MASTER THESIS

A STUDY ASSESSING THE EFFECT OF A STRUCTURED MEDICATION REVIEW ON QUALITY OF LIFE IN PATIENTS WITH PARKINSON'S DISEASE

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'If you are the smartest person in the room, you are in the wrong room'

This thesis is the final result of my assignment for the master program Health Sciences at the University of Twente. Although people made me afraid of writing a master thesis during my college years, I have experienced this last period as one of the most challenging and pleasurable periods during my study.

From February until April 2014, my main task was to write a proper study protocol for the Medical Ethical Review Board Twente. I am proud to be able to say that this protocol received almost immediately positive approval. In May 2014, I had the great task to organize a master class for all pharmacists in the region of Enschede. Subsequently, the first patients were included in the study relatively fast so that we were able to perform baseline analyses for this thesis. Hopefully, the development of the current study structure will proof to function in the continuation of the elaborate research, for which we received a grant of the Royal Dutch Society for Pharmacy (KNMP).

This thesis also means that I will no longer be a student. Over the course of my unforgettable time as a student, I have seen two studies, several universities in various countries, passed courses, high grades and perhaps most important: many inspiring people that I am proud to call my friends now. Also during the past few months, I met a lot of smart and inspiring people, so I noticed that I was never *'in the wrong room'*. Therefore, I would like to thank my supervisors prof. dr. J.A.M. van der Palen and dr. C.J.M. Doggen for their advice and constructive feedback on this thesis. Special thanks to prof. dr. J.A.M. van der Palen for his daily guidance, flexibility and enthusiasm. Each time after leaving your office, I felt like I could improve the study as well as myself, which resulted in increased learning experiences. I was pleased to meet you at the train station: this has led to the great opportunity to prepare and to conduct a medical scientific research in the MST hospital. In addition, I would like to thank dr. L.D.A. Dorresteijn for her professional guidance and input to improve patient care, to optimize the research process and to learn about Parkinson's Disease. Also thanks to drs. K. ter Huurne, drs. K.L.L. Movig and all other pharmacists in the region of Enschede for their medical expertise and collaboration.

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ABSTRACT

Background: Parkinson's Disease (PD) is a progressive disease resulting from degeneration of dopaminergic neurons within the substantia nigra. The golden standard for the management of PD is drug treatment to suppress (motor) symptoms. However, a considerable amount of PD patients do not fully benefit from their medical treatment due to complicated medication schedules, decreased adherence and progression of non-motor features. A potential intervention to enhance medication adherence is performing a structured medication review. As part of the 'Medication Review in Parkinson'-study, the aim of this interim study is to give a description of participating PD patients at baseline and to assess whether the randomization process has generated two comparable groups prior to the intervention. In addition, subgroups of participants at baseline will be analyzed to measure similarities with other groups of PD patients, ensuring that possible future results of the 'Medication Review in Parkinson'-study might be generalizable to other populations.

Methods: PD patients (N = 38; 58% men; mean age = 70.8 years, SD ± 6.5) who received treatment at the department of Neurology at Medisch Spectrum Twente (MST), Enschede, The Netherlands, in June and July 2014, were included in a randomized controlled trial. They completed a set of validated questionnaires after informed consent and prior to the intervention, assessing quality of life (PDQ-39), non-motor symptoms (NMSQuest), and health status (EQ-5D and VAS). In addition, personal carers' quality of life (PDQ Carer) was measured (N = 23).

Results: Baseline comparisons showed one imbalanced factor in the amount of medication (lower in the control group) at baseline prior to the intervention. Baseline measurements in subgroups of these PD patients showed an association between medication use and two sub-scores of the PDQ-39 prior to the intervention. PD patients taking eight or more medications have more restrictions in mobility (-20.6 (-32.9;-8.2)) and daily activities (-18.0 (-34.0;-2.1)) than PD patients taking four to seven medications. PD patients taking eight or more medications also have lower scored on the EQ-5D and thus have lower health state experiences (0.14 (0.02;0.27)). Another association between gender and three sub-scores of the PDQ-39 indicated that women have more restrictions in mobility (-15.2 (-28.2;-2.2)), while men experience more problems with cognitions (12.9 (0.6;25.1)) and communication (20.4 (7.7;33.1)). Disease severity as measured by Hoehn & Yahr stages was associated as well with two sub-scores of the PDQ-39. PD patients categorized in advanced stages have more restrictions in mobility (-19.1 (-32.1;-6.0)) and daily activities (-28.0 (-42.8;-13.2)) than PD patients categorized in early stages of PD. Age differences between groups were not significantly associated with questionnaire results.

Conclusion: As part of the 'Medication Review in Parkinson'-study, randomization has generated two quite comparable groups with similar patient characteristics in the current study population of PD patients at baseline, prior to the intervention of a structured medication review. Analyses on subgroups of PD patients at baseline showed that differences in questionnaire results depend on patient characteristics (gender, age, medication use, disease severity) and showed similarities with other groups of PD patients. Therefore, we might have a representative sample, which is important to conclude in order to generalize future results of the 'Medication Review in Parkinson'-study to the general population of PD patients.

INTRODUCTION

Parkinson's Disease (PD) is a progressive, neurodegenerative and age-related disease resulting from degeneration of dopaminergic neurons within the substantia nigra, which leads to a shortage of dopamine in the brain (1). PD is clinically characterized by motor symptoms as tremor, rigidity, bradykinesia and postural instability (2) (3). Other symptoms include non-motor symptoms as cognitive dysfunction, depression, pain, sleep disorders, constipation, and genitourinary problems. Both motor and non-motor symptoms contribute to the reduction of functional abilities, shortened life expectancy, and reduced quality of life (QoL) (4) (5) (6). The symptoms occur across all stages of PD, but become increasingly prevalent during an advanced stage of the disease. When the disease progresses, also motor fluctuations and dyskinesia occur. Patients feel alterations between periods of being 'on' often with dyskinesia, in which the patient enjoys a good response to medication, and being 'off', in which the patient experiences symptoms of the underlying Parkinsonism (7).

The golden standard for the management of PD is drug treatment: the most commonly used medications are dopamine replacements and dopamine agonists (8) (9). PD patients need to take a variety of these medications at different doses and at different times each day. Since the disease progresses and the therapeutic window narrows, the dosing frequency will increase, which might cause complicated medication schedules (10) (11). Therefore, keeping track of anti-Parkinson regimens can be challenging, but essential for controlling symptoms and maximizing desired patient outcomes (9) (12) (13) (14). Simultaneously, possible additional medication might be prescribed due to comorbidity, which contributes to more complicated schedules and decreased medication adherence (10). Medication adherence can generally be defined as the extent to which patients take medication as prescribed by their healthcare providers, which is certainly important for PD patients to avoid fluctuations of functioning due to missed or wrong doses (15). Unfortunately, suboptimal adherence to medical treatment is an extensive problem that can be caused by complicated schedules and motor limitations (10). Several other causes for non-adherence are misconceptions about medication, fear of side effects and interactions between various medications, and as PD patients also have problems with cognition, polypharmacy easily leads to missing doses (12) (15) (16) (17). Important risk factors of polypharmacy are insufficient knowledge, an excess of healthcare providers at the same time, poor communication about medication between healthcare providers and patients, poor registration and monitoring, and sometimes simultaneously provision of medication by various pharmacies (17) (18) (19). Due to this inappropriate use of multiple drug regimens, a considerable amount of PD patients do not fully benefit from their medical treatment (15) (20).

