver Burden Index, CarerQol-7D, Utrechtse Proactieve Coping Competentielijst) at home at t0, t1 and t2. Finally, every three months patients and their caregivers will complete an online questionnaire about healthcare utilization and costs.

The hospitals included in the trial are:
- Maasziekenhuis Pantein in Boxmeer
- Gelre Ziekenhuis in Zutphen
- BovenIJ Ziekenhuis in Amsterdam
- Careyn/St. Antonius Ziekenhuis in Utrecht
- Waterlandziekenhuis in Purmerend
- Rode Kruis Ziekenhuis in Beverwijk

- TweeSteden/Elisabeth Ziekenhuis in Tilburg
- Maxima Medisch Centrum in Eindhoven

4. STUDY POPULATION

4.1 Population (base)

Dutch patients with Parkinson's disease (n=240), male and female, age 18 years or older at the time of PD diagnosis. The subjects will be selected from the PD patient population of each of the included eight hospitals. The likelihood that each hospital can include 30 patients is high, because they have all checked the number of patients in their patient population that has not been treated by a PDNS over the past two years and indicated that the inclusion target is feasible.

4.2 Inclusion criteria

1. Patients with idiopathic Parkinson's disease:
- that have sufficient knowledge of the Dutch language;
- that were 18 years of older at the time of diagnosis;
- in all disease stages, regardless of disease severity or disease duration;
- who are currently not treated by a PDNS and who have not been treated by a PDNS in the past two years;
- who have a score of ≥18 on the Mini-Mental State Examination (MMSE) and ≥12 on the Frontal Assessment Battery (FAB).

4.3 Exclusion criteria

1. Patients with 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. MSA, PSP).
2. Patients with idiopathic PD that live in a nursing home or another type of residential care facility (because the PDNS is not operational there).
3. Any other medical or psychiatric disorder that, in the opinion of the researcher, may compromise participation in the study.

4.4 Sample size calculation

We have selected two primary outcomes: PDQ-39 and MDS-UPDRS part III (motor score). The effect size for our sample size calculation is based on the PDQ-39 score, as observed in one of our previous studies in a similar population of PD patients, where we compared another type of healthcare intervention (multidisciplinary care) with usual care. 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) (17). Using a significance level of alpha=0.025 (instead of 0.05 because of two primary endpoints) and a power of 80%, a sample of 93 patients in each group would be needed. Taking into account an attrition rate of 20% (which seems very reasonable based on our prior experience in large trials (9,10,17,18,19) where attrition rate

was much lower than this), 117 patients are needed per group (a total of 234). We have rounded this up to 120 patients per group (a total of 240). This means that all eight participating hospitals need to include a total number of 30 patients.

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

The PDNS intervention will be performed according to the Dutch Guideline on PDNS care published in 2015 (12). The intervention is not standardized, but tailored to the patients' and caregivers' needs. This includes the following aspects:

1. Assessment of individual care needs of PD patients and their caregivers. The PDNS performs a specific nursing assessment related to the medical, physical, psychological and social domains.

2. Development of a patient-centered treatment plan that supports patients and caregivers in self-management. The PDNS composes a multidisciplinary care plan, based on the results of the assessment, and as prioritized by the patient and caregiver (shared decision making). This treatment plan is developed according to the national self-management framework (20). The PD nursing guideline includes a patient-centered treatment plan that describes all actions to be taken to realize patient-specific goals.

3. Specific nursing interventions. The nursing intervention varies across different disease stages and is always tailored to the specific problems and needs of individual patients and their caregivers. The PD nursing guideline describes specific interventions for the following problems: mental functions, fatigue, sleep, urogenital functions, sexuality, medication adherence, orthostatic hypotension, caregiver burden, coping, mobility, self-management, and dietary issues. Three general important PDNS interventions include: providing information and education, disease management (e.g. monitoring treatment effects, considering advanced treatment options such as Deep Brain Stimulation), and monitoring (e.g. screening on non-motor symptoms, caregiver burden).

4. Collaboration with other healthcare professionals. The PDNS stimulates and supports multidisciplinary collaboration between healthcare professionals based on the individual patient-centered plan. Furthermore, the PDNS plays a pivotal role in the timely referral to other healthcare workers.

Patients have regular contact with their PDNS about the progress and realization of the personal goals, mostly by telephone, but also during face-to-face contacts and sometimes during additional home visits. The optimal frequency of contacts varies, depending on the

disease stage and individual patient needs.