A potential intervention to enhance medication adherence is performing a structured medication review. A structured medication review is defined as 'a structured, critical examination of a patient's medication with the objective of reaching an agreement with the patient about treatment, optimizing the impact of medication, minimizing the number of medication-related problems and reducing waste' (21). Structured medication reviews might be periodic and successful evaluations to improve medication safety in polypharmacy and to guarantee continuity of care in a systematic way (19) (22) (23). They are intended to increase efficiency and effectiveness in terms of medication adherence, which may result in simplified dosing, increased customized care and shared decision-making (24) (25). However, there is limited research on effectiveness, clinical outcomes, QoL and feasibility of medication assessment within primary care (19) (25) (26).

The 'Medication Review in Parkinson'-study is a randomized controlled trial (RCT) that has started in June 2014 to assess whether a structured medication review as intervention in primary care improves medication adherence in patients with PD after a follow-up of three months and six months. As part of the 'Medication Review in Parkinson'-study, the aim of this interim study is to give a description of participating PD patients at baseline as a reference point for the trial and to assess whether the randomization process has generated two comparable groups prior to a structured medication review. In addition, subgroups of participating PD patients at baseline will be analyzed to measure baseline characteristics and similarities with other groups of PD patients prior to the intervention, ensuring that possible future results of the 'Medication Review in Parkinson'-study might be generalizable to other populations. Therefore, we hypothesized that:

A) There is a difference in outcomes on questionnaire data of the Parkinson's Disease Questionnaire-39 (PDQ-39), Non Motor Symptoms Questionnaire (NMSQuest), EuroQOL-5 Dimensions (EQ-5D), Visual Analogue Scale (VAS) and the Parkinson's Disease Questionnaire Carer (PDQ Carer) at baseline between PD patients taking four to seven medications and PD patients taking eight or more medications;

B) There is a difference in outcomes on questionnaire data of the PDQ-39, NMSQuest, EQ-5D, VAS and the PDQ Carer at baseline between PD patients younger than seventy years and PD patients aged over seventy years;

C) There is a difference in outcomes on questionnaire data of the PDQ-39 at baseline between men with PD and women with PD;

D) There is a difference in outcomes on questionnaire data of the PDQ-39 at baseline between patients categorized in early stages of PD and patients categorized in advanced stages of PD according to the Hoehn & Yahr (H&Y) stages (27).

METHODS/DESIGN

The 'Medication Review in Parkinson'-study is designed as a RCT: half of the randomly assigned patients will receive the intervention, while the control group will not receive the structured medication review and receives usual care. This implies that community pharmacists will perform a structured medication review as one-time assessment within the intervention group (Appendix 1), which occurs after the inclusion of patients, the baseline measurements and the randomization process. For the current interim study, baseline analyses are performed after randomization, but prior to the intervention (Figure 1). This means that baseline analyses are considered to be preliminary analyses prior to a structured medication review, examining baseline balance and subgroups of participants.

Participants

The study population consists of adults (≥ 18 years) diagnosed with PD according to the UK-brain banking criteria (28), who receive treatment at the department of Neurology at Medisch Spectrum Twente (MST), Enschede, The Netherlands, in June and July 2014, as part of the 'Medication Review in Parkinson'-study (NL48661.044.14). These patients need to express motor complications or non-motor symptoms due to the disease, and need to take four or more different medications daily at four or more intake moments to suppress PD-related symptoms and to treat other comorbidities. Patients were excluded if they were not able to read and write the Dutch language, if they were resident in a nursing home and unable to administrate own medication, if they received a structured medication review within a year before the study or if they did not gave informed consent.

The study is conducted in agreement with the principles of the Helsinki Declaration and in accordance with the Medical Research involving Human Subjects Act (WMO). The research protocol (Appendix 2) is registered in the Dutch clinical trial register (NTR4500) and has been approved by the Medical Ethical Review Board Twente.

Outcomes

Information on demographic and clinical characteristics was obtained from the patients' medical records and outpatient appointments at the Neurology department of MST. The eligible patients and personal caregivers completed a set of validated and standardized questionnaires after informed consent and prior to the intervention.

As primary outcome at baseline, disease-specific QoL was measured using the PDQ-39 (29). This instrument has 39 items to measure eight domains of mobility, activities in daily living, emotional wellbeing, stigma, social support, cognitions, communication, and physical discomfort. PDQ-39 can be used to assess effectiveness of treatment, in which dimension scores are coded on a scale of 0 to 100: higher scores indicate lower QoL (30).

Secondary outcomes at baseline were measurements of non-motor symptoms, health status, and personal carers' QoL. The outcomes on non-motor symptoms were measured using the disease-specific NMSQuest, which exists of 30 yes (one point) or no (no point) questions: higher scores indicate more non-motor symptoms (31). The outcomes on (the experience of) health status were measured using the EQ-5D and the VAS. The EQ-5D is a generic instrument to measure QoL, which comprises five domains (mobility, self-care, pain/discomfort, daily activities, physiological status) with five possible answers: higher scores indicate a better health status (32). In addition, the outcomes on the experience of health status were measured using the VAS, which is ranging from 0 (worst experience) to 100 (best experience) (33). The outcomes on QoL for personal carers of PD patients were measured using the PDQ Carer questionnaire, which has 29 items to measure four domains of social and personal activities, anxiety and depression, self-care, and stress: higher scores indicate more impact on the personal carer (34).

Figure 1 Consort flow diagram of the progress through the phases for the current interim study, as part of 'Medication Review in Parkinson'-study
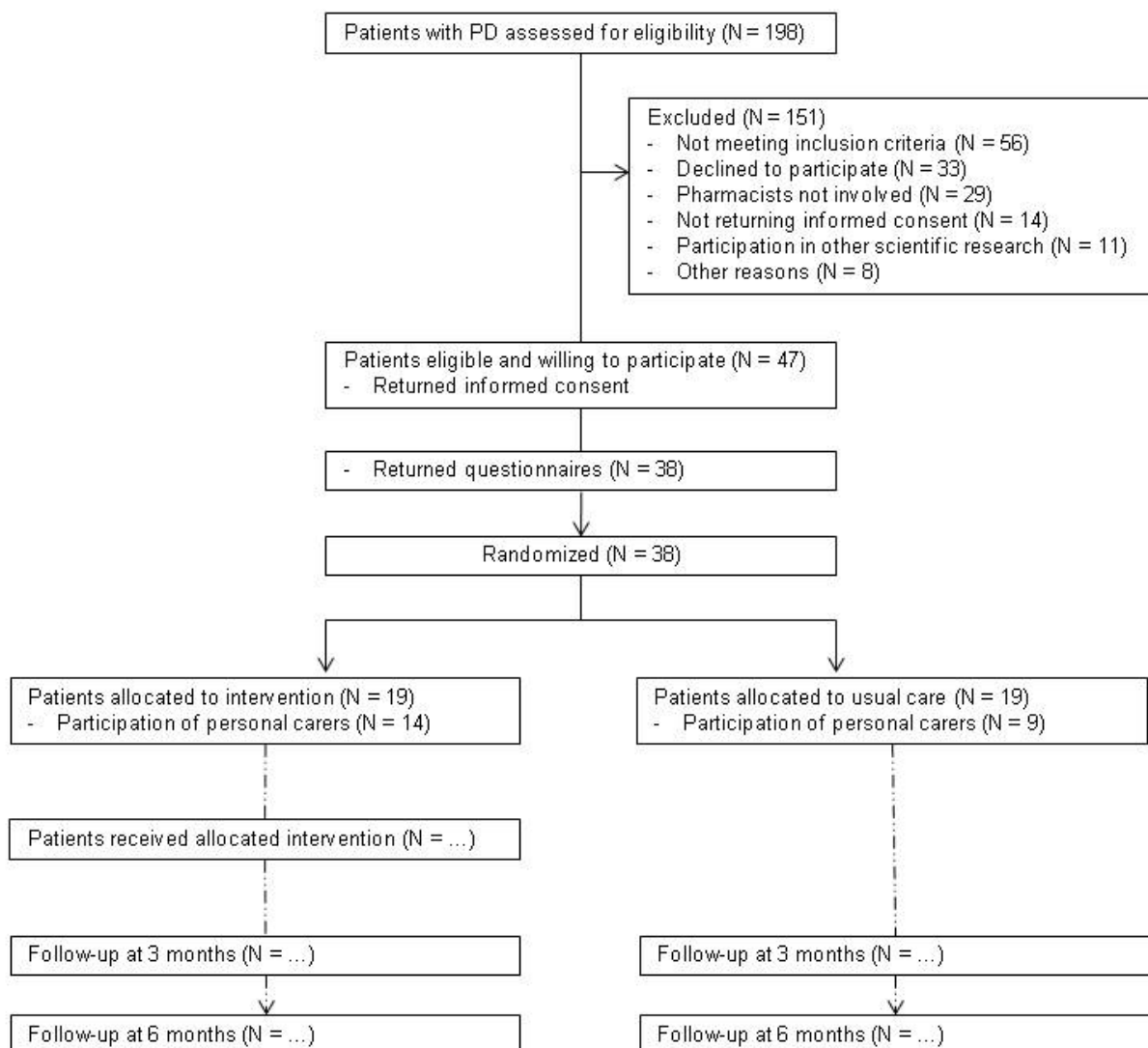
Statistical methods