Importantly, for the purpose of this study, we will implement an increase in nursing staff capacity of the existing nurses in the participating hospitals. This will allow us to study the real impact of adding PDNS care to current usual care. The participating 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 PD guideline.

We will study the treatment given by these PDNS to patients with PD in all disease stages. Because of the large variation in problems encountered in different disease stages, the intervention will consist of a combination of actions tailored to each individual patient's and caregiver's needs. The usual care PDNS is trained to make such decisions about the optimal care for each patient based on an extensive assessment and continuous monitoring.

We will compare PDNS care to continued PD care that is otherwise comparable, but without a nursing intervention. Specifically, PD patients in the control group (who will be matched for baseline characteristics to the intervention patients) will receive usual care without any form of nursing care, but with no restrictions to any other medical treatments. This can be achieved by randomizing comparable patients within hospitals, so that other important elements of care (including in particular the treating neurologist) remain comparable between the two intervention arms.

5.2 Use of co-intervention (if applicable)

NOT APPLICABLE

5.3 Escape medication (if applicable)

NOT APPLICABLE

6. INVESTIGATIONAL PRODUCT

NOT APPLICABLE

7. NON-INVESTIGATIONAL PRODUCT

NOT APPLICABLE

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

The co-primary outcome measures of the study are:

Outcome measure	Scale/questionnaire
Quality of life	Parkinson's Disease Questionnaire (PDQ-39)
Motor symptoms	Movement Disorders Society-sponsored revision of the Unified Parkinson's Disease Rating Scale part III (MDS-UPDRS part III)

8.1.2 Secondary study parameters/endpoints (if applicable)

The secondary outcome measures of the study are:

Patient-related outcome measures

Outcome measure	Scale/questionnaire
Longitudinal PD symptoms	Movement Disorders Society-sponsored revision of the Unified Parkinson's Disease Rating Scale Part I, II, IV
Mobility	Timed Up and Go Test (TUG)
Bradykinesia	Pegboard Test
Non-motor symptoms (anxiety and depression)	Hamilton Anxiety and Depression Scale (HADS)
Non-motor symptoms (e.g. sleep, cognition, urinary tract problems and constipation)	Scales for Outcomes in Parkinson's Disease – Autonomic questionnaire (SCOPA-AUT)
Health-related quality of life	EuroQoL5D (EQ5D)
Experienced quality of care	Consumer Quality Index (CQI)
Self-management	Patient Activation Measure (PAM)
Medication adherence	Morisky Medication Adherence Scale (MMAS)

Caregiver-related outcome measures

Outcome measure	Scale/questionnaire
Health-related quality of life	EuroQoL5D (EQ5D)
Caregiver burden	Zarit Caregiver Burden Index (ZBI)
Caregiver quality of life	CarerQol-7D
Skills of proactive coping	Utrechtse Proactieve Coping

	Competentielijst (UPCC)

Healthcare consumption and costs

Outcome measure	Scale/questionnaire
Medical consumption of the patient	Medical Consumption Questionnaire (MCQ)
Productivity loss of working PD patients	Productivity Cost Questionnaire (PCQ)
Productivity loss of caregivers	Cost questionnaire specifically aimed at caregivers

8.1.3 Other study parameters (if applicable)

Not applicable.

8.2 Randomisation, blinding and treatment allocation

Eligible patients will be randomized within hospitals, and at the patient level, between the PDNS care intervention group and the control group (no nursing intervention, usual care). Patients will be allocated randomly using a computerized sequence, in a 1:1 ratio, and we will stratify for age, gender and disease duration. The randomization code will be prepared by an independent statistician and performed by Dr. Nienke de Vries-Farrouh, project leader, since the study is single-blind and the researcher performing the MDS-UPDRS, TUG, Pegboard Test and the data analysis will be blinded for group allocation. Patients will receive a unique personal identification code that refers back to the name of the study (e.g. PDNS01, PDNS02, etc): a consecutive number based on the order of enrolment.

8.3 Study procedures

Patients will be approached for participation using three scenarios. In the first scenario, the involved neurologists in each participating center will identify eligible patients from their electronic patient file and inform these patients in their clinic about the study. They will also specifically ask the patients whether they agree with providing the researcher with their personal telephone number. If these patients agree to be approached by a researcher, they will be provided with the patient information letter. A researcher from the Radboudumc will contact the patient by telephone after 7 days to answer questions and obtain consent for participation.
In the second scenario, neurologists in each hospital will also identify eligible patients using their electronic patient file and subsequently approach them by directly sending out a letter (‘voorbrief’) including a short description of the study. This will also include a self-addressed envelope, and if patients want to be approached, they can sign and send back a short form (saying “I want to receive further information about the study and the researcher is allowed to contact me by telephone”), using this self-addressed envelope.