Categorical data are presented as numbers with corresponding percentages. The Chi-square test (or Fisher's exact test as appropriate) was used to analyze categorical variables, whereas Student's t-tests for independent samples were used to analyze continuous variables between groups (or Mann-Whitney U tests for non-parametrically distributed variables as appropriate). These continuous data are presented as means with SD (±) or as median with minimum–maximum ranges as appropriate and corresponding confidence intervals (35). It is important to note that the results of questionnaire data are presented as means with SD (±) in order to make comparisons with other scientific studies, while in some sub-analyses medians with minimum–maximum ranges would have been more appropriate due to the small number of participants. Linear regression analysis was performed to assess the univariate relation of patient gender on disease-specific QoL outcomes. Linear regression analysis was performed as well to assess whether disease severity as categorized by H&Y stages of PD was associated with disease-specific QoL outcomes. These H&Y stages were combined in early stages (1-2.5) and advanced stages of PD (3-5) due to the small population (25). P-values of <0.05 were considered statistically significant. SPSS® version 21.0 (SPSS IBM, New York, U.S.A) was used to perform the statistical analyses.

RESULTS

Baseline comparisons

A total of 198 PD patients were assessed for eligibility, of which 75 patients were eligible. These patients received a patient information letter with an informed consent form. A number of 47 PD patients provided informed consent for study participation, of which 38 patients returned the questionnaires and were randomized: 19 patients were allocated to the intervention group, whereas 19 patients were allocated to the control group. Demographic and clinical characteristics of this current study population with questionnaire data at baseline are shown in Table 1.

Table 1 Demographic and clinical characteristics with questionnaire data at baseline (N=38)

	All PD patients (N = 38)	Intervention group (SMR)[1] (N = 19)	Control group (usual care) (N = 19)	P-value	Difference in groups (95% CI) (I-C)[2]
Sex (N (%))				0.51	0.1 (-0.2;0.4)
Men	22 (57.9%)	10 (52.6%)	12 (63.2%)		
Women	16 (42.1%)	9 (47.4%)	7 (36.8%)		
Age	70.8 (6.5)	69.8 (6.6)	71.8 (6.4)	0.35	-2.0 (-6.3;2.3)
HY Scale[3] (N (%))				0.73	0.1 (-0.3;0.3)
1-2.5	25 (65.8%)	12 (63.2%)	13 (68.4%)		
3-5	13 (34.2%)	7 (36.8%)	6 (31.6%)		
Number of medications (median (min-max))	7 (4-17)	8 (4-12)	7 (4-17)	<0.05	2 (0;3)
Number of intake moments (median (min-max))	5 (4-9)	6 (4-9)	5 (4-8)	0.40	0 (-1;1)
PDQ-39 TOT[4]	36.0 (11.3)	37.5 (11.8)	34.4 (10.8)	0.56	3.2 (-4.3;10.6)
Mobility	45.7 (20.7)	48.6 (20.9)	42.9 (20.7)	0.37	5.7 (-8.0;19.3)
Activities in daily living	44.1 (25.0)	46.5 (28.2)	41.7 (21.8)	0.67	4.8 (-11.8;21.4)
Emotional wellbeing	33.6 (18.1)	35.3 (19.4)	31.8 (16.9)	0.45	3.5 (-8.5;15.5)
Stigma	25.7 (16.8)	27.3 (17.8)	24.0 (16.0)	0.54	3.3 (-7.9;14.4)
Social support	18.8 (21.5)	16.0 (21.9)	21.5 (21.3)	0.31	-5.5 (-19.7;8.7)
Cognitions	36.3 (19.3)	35.9 (20.1)	36.8 (19.0)	0.89	-1.0 (-13.8;11.9)
Communication	35.7 (21.4)	41.7 (21.0)	29.8 (20.7)	0.09	11.8 (-1.9;25.5)
Physical discomfort	47.8 (19.3)	49.1 (19.2)	46.5 (19.9)	0.73	2.6 (-10.2;15.5)
NMSQuest[5]	10.8 (5.3)	11.7 (5.4)	10.0 (5.1)	0.32	1.7 (-1.7;5.2)
EQ-5D[6]	0.67 (0.20)	0.66 (0.19)	0.68 (0.21)	0.75	0.02 (-0.15;0.11)
VAS[7]	65.6 (11.7)	63.9 (13.1)	67.2 (10.3)	0.41	-3.2 (-10.9;4.5)

Presented as *mean* (SD) unless otherwise indicated. [1]*(SMR):* Structured medication review, [2]*(I-C):* Intervention group minus control group, [3]*HY Scale:* Hoehn & Yahr Scale, [4]*PDQ-39 TOT:* Parkinson's Disease Questionnaire-39 Total score of all domains, [5]*NMSQuest:* Non-Motor Symptoms Questionnaire, [6]*EQ-5D:* EuroQOL-5 Dimensions, [7]*VAS:* Visual Analogue Scale

Prior to the intervention of a structured medication review, baseline measurements show a significant difference in the amount of medication between the intervention group and the control group, which indicates that patients allocated to the intervention group use more medication at baseline (2 (0;3)). Another remarkable difference is that patients allocated to the intervention group have worse baseline scores on communication of the PDQ-39 (11.8 (-1.9;25.5)). Other baseline measurements are comparable between the two groups. The same applies to outcomes on personal carers' QoL (Table 2).

Table 2   Results of questionnaire data at baseline on personal carers' QoL (N=23)

	All personal carers (N = 23)	Intervention group (SMR)[1] (N = 14)	Control group (usual care) (N = 9)	P-value	Difference in groups (95% CI) (I-C)[2]
PDQ Carer TOT[3]	29.4 (15.1)	27.7 (16.1)	32.1 (13.8)	0.52	-4.4 (-18.0;9.2)
Social and personal activities	29.2 (19.5)	26.6 (18.8)	33.1 (21.0)	0.37	-6.5 (-23.9;11.0)
Anxiety and depression	35.3 (17.2)	31.5 (19.0)	41.2 (12.6)	0.18	-9.7 (-24.6;5.3)
Self-care	17.8 (16.0)	18.9 (16.4)	16.1 (16.2)	0.64	2.8 (-11.7;17.3)
Stress	35.3 (18.4)	33.7 (19.2)	38.0 (17.9)	0.56	-4.3 (-21.0;12.3)

Presented as *mean* (SD). [1]*(SMR):* Structured medication review, [2]*(I-C):* Intervention group minus control group, [3]*PDQ Carer TOT:* Parkinson's Disease Questionnaire Carer Total score of all domains

Subgroup analyses

Subgroups of participating PD patients at baseline are analyzed as described at page 8-9. As shown in Table 3, PD patients taking eight or more medications have more restrictions in mobility (-20.6 (-32.9;-8.2)) and daily activities (-18.0 (-34.0;-2.1)) than PD patients taking four to seven medications, measured by the PDQ-39. PD patients taking eight or more medications also have lower scores on the EQ-5D and thus have lower health state experiences (0.14 (0.02;0.27)). The results of the PDQ Carer questionnaire do not show significant differences between the amount of medication taken by PD patients and their personal carers' QoL (Table 4).

Furthermore, as presented in Table 3 and Table 4, no significant differences were found on questionnaire data between PD patients aged over seventy years and PD patients younger than seventy years.

Table 3 Results of questionnaire data at baseline between –
Left: PD patients taking 4 to 7 medications vs. ≥ 8 medications (N=38)
Right: PD patients aged < 70 years vs. ≥ 70 years (N=38)

	Patients taking 4-7 med. (N = 23)	Patients taking ≥8 med. (N = 15)	P-value	Difference in groups (95% CI) (L-M)[1]	Patients < 70 years (N = 15)	Patients ≥ 70 years (N = 23)	P-value	Difference in groups (95% CI) (Y-O)[2]
PDQ-39 TOT[3]	33.2 (9.9)	40.2 (12.3)	0.06	-6.9 (-14.2;0.4)	36.5 (11.7)	35.6 (11.2)	0.80	1.0 (-6.7;8.6)
Mobility	37.6 (20.2)	58.2 (14.8)	<0.01	-20.6 (-32.9;-8.2)	47.2 (20.7)	44.8 (21.5)	0.73	2.4 (-11.7;16.5)
ADL[4]	37.0 (21.4)	55.0 (26.8)	<0.05	-18.0 (-34.0;-2.1)	45.8 (24.9)	42.9 (25.5)	0.73	2.9 (-14.1;19.9)
EW[5]	31.5 (16.2)	36.7 (20.7)	0.29	-5.1 (17.3;7.0)	36.1 (14.7)	31.9 (20.0)	0.68	4.2 (-8.0;16.4)
Stigma	26.1 (18.3)	25.0 (14.8)	0.86	1.1 (-10.4;12.6)	24.6 (19.5)	26.4 (15.2)	0.91	-1.8 (-13.2;9.7)
Social support	18.1 (20.2)	19.7 (24.1)	0.98	-1.6 (-16.3;13.1)	14.7 (22.4)	21.4 (21.0)	0.30	-6.7 (-21.2;7.8)
Cognitions	34.0 (17.6)	40.0 (21.8)	0.29	-6.0 (-19.0;7.0)	36.7 (19.9)	36.1 (19.3)	0.86	0.5 (-12.6;13.7)
Communication	35.9 (19.7)	35.6 (24.5)	0.91	0.3 (-14.3;14.9)	40.0 (24.2)	33.0 (19.4)	0.39	7.0 (-7.4;21.4)
Pd[6]	45.7 (19.9)	51.1 (18.6)	0.46	-5.5 (-18.5;7.6)	47.2 (23.1)	48.2 (17.0)	0.88	-1.0 (-14.2;12.2)
NMSQuest[7]	9.7 (4.4)	12.6 (6.2)	0.09	-2.9 (-6.4;0.5)	10.2 (4.5)	11.2 (5.8)	0.57	-1.0 (-4.6;2.6)
EQ-5D[8]	0.72 (0.21)	0.58 (0.15)	<0.05	0.14 (0.02;0.27)	0.70 (0.17)	0.64 (0.21)	0.37	0.06 (-0.07;0.20)
VAS[9]	68.1 (9.6)	61.6 (13.7)	0.09	6.5 (-1.1;14.2)	69.0 (10.2)	63.3 (12.3)	0.15	5.7 (-2.1;13.5)

Presented as *mean* (SD). [1]*(L-M):* Less medications minus more medications, [2]*(Y-O):* Younger patients minus older patients, [3]*PDQ-39 TOT:* Parkinson's Disease Questionnaire-39 Total score of all domains, [4]*Adl:* Activities in daily living, [5]*Ew:* Emotional wellbeing, [6]*Pd:* Physical discomfort [7]*NMSQuest:* Non-Motor Symptoms Questionnaire, [8]*EQ-5D:* EuroQOL-5 Dimensions, [9]*VAS:* Visual Analogue Scale

Table 4 Results of questionnaire data at baseline on –
Left: personal carers' QoL of PD patients taking 4 to 7 medications vs. ≥ 8 medications (N=23)
Right: personal carers' QoL of PD patients aged < 70 years vs. ≥ 70 years (N=23)

	PC[1] of patients 4-7 med. (N = 13)	PC[1] of patients ≥8 med. (N = 10)	P-value	Difference in groups (95% CI) (L-M)[2]	PC[1] of patients < 70 years (N = 10)	PC[1] of patients ≥ 70 years (N = 13)	P-value	Difference in groups (95% CI) (Y-O)[3]
PDQ Car TOT[4]	28.0 (16.2)	31.3 (14.2)	0.52	-3.3 (-16.7;10.2)	30.3 (12.8)	28.8 (17.1)	0.61	1.5 (-12.0;15.0)
S&P activities[5]	27.7 (21.0)	31.0 (18.3)	0.56	-3.3 (-20.7;14.0)	32.1 (20.9)	26.9 (18.8)	0.56	5.2 (-12.1;22.4)
A&D[6]	35.3 (19.4)	35.4 (14.7)	0.88	-0.2 (-15.5;15.2)	34.6 (14.8)	35.9 (19.4)	0.69	-1.3 (-16.7;14.1)
Self-care	15.0 (14.6)	21.5 (17.8)	0.38	-6.5 (-20.5;7.5)	18.5 (9.7)	17.3 (20.0)	0.38	1.2 (-12.1;14.5)
Stress	34.0 (19.2)	37.1 (18.3)	0.83	-3.1 (-19.5;13.3)	35.8 (17.7)	34.9 (19.7)	0.88	0.9 (-15.6;17.4)

Presented as *mean* (SD). [1]*PC:* Personal Carers, [2]*(L-M):* Less medications minus more medications, [3]*(Y-O):* Younger patients minus older patients, [4]*PDQ Car TOT:* Parkinson's Disease Questionnaire Carer Total score of all domains, [5]*S&P activities:* Social and Personal activities, [6]*A&D:* Anxiety and Depression

In univariate analyses, neither gender (3.2 (-4.3;10.8)) nor disease severity as categorized by H&Y stages (-4.9 (-12.7;2.8)) were significantly associated with the total score of the PDQ-39 (Table 5). However, an association between gender and three sub-scores of the PDQ-39 indicates that women have more restrictions in mobility (-15.2 (-28.2;-2.2)), while men experience more problems with cognitions (12.9 (0.6;25.1)) and communication (20.4 (7.7;33.1)). Next to this, an association between disease severity and two sub-scores of the PDQ-39 indicates that PD patients categorized in advanced stages have more restrictions in mobility (-19.1 (-32.1;-6.0)) and daily activities (-28.0 (-42.8;-13.2)) than PD patients categorized in early stages of PD.