We will ask the patient to directly fill out their telephone number on the form, so that we do not have to obtain this number from the patient file. Also if patients do not want to be approached, they can sign and send back the short form (saying “I do not want to receive any further information about the study and I do not wish to be approached”), using this self-addressed envelope. If we do not receive any reply, the patient will not be contacted. If the patient is interested to participate, the researcher will send the patient information letter. After one week, the researcher will contact the patient again to answer questions and obtain consent for participation.
In the third scenario, we will organise an ‘information meeting’ for patients in the participating center (where also the PDNS and neurologist may be present). Patients will be invited for this meeting by their treating neurologist. After the information meeting, patients can register with the research team by providing their telephone number. Patients will also be provided with the patient information letter. When patients require more time to consider participation, they will also receive with the patient information letter and a ‘registration card’ which they can fill out at home and send back directly to the research team. On this registration card, permission will be asked for being contacted by the researcher” The researcher will contact each patient after seven days to answer questions and obtain consent for participation. In each center one of these scenarios will be chosen based on the preferences of the center. However, the first and second scenario are preferred and the third scenario (information meeting) will only be used when inclusion rates are insufficient.

During the study period, patients will be in contact with their PDNS based on their individual needs and preferences. These appointments may also be conducted by telephone. The amount of contact may vary from once a month to once every few months. However, currently in the Netherlands on average patients are seen by their PDNS twice a year, with other two interim telephone consultations per year.

At baseline (t0), each patient will visit his/her own hospital, where the Radboudumc researcher will obtain informed consent. Afterwards, the MDS-UPDRS, TUG and Pegboard Test will be performed. This appointment will take approximately 60 minutes. Furthermore, the patients will complete a set of questionnaires at home, online or on paper (PDQ-39, HADS, SCOPA-AUT, EQ5D, CQI, PAM, MMAS), which will also take approximately 60 minutes to complete. The caregiver will complete the EQ5D, ZBI, CarerQol-7D and UPCC, which takes approximately 30 minutes to complete.

After 12 months (t1) and after 18 months (t2) the patient will visit the Radboudumc researcher again in his/her own hospital. Also then, the MDS-UPDRS, TUG and Pegboard Test will be performed. Furthermore, patients will complete the same set of questionnaires at home, online or on paper (PDQ-39, HADS, SCOPA-AUT, EQ5D, CQI, PAM, MMAS). The caregiver will complete the EQ5D, ZBI, CarerQol-7D and UPCC.

Every three months, patients will complete a questionnaire regarding healthcare utilization

and costs over the past three months, to be completed online or on paper (MCQ). This questionnaire takes approximately 30 minutes to complete. Patients that are still working will also complete the PCQ, which takes approximately 20 minutes to complete. Caregivers will complete a cost questionnaire specifically aimed at caregivers, taking approximately 20 minutes to complete.

Data from all paper-based questionnaires (MDS-UPDRS, TUG, Pegboard Test) and online CRFs (the remaining questionnaires) will be entered manually into the data management system Castor. When patients are not able to fill out questionnaires online, they also have the opportunity to do this on paper. We will then send out the questionnaires and patients can send the completed questionnaires back by post. We will compile a Trial Master File (TMF) in the Radboudumc where all original collected data will be safely stored. The original signed informed consent forms and copies of the collected data will be stored in the participating center in an Investigator Site File.

8.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

8.4.1 Specific criteria for withdrawal (if applicable)

Currently, PDNS care is not ‘usual care’. Therefore, there are no strict indications for PDNS care. However, when the treating physician considers the overall health of the patient in the control group compromised by not receiving care from a PDNS, these patients will withdraw from the study and receive this care. This will be reported to the researchers. However, this patient will still be evaluated at the pre-defined measurement points, following the intention-to-treat principle.

8.5 Replacement of individual subjects after withdrawal

Patients who withdraw will not be replaced. In the sample size calculation, we have taken into account an attrition rate of 20%. This gives our study enough power to complete, even if 24 patients in each group will be withdrawn.

8.6 Follow-up of subjects withdrawn from treatment

Following the intention to treat principle, we will see every included patient at the pre-defined follow-up appointments (baseline, after 12 months, and after 18 months). Therefore, when patients are withdrawn from the control group because they need PDNS care, we will still perform the follow-up measurements.

8.7 Premature termination of the study

We cannot think of any direct reason why the study would be prematurely terminated, because the study intervention is of very low-risk. We cannot guarantee that we will achieve the aimed inclusion rate of 240 patients (however, we do think that this is very feasible (see paragraph 4.1)). Furthermore, the inclusion may be slower than initially expected. In these cases, the study may temporarily be delayed and adjustments will be made before continuation.

9. SAFETY REPORTING

9.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the experimental intervention by the PDNS. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

9.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events.

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Not applicable.

9.3 Annual safety report

Not applicable.

9.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

9.5 Data Safety Monitoring Board (DSMB) / Safety Committee

Not applicable.

10. STATISTICAL ANALYSIS

10.1 Primary study parameter(s)

Statistical analyses will be performed based on the intention-to-treat principle. 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 variables. Baseline values, center, age at baseline, Hoehn & Yahr stage and disease duration will serve as covariates. Missing data will be imputed, patients with missing data will therefore be included in the analysis.

The cost-effectiveness 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. A health perspective will be presented as a scenario (and potential input for the Budget Impact Analysis). The CEA timeframe adheres to the clinical study protocol and evaluates cost-effectiveness up to 12 months after randomization. Cost will be measured using a healthcare utilization questionnaire. We will use a PD-specific quality of life measure (PDQ-39) and a generic quality of life scale (EQ5D-5L) to evaluate effects. 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 the PDNS. 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 health care (22). Costs will be analyzed using a mixed model approach or a generalized linear model approach with a gamma distribution using a log link to account for possible skewness of the cost data. QALYs with the EQ-5D 5L will be calculated using the trapezium rule. The potential difference in QALYs will be researched with a regression approach.

The cost analysis exists of two main parts. First, on patient level, volumes of care will be measured prospectively over the time path of the study using patient level questionnaires and Case Report Forms (CRFs), complemented, if necessary, by data from the hospital administration system. The CRF will be developed in a way that it structures and uniforms healthcare consumption for this particular target population.

Second, per item of healthcare consumption, standard cost-prices will be determined using the guideline for performing economic evaluations (22). If standardized prizes are

not available full cost prices will be determined using activity based costing. Productivity losses for patients and caregivers will be assessed using the Productivity Cost Questionnaire or elements from it. The friction cost-method will be applied following the Dutch guidelines (22).

10.2 Secondary study parameter(s)

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 other secondary outcome measures (MDS-UPDRS part I, II, IV, TUG, Pegboard Test, HADS, SCOPA-AUT, EQ5D, CQI, PAM, MMAS, ZBI, CarerQoL-7D, UPCC, and healthcare costs).

The PDQ-39 is the most comprehensive and widely used instrument to measure PD-specific quality of life. It consists of 39 items and is organized in 8 domains (mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication and pain) and a summary index.

To measure the quality of the health status of the patients, a validated so-called health related quality of life (HRQoL) instrument will be used, the EuroQol-5D (21). This HRQoL instrument will be completed by patients and is available in a validated Dutch translation (EQ-5D-5L) (ZIN, 2015). The EQ-5D is a generic HRQoL instrument comprising five domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The EQ-5D index is obtained by applying predetermined weights to the five domains. This index gives a societal-based global quantification of the patient's health status on a scale ranging from 0 (death) to 1 (perfect health). Patients will also be asked to rate their overall HRQoL on a visual analogue scale (EQ- 5D VAS) consisting of a vertical line ranging from 0 (worst imaginable health status) to 100 (best imaginable) (21).

10.3 Other study parameters

Not applicable.

10.4 Interim analysis (if applicable)

In view of the objective of this study, we will not perform an interim analysis.

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

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 (version 7, 2013), and the Medical Research Involving Human Subjects Act (WMO).

11.2 Recruitment and consent

This study will be conducted in accordance with the provisions of 21 Code of Federal Regulations (CFR) Part 50. As described in paragraph 8.3, two scenarios will be used for recruitment, depending on the preferences of participating hospitals. If patients agree to be approached by a researcher using either of these two scenarios, a Radboudumc researcher will contact the patient by telephone after 7 days to answer questions and to discuss the consent. In accordance with relevant regulations, an informed consent agreement explaining the procedures and requirements of the study, how subjects' confidentiality will be maintained, and any potential hazards/risks will be explained to each subject. Each subject 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 form immediately after the subject has signed it. The subject is assured of the freedom to withdraw from participation in the study at any time. The original signed consent form is in the participating center and each subject will receive a copy of the signed consent form.