Table 5   Results of questionnaire data at baseline on disease-specific QoL of –
  Left: men with PD vs. women with PD (N=38)
  Right: patients categorized in early stages of PD vs. advanced stages of PD (N=38)

	Men (N = 22)	Women (N = 16)	P-value	Difference in groups (95% CI) (M-W)[1]	H&Y[2] stages 1-2.5 (N = 25)	H&Y[2] stages 3-5 (N = 13)	P-value	Difference in groups (95% CI) (E-A)[3]
PDQ-39 TOT[4]	37.3 (13.2)	34.1 (7.9)	0.38	3.2 (-4.3;10.8)	34.3 (11.2)	39.2 (11.1)	0.21	-4.9 (-12.7;2.8)
Mobility	39.3 (18.9)	54.5 (20.4)	<0.05	-15.2 (-28.2;-2.2)	39.2 (19.0)	58.3 (18.6)	<0.01	-19.1 (-32.1;-6.0)
Adl[5]	42.4 (22.1)	46.4 (29.1)	0.69	-3.9 (-20.7;12.9)	34.5 (19.7)	62.5 (24.2)	<0.01	-28.0(-42.8;-13.2)
Ew[6]	35.8 (18.3)	30.5 (17.7)	0.46	5.3 (-6.7;17.4)	35.5 (17.0)	29.8 (20.0)	0.48	5.7 (-6.8;18.2)
Stigma	27.8 (19.2)	22.7 (12.9)	0.34	5.2 (-6.0;16.4)	26.8 (19.3)	23.6 (10.9)	0.56	3.2 (-8.6;15.0)
Social support	23.3 (23.1)	12.5 (17.9)	0.13	10.8 (-3.3;24.9)	18.3 (17.6)	19.6 (28.3)	0.39	-1.2 (-16.3;13.9)
Cognitions	41.8 (19.1)	28.9 (17.4)	<0.05	12.9 (0.6;25.1)	38.3 (16.9)	32.7 (23.5)	0.43	5.6 (-7.9;19.0)
Communication	44.3 (19.3)	24.0 (18.7)	<0.01	20.4 (7.7;33.1)	36.0 (19.4)	35.3 (25.7)	0.86	0.7 (-14.3;15.8)
Pd[7]	43.9 (21.2)	53.1 (15.5)	0.18	-9.2 (-21.9;3.5)	45.7 (19.9)	51.9 (18.4)	0.43	-6.3 (-19.7;7.2)

Presented as *mean* (SD). [1]*(M-W):* Men minus women, [2]*HY Scale:* Hoehn & Yahr Scale, [3]*(E-A):* Early stages of PD minus Advanced stages of PD, [4]*PDQ-39 TOT:* Parkinson's Disease Questionnaire-39 Total score of all domains, [5]*Adl:* Activities in daily living, [6]*Ew:* Emotional wellbeing, [7]*Pd:* Physical discomfort

DISCUSSION

To evaluate the current study population of PD patients prior to intervention, this interim study aimed to determine differences and similarities in patient characteristics at baseline. Baseline comparisons were performed to compare the baseline characteristics of 38 participating patients in two study groups. The analyses showed a significant difference in medication use between the intervention group and the control group, which indicated that the amount of medication (lower in the control group) was the only imbalanced factor at baseline prior to the intervention. No other significant differences were found between both groups before entering the study. This implies that the randomization process has generated two quite comparable groups in the current study population of PD patients at baseline. However, due the fact that baseline characteristics are unbalanced between the two study groups and are related to outcomes at randomization, the use of change scores or covariate-adjusted analyses for the comparison of mean differences may aim to refine the analysis of the overall treatment difference at the end of the trial (36) (37). These solutions might be appropriate to take account of chance imbalances at baseline between groups if including more patients during the further trial will not rectify the problem.

Subgroups of participating PD patients at baseline were analyzed to explore whether differences in questionnaire results depend on certain patient characteristics and to measure similarities with other groups of PD patients prior to the intervention.

An association between increasing medication use and a decreasing total score of the PDQ-39 was expected since QoL is a multidimensional concept that encompasses several domains and is associated with polypharmacy (29) (38). However, an association between medication use and only two sub-scores of the PDQ-39 was found. PD patients taking eight or more medications have more restrictions in mobility and daily activities than PD patients taking four to seven medications. These physical limitations could be the reason that extra medications would be prescribed (due to side effects or comorbidities) and might explain why there are no differences in non-physical domains. The total score of the PDQ-39 was not different between groups, which implies that other variables than mobility and activities in daily living might be as important to predict QoL. This corresponds to a study that identifies factors to determine QoL in PD patients, which states that also cognitive impairment and depression have great influence (30). An association between medication use and lower scores on the EQ-5D questionnaire indicated that PD patients taking eight or more medications have lower health state experiences. This is in line with a previous study on polypharmacy in elderly patients, stating that the inappropriate use of multiple drug regimens increases the risks of adverse drug reactions and drug-drug interactions in polypharmacy, which has a negative impact on the health status of elderly patients (38).

According to our subgroup analyses, it can be concluded that PD patients with increased medication use have worse scores on questionnaires. However, total scores of the PDQ-39, NMSQuest and VAS were not significant, whereas all *p*-values were tending toward significance. The small number of participants in the subgroups could explain this. Another explanation is the debatable issue of the artificial cut-off point: the median for the amount of medication is eight in the intervention group and seven in the control group. Therefore, it is difficult to differentiate a significant result where the cut-off point is set at eight, whereas in these small groups less than four medications is not even appropriate. Including more patients could possibly solve the problem.

Age differences between groups were not significantly associated with questionnaire results at baseline. However, PD patients aged over seventy years do have lower scores on the NMSQuest, the EQ-5D and the VAS than PD patients younger than seventy years, while they score better on most domains of the PDQ-39. In previous studies on quality of life in PD, increasing age was only correlated with the physical domains of the PDQ-39. Otherwise age had no significant impact on QoL in PD patients (39) (40). This phenomenon also applies to our study. Possible causes might be that younger patients value their QoL differently due to factors as future perspectives and disease acceptance. Since younger patients live more actively with more responsibilities and expectations than older patients, the interference of PD symptoms in daily living is likely to cause more burden in younger patients (39). According to an earlier study measuring QoL in patients with PD, age (being younger or older than 70 years) had no significant impact on EQ-5D and VAS scores (32). In addition, no association of age with NMS scores was found (41).

Since PD is characterized by increasing dependence on patients' caregivers, the expectation for results of the PDQ Carer was that caregiver-burden would be associated with worse patients' QoL scores (42). According to our study, neither the amount of medication taken by PD patients nor different ages of PD patients were significantly associated with personal carers' QoL. However, it is remarkable that personal carers of patients taking eight or more medications have worse scores on QoL and that personal carers of patients aged over seventy years score better on QoL, which is in line with outcomes of the PDQ-39 in the previous subgroup analyses.

An association between gender and three sub-scores of the PDQ-39 indicated that women have more restrictions in mobility, while men experience more problems in cognitions and communication. A previous study assessing QoL, as measured by the PDQ-39, argued that there is no difference between sexes in QoL of PD patients (39). This corresponds to the total score of the PDQ-39 in our subgroup analyses. Other studies stated that women scored worse on physical disabilities and depression (40) (43). Cognitive gender differences in PD influencing QoL outcomes have been largely unexamined (44).

No association between disease severity and the total score of the PDQ-39 was found. However, physical sub-scores of the PDQ-39 showed significant differences in mobility and daily activities, which is a logical result as the H&Y scale quantifies disease severity based on mobility. Other studies indicated that the total score of the PDQ-39 was significantly different for different stages of illness and correlated significantly with disease severity as measured by the H&Y scale (39) (45).

The aforementioned subgroup analyses in this interim study showed that baseline results on subgroups in the current study population of PD patients are consistent with earlier studies. Therefore, we might have a representative sample, which is important for the possible generalizability of future results to external populations of other (study-eligible) PD patients beyond the current study population. In addition, it will be particularly useful for pharmacists to know whether conclusions can be drawn about other groups of complex (non-PD) patients: currently, no clear patient group can be differentiated that might benefit of medication reviews (19). However, we are unable to state that patients who might really benefit are included in the study, since those patients could have declined to participate in practice. Unfortunately, only patients who were willing to participate are included.

The amount of participating patients in the study was not expected in advance. In a relatively short inclusion period, 38 patients agreed to participate, which might say something about the importance of the intervention. Other strengths are the validated and reliable measurement instruments used in the study. The disease-specific PDQ-39 is useful because of its responsiveness to change for which minimally important differences per dimension can be calculated during the further stage of the trial (46) (47). However, the PDQ-39 lacks items addressing sleeping problems and sexuality (29). Therefore, the disease-specific NMSQuest is a use-ful screening tool that recognizes non-motor symptoms to initiate further investigation (41). Both the EQ-5D and VAS have shown to be valid and reliable in the general population and in a variety of disorders, including PD. The VAS is designed to present a rating scale with minimum constraints to the respondent. However, the instrument gives an indication at a particular moment in time, for which alterations between periods of being 'on' and being 'off' were not taken into account. This also applies to the process of determining H&Y stages, for which officially 'on' and 'off' scores should be noted. Therefore, the H&Y scale is more useful to assess treatment response in populations of PD patients, and less appropriate for measuring progression of a single person over time (25). For all mentioned measurements should be taken into account that it is difficult to measure improvements in PD patients, because of the chronic deterioration of the disease. Therefore, significant differences as well as clinically relevant differences should be measured (47).

It can be concluded that as part of the 'Medication Review in Parkinson'-study, randomization has generated two quite comparable groups with similar patient characteristics in the current study population of PD patients at baseline, prior to the intervention of a structured medication review. Analyses on subgroups of PD patients at baseline showed that differences in questionnaire results depend on patient characteristics (gender, age, medication use, disease severity) and showed similarities with other groups of PD patients. Therefore, we might have a representative sample, which is important to conclude in order to generalize future results of the 'Medication Review in Parkinson'-study to the general population of PD patients.

REFERENCES

1. Dauer W, et al. Parkinson's Disease: Mechanisms and Models. Neuron. **2003**;39(6): 889-909.

2. Parkinson J. An essay on the shaking palsy. Whittingham and Rowland. London. **1817**.

3. Jankovic J, et al. Handbook of Parkinson's Disease: Pathophysiology and clinical assessment of motor symptoms in Parkinson's Disease. New York. **1992**.

4. Chaudhuri KR, et al. Non-motor symptoms of Parkinson's Disease: diagnosis and management. Lancet Neurol. **2006**;5(3):235-245.

5. Schulman LM, et al. Non-recognition of depression and other non-motor symptoms in Parkinson's Disease. ELSEVIER. **2002**;8(3):193-197.

6. Poewe W. Non-motor symptoms in Parkinson's Disease. The Scientific and Clinical Basis for Future Therapies in Parkinson's Disease. Eur J Neurol. **2008**;15(s1):14-20.

7. Marsden CD, Parkes JD. 'On-off' effects in patients with Parkinson's Disease on chronic Levodopa therapy. Lancet Neurol. **1976;**307(7954):292-296.

8. Leoni O, et al. Drug prescribing patterns in Parkinson's Disease: A pharmacoepidemiological survey in a cohort of ambulatory patients. Pharmacoepid Drug Saf. **2002**;11:149-157.

9. Clarke CE. Has drug therapy changed the natural history of Parkinson's Disease? J Neurol. **2010**;257(2):262-267.

10. Aerts MB, et al. Stand van zaken - Onvoldoende therapietrouw bij ziekte van Parkinson. Nederlands Tijdschrift voor Geneeskunde. **2011**;155(21):967.

11. Tarrants ML, et al. Drug therapies for Parkinson's Disease: A database analysis of patient compliance and persistence. Am J Geriatr Pharmacother. **2010**; 8(4):374-383.

12. Grosset KA, et al. Medicine-taking behavior: Implications of suboptimal compliance in Parkinson's Disease. Mov Disord. **2005**;20:1397-1404.

13. Kulkarni AS, et al. Medication adherence and associated outcomes in medicare health maintenance organization-enrolled older adults with Parkinson's Disease. Mov Disord. **2008**;23:359-365.

14. Wei Y, et al. Antiparkinson Drug Use and Adherence in Medicare Part D Beneficiaries With Parkinson's Disease. ELSEVIER, Clinical Therapeutics. **2013**;35(10):1513-1525.

15. Osterberg L, Blaschke T. Adherence to Medication. New Engl J Med. **2005**;353:487-97.

16. Davis KL, et al. Prevalence and cost of medication nonadherence in Parkinson's Disease: evidence from administrative claims data. Mov Disord. **2010**;25:474-80.

17. KNMP, AccreDidact. Polyfarmacie. [Online]; **2013**. Available from: elearning.accredidact.nl/nascholingsartikel/t/2013_5_polyfarmacie#eindtoets.

18. Lemmens LC, Weda M. RIVM: Polifarmacie bij kwetsbare ouderen. Inventarisatie van risico's en mogelijke interventiestrategieën. [Online]; **2013**. Available from: http://www.rivm.nl/dsresource?objectid-rivmp:213828&type=org&disposition=inline.

19. Van Marum RJ, et al. Multidisciplinaire Richtlijn Polyfarmacie bij ouderen. Utrecht. **2012**.

20. Stewart RB, et al. Polypharmacy in the Aged. Drugs Aging. **1995**;4(6):449-61.

21. Shaw J, et al. Task Force on Medicines Partnership. The National Collaborative Medicines Management Servive Program & the National Prescribing Centre (NPC). Room for Review. A guide to medication review. [Online]; **2012**. Available from: https://www.npc.nhs.uk/review_medicines/intro/resources/room_for_review.pdf.

22. Krska J, et al. Pharmacist-led medication review in patients over 65: a randomized controlled trial in primary care. Oxford Journals, Age Ageing. **2001**;30(3):205-211.

23. Ahmad A, et al. Effect of medication review and cognitive behaviour treatment by community pharmacists of patients discharged from the hospital on drug related problems and compliance. BMC Public Health. **2010**;10(133):1-10.

24. Geurts MM, et al. Medication review and reconciliation with cooperation between pharmacist and general practitioner and the benefit for the patient: a systematic review. Br J Clin Pharmacol. **2012**;74(1):16-33.

25. Bloem BR, et al. Multidisciplinaire richtlijn Ziekte van Parkinson. Alphen a/d Rijn. **2010**.

26. Leendertse AJ, et al. Preventing hospital admissions by reviewing medication (PHARM) in primary care: design of the clustered randomised, controlled, multi-centre PHARM-study. BMC Health Serv Res. **2011**;11(4):1-13.

27. Müller J, et al. Progression of Hoehn and Yahr stages in parkinsonian disorders: A clinicopathologic study. J Neurol. **2000**;55(6):888-891.

28. Hughes AJ, et al. Accuracy of clinical diagnosis of idiopathic Parkinson's Disease: a cli-nicopathological study of 100 cases. J Neurol Neurosurg Psychiatry. **1992**;55(3):181-184.

29. Marinus J, et al. Health related quality of life in Parkinson's Disease: a systematic review of disease specific instruments. J Neurol Neurosurg Psychiatry. **2002**;72:241-248.

30. Schrag A, et al. What contributes to quality of life in patients with Parkinson's Disease? J Neurol Neurosurg Psychiatry. **2000**;69(3):308-312.

31. Hwynn N, et al. The Frequency of Nonmotor Symptoms among Advanced Parkinson Patients May Depend on Instrument Used for Assessment. Parkinson's Disease. **2011**.

32. Schrag A, et al. The EQ-5D -a generic quality of life measure- is a useful instrument to measure quality of life in patients with Parkinson's Disease. J Neurol Neurosurg Psychiatry. **2000**;69:67-73.

33. Rabin R, et al. EQ-5D: a measure of health status from the EuroQol group. Ann Med. **2001**;33(5):337-343.

34. Morley D, et al. The PDQ-Carer: Development and validation of a summary index score. ELSEVIER, Parkinsonism Relat Disord. **2013**;19(4):448-449.

35. Altman DG, et al. Statistics with Confidence. BMJ Books. **2000**.

36. Pocock SJ, et al. Subgroup analysis, covariate adjustment and baseline comparisons in clinical trial reporting: current practiceand problems. Stat Med. **2002**;21(19):2917-2930.

37. Vickers AJ, et al. Analysing controlled trials with baseline and follow up measurements. BMJ. **2001**;323(7321):1123-1124.

38. Montamat SC, Cusack B. Overcoming problems with polypharmacy and drug misuse in the elderly. Clin Geriatr Med. **1992**;8(1):143-58.

39. Schrag A, et al. How Does Parkinson's Disease Affect Quality of Life? A Comparison With Quality of Life in the General Population. Mov Disord. **2000**;15(6):1112-1118.

40. Kuopio AM, et al. The quality of life in Parkinson's disease. Mov Disord. **2000**;2:216-223.

41. Chaudhuri KR, et al. International multicenter pilot study of the first comprehensive self-completed nonmotor symptoms questionnaire for Parkinson's Disease: The NMSQuest study. Mov Disord. **2006**;21(7):916-923.

42. Schrag A, et al. Caregiver-burden in Parkinson's disease is closely associated with psychiatric symptoms, falls, and disability. Parkinsonism Relat Disord. **2006**;12(1):35-41.

43. Shulman LM. Gender differences in Parkinson's Disease. Gend. Med. **2007**;4(1):8-18.

44. Miller IN, et al. Gender differences in Parkinson's Disease: clinical characteristics and cognition. Mov Disord. **2010**;25(16):2695-2703.

45. Slawek J, et al. Factors affecting the quality of life of patients with idiopathic Parkinson's disease -a cross-sectional study in an outpatient clinic attendees. ELSEVIER, Parkinsonism Relat Disord. **2005**;11(7):465-468.

46. Peto V, et al. The development and validation of a short measure of functioning and well being for individuals with Parkinson's disease. Qual Life Res. **1995**;4:241-248.

47. Peto V, et al. Determining minimally important differences for the PDQ-39 Parkinson's Disease Questionnaire. Age Ageing. **2001**;30:299-302.

APPENDIX 1. PROTOCOL FOR A STRUCTURED MEDICATION REVIEW BY COMMUNITY PHARMACISTS

STAPPENPLAN MEDICATIE BEOORDELING	

Stap 0: Voorbereiding
Verzamelen van gegevens:
- Opvragen van ziektebeelden bij huisarts van desbetreffend patiënt
- Voorgeschiedenis / episodelijst / probleemlijst (o.a. stoelgang)
- Metingen (bloeddruk / pols / gewicht)
- Laboratoriumwaarden (nier- en leverfunctie, Na, K, evt. HbA1c, lipidensprectrum etc.)
- Medicatieoverzicht

Tijdsduur stap 0:

Stap 1: Farmacotherapeutische anamnese
Bespreking (telefonisch) met patiënt (en evt. met mantelzorger) op basis van medicatieoverzicht van:
- Actueel geneesmiddelengebruik en gebruiksgemak
- Bijwerkingen, allergieën
- Ervaringen, problemen en kennis van de patiënt
- Zorgen en verwachtingen van de patiënt
- Indien nodig: overleggen en aanvragen laboratoriumwaarden

Tijdsduur stap 1:

Stap 2: Farmacotherapeutische analyse
Ordening van de gegevens, nagaan of er sprake is van:
- Onderbehandeling / overbehandeling
- Effectiviteit van de medicatie
- (potentiële) bijwerkingen
- Klinisch relevante contra-indicaties en interacties
- Onjuiste doseringen
- Gebruiksgemak

Tijdsduur stap 2:

Stap 3: Overleg arts en apotheker (en evt. behandelend neuroloog / specialist), opstellen farmacotherapeutisch behandelplan:
Bespreking en notering van:
- Behandelingsdoelen
- Gesignaleerde problemen (uit stap 1 en 2)
- Prioritering
- Verdieping van acties tussen arts en apotheker
- Evaluatie

Tijdsduur stap 3:

Stap 4: Overleg met patiënt, vaststellen farmacotherapeutisch behandelplan
- Terugkoppeling van afgesproken interventies naar de patiënt, patiënt naar apotheek laten komen
- Aanpassing van het actuele medicatieoverzicht
- Rapport aan huisarts + andere behandelaars (neuroloog / specialist)
- Notitieformulier medicatie beoordeling gesprek retourneren naar MST

Tijdsduur stap 4:

Stap 5: Follow-up en monitoring
- Evaluatie door arts en apotheker van afgesproken interventies binnen 4 maanden na overleg met patiënt
- Rapportage van evaluatie en monitoring in het farmacotherapeutisch behandelplan

Tijdsduur stap 5:

Vervolg review: min. 1 x per jaar

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RESEARCH PROTOCOL

**A Study Assessing The Effect Of A Structured Medication Review
On Quality Of Life In Patients With Parkinson's Disease
(April 2014)**

PROTOCOL TITLE 'A Study Assessing The Effect Of A Structured Medication Review On Quality Of Life In Patients With Parkinson's Disease – P14-10'

Protocol ID	NL48661.044.14
Short title	Medication review in Parkinson
EudraCT number	Not applicable
Version	2.0
Date	April 24, 2014
Coordinating investigator/project leader	*L.D.A. (Lucille) Dorresteijn, Neurologist* Department of Neurology Medisch Spectrum Twente, Enschede L.Dorresteijn@mst.nl 053-4872850
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PROTOCOL SIGNATURE SHEET

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Coordinating Investigator/project leader: L.D.A. (Lucille) Dorresteijn, Neurologist, MST		24-4 '14
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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
CA	Competent Authority
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
CV	Curriculum Vitae
DSMB	Data Safety Monitoring Board
EudraCT	European drug regulatory affairs Clinical Trials
GCP	Good Clinical Practice
HY	Hoehn and Yahr scale
IC	Informed Consent
KNMP	Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie
METC	Medical research ethics committee (MREC); (in Dutch, METC; medisch ethische toetsing commissie)
MST	Medisch Spectrum Twente
NHG	Nederlands Huisartsen Genootschap
PD	Parkinson's Disease
QALYs	Quality Adjusted Life Years
(S)AE	(Serious) Adverse Event
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
WMO	Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen

SUMMARY

Rationale: Parkinson's Disease (PD) is a progressive, neurodegenerative disease resulting from degeneration of dopaminergic neurons within the substantia nigra, which leads to a shortage of dopamine in e.g. the striatum. Patients with PD need to take a variety of anti-Parkinson medications in order to manage the symptoms of the disease. Next to this, possible other medications might be prescribed due to comorbidity. Since all these medications need to be taken at different doses and at different times of a day, this can result in complicated medication schedules. Due to these multiple drug regimens, decreased medication adherence occurs, which means that a considerable amount of patients with PD do not fully benefit from their medical treatment. A potential intervention to enhance medication adherence is by performing a structured medication review. The aim of this study is to assess whether a structured medication review in primary care improves medication adherence and leads to positive patient outcomes in patients with PD. The expectation is that the results of this study might be used to improve daily treatment of patients with PD.

Objective: The primary objective of the study is to determine whether a structured medication review leads to better quality of life in patients with PD, compared to patients with PD who will not receive a structured medication review during follow-up and get usual care. The secondary objectives are to measure the effects between the intervention group and the control group in physical disability, activities in daily life, non-motor symptoms, cost-effectiveness, health state, and personal carer's quality of life.

Study design: The study will be designed as a randomized controlled trial (RCT) with a follow-up of six months. Half of the randomly assigned patients will receive the intervention, while the other half will not receive the intervention and receives usual care.

Study population: The study population consists of adult participants diagnosed with PD. These patients need to express motor complications or non-motor symptoms due to the disease, and need to take four or more different medications daily at four or more intake moments to suppress PD-related symptoms and to treat other comorbidities.

Intervention: As intervention, community pharmacists will perform the structured medication reviews as one-time assessment at the start of the study within the intervention group. Measurements at baseline will be done before the intervention. The follow-up measurements will take place after three months and six months.

Nature and extent of the burden and risks / benefits associated with participation:
The intervention is a useful tool that does not cause a burden for participants and is not associated with risks. During the study, solely patients with PD in the intervention group might benefit from the investigation. Patients in the control group will not receive the intervention and will not benefit.

1. INTRODUCTION

1.1 Background

Parkinson's Disease (PD) is a progressive, neurodegenerative and age-related disease resulting from degeneration of dopaminergic neurons within the substantia nigra, which leads to a shortage of dopamine in the striatum (1). In the Netherlands, there are approximately 35000 patients with PD. Because of the aging population, the expectation is that this amount will increase to 75000 patients with PD in 2025 (2).

PD is characterized clinically by tremor, rigidity, bradykinesia and postural instability (3) (4). These motor symptoms are caused by dopamine deficiency within the basal ganglia. Other symptoms include non-motor symptoms, such as cognitive dysfunction, depression, anxiety, pain, sleep disorders, constipation, and genitourinary problems. Both motor and non-motor symptoms contribute to the reduction of functional abilities, shortened life expectancy, and reduced quality of life (5) (6) (7). The symptoms occur across all stages of PD, but become increasingly prevalent during an advanced stage of the disease. After disease progression (approximately 5 years) also motor fluctuations and dyskinesia occur. Patients feel alterations between periods of being 'on', during which the patient enjoys a good response to medication, and being 'off', during which the patient experiences symptoms of their underlying Parkinsonism. Dyskinesia consists of abnormal involuntary movements that are usually choreic or dystonic but, when more severe, may be ballistic or myoclonic. Dyskinesia usually appears when the patient is 'on' (8).

The golden standard for the management of PD is drug treatment to increase the dopaminergic activity in the brains and to suppress the motor fluctuations and non-motor symptoms, which can be realized by various types of medication. The most commonly used medicines are dopamine replacements (e.g. Levodopa) and dopamine agonists (e.g. Ropinirole) (9) (10). Patients with PD need to take a variety of these medications in order to manage the symptoms of the disease. This causes complicated medication schedules, since all these medications need to be taken at different doses and at different times of a day (11). Keeping track of medications can be a challenging task, because when the disease progresses and the therapeutic window narrows, the dosing frequency will increase (12). It means that patients with PD need to take more and more anti-Parkinson medications, which possibly have lasting effects on the motor symptoms of the disease. Therefore, anti- Parkinson medication regimens are essential for controlling symptoms and maximizing desired patient outcomes (10) (13) (14) (15). The effectiveness of PD medicines tends to decrease after several years of usage, which leads to end-of-dose

deterioration and fluctuations in response to medicines, while in the early phase of the disease patients experience a smooth and even response to the early stages of Levodopa treatment (5) (16). Simultaneously, patients with PD need to take many extra medicines due to comorbidity, which also contributes to more complicated schedules (11).

To achieve good results, medication adherence is important for patients with PD to avoid fluctuations of functioning due to missed doses or wrong doses (11) (17). Medication adherence can generally be defined as the extent to which patients take medications as prescribed by their healthcare providers (18). Consistent adherence increases survival and extends independence (19). Unfortunately, suboptimal adherence to medical treatment is still an extensive problem: it means a follow-up of less than 80% of the total medication prescription, which often leads directly to an increase in motor complications (11) (18). This problem arises especially among patients with chronic diseases, where consistent adherence is on average merely 50%, resulting in undesired health outcomes, reduced quality of life, and unnecessary, increasing healthcare costs (18) (20) (21) (22). In addition to this last phenomenon, it has been shown that reduced adherence in PD entails an increase of 20% in healthcare costs per year (23).

Next to complicated medication schedules and functioning limitations, there are several other causes for suboptimal medication adherence: patients can have misconceptions about medicines, patients can be afraid of side effects because of interactions between various medications, and as patients with PD also have problems with cognition, polypharmacy easily leads to missing doses of medication due to comorbidity (11) (13) (24). Important risk factors of polypharmacy are insufficient knowledge of interactions, an excess of healthcare providers at the same time (which may lead to comorbidity and pigeonholing), poor communication about medication between healthcare providers and patients, poor registration and monitoring of medication, and sometimes simultaneously provision of medicines by various pharmacies (24) (25) (26). Drug related problems could be caused by this inappropriate use of multiple drug regimens, because it increases the risks of adverse drug reactions and drug-drug interactions, which has a significant impact on the health status of elderly individuals (27). Due to these multiple drug regimens, decreased medication adherence occurs and means that a considerable amount of patients with PD do not fully benefit of their medical treatment (18) (28).

1.2 Rationale of the investigation

There are several interventions to enhance medication adherence, including behavioral interventions, and the usage of ICT and e-Health (11) (29) (30). Another potential way to improve medication adherence is by performing a structured medication review. A medication review can be defined as 'a structured, critical examination of a patient's medicines with the objective of reaching an agreement with the patient about treatment, optimizing the impact of medicines, minimizing the number of medication-related problems and reducing waste' (31). Medication reviews might be periodic and successful evaluations to improve medication safety in polypharmacy and to guarantee continuity of care in a systematic way. These reviews are intended to increase efficiency and effectiveness in terms of medication adherence, but it requires good collaboration between healthcare providers and involvement of the patient in the process (32) (33) (34) (35). Therefore, clear communication, continuous registration, and monitoring the long-term effects of medication and diseases are essential (21) (28). The role of the pharmacist as healthcare provider can be strengthened in this situation (24). When pharmacists perform a structured medication review, the dosing frequency of prescribed medicines and the complexity of medication schedules for patients with PD could be reduced, which possibly leads to simplified dosing and improved adherence (31). This may also result in increased customized care and shared decision-making, because patient preferences can be taken into account (24) (30) (36).

To date, performing medication reviews is formally a task of pharmacists, but this is often not done according to a clear protocol or during structural time periods. Official guidelines show that all people over 75 years should have their medicines reviewed at least annually and those taking four or more medicines should have a review 6-monthly (31). Unfortunately, this is not the case in the Netherlands. In fact, there is very limited research on effectiveness, clinical outcomes like quality of life, and feasibility of medication assessment within primary care in the Netherlands (26).

The present randomized controlled study aims to assess whether a structured medication review in primary care improves medication adherence and leads to better quality of life in patients with PD.

2. OBJECTIVES

2.1 Primary Objectives (Hypothesis)

The primary objective of the study is to assess whether a structured medication review improves medication adherence and leads to better quality of life in patients