The consent process for each subject who signs the informed consent form will be documented in the subject's source (e.g., research file, research progress note) and includes the title of the study, that the consent was discussed with an opportunity for questions and answers, how the subject demonstrated comprehension, that the consent was signed prior to the first study procedure, and that the subject received a signed copy of the consent.

11.3 Objection by minors or incapacitated subjects (if applicable)

Not applicable.

11.4 Benefits and risks assessment, group relatedness

The intervention evaluated in this study is non invasive and of very low risk, which therefore causes the risks associated with this study to be negligible. The risk not associated with this intervention itself, but rather with the organization of PDNS care in the Netherlands, consists of the following: during the study, each hospital receives budget to increase their PDNS capacity to provide care to 15 patients in the intervention group. However, when the study is finished, there is a chance that PDNS care for these patients will be cancelled because the extra nursing capacity is no longer paid by the study. Each hospital will, in the end, make its own decisions regarding the continuation of care for the patients participating in the study. The 15 patients in the control group will not be allowed to receive PDNS care during the study period.

PDNS care is currently only partially implemented in the Netherlands, and therefore not 'usual care'. The 240 patients included in this study do not receive PDNS care at the moment, mainly due to a lack of scientific evidence of its cost-effectiveness. With positive results, it is more likely that PDNS care will be further implemented for all PD patients. In addition, it is possible that, in the case of positive patient experiences, participating hospitals will increase their own budget for increasing PDNS capacity. Furthermore, besides PDNS care, there are no restrictions to other medical treatments for the patients in the control group, and they can visit all other available healthcare providers (e.g. physiotherapist, psychologists).

11.5 Compensation for injury

In accordance with article 7 of the WMO, we will submit a written request for exemption from the liability insurance. If this request is not accepted, we will submit an amendment and include information about the liability insurance below.

11.6 Incentives (if applicable)

We will offer compensation for travel expenses to all subjects for travelling to the hospital for the assessments on t0, t1 and t2.

Each participating hospital will receive compensation for the increased PDNS capacity, which includes 65 Euros per hour (= 4 hours per week). In case of unforeseen extra healthcare costs, there is room to expand this compensation up to a certain extent.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

1. Data from all paper-based CRFs (MDS-UPDRS, TUG, Pegboard Test) will be entered manually into a data management system (Castor). Online CRFs (the remaining questionnaires) will automatically be recorded in Castor. CRFs only contain a personal identification code. This means that patients are given a personal unique identification code (e.g. PDNS01, PDNS02, etc). The executive researchers (Dr. Nienke de Vries-Farrouh and Drs. Danique Radder) own the key and will be able to track back data to the individual patient. Additionally, only the assigned research team has exclusive authorization rights to access data. Personal data will be kept separately from the experimental data acquired.
2. Clinical notes taken by the PDNS during the initial assessment and follow-up will be documented in a pre-defined paper-based study diary according to a structured format, using the unique personal identification code. PDNS are instructed to make notes according to this structured format, without mentioning personal information that traces back to an individual patient. We will collect this information because we want to obtain information on what exact interventions have been used by the PDNSs, to be used for a process analysis at the end of the study. The study diary will be handed over to the research team after the last patient has completed the 18-month follow-up.

12.2 Monitoring and Quality Assurance

Data-entry errors will be checked by re-entering a sample of 5% of all CRFs, in an emptied copy of the original data-entry format. An independent monitor from the Clinical Research Center Nijmegen (CRCN) will be appointed to check the following:

1. 10% of informed consent forms (n=24)
2. 5% on in- and exclusion, plus the first three participants (n=15)
3. 5% source document verification (n=12)
4. 5% on SAEs and SUSARs (n=12)

In case of substantial errors, monitoring intensity will be increased. Monitoring starts after the baseline assessments of the first 5 patients have been entered and continues until the last CRFs have been entered in the database.

In addition, the coordinating researcher will check the quality of data-entry and handling by the research team on a continuous basis.

12.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

12.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/serious adverse reactions, other problems, and amendments.

12.5 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

12.6 Public disclosure and publication policy

The sponsors ZonMw and Zambon will not in any way be involved in the manuscripts and abstracts that result from the study data. ZonMw and Zambon will be cited as a funding source.

The study will be registered in the public trial registry ClinicalTrials.gov on short notice.

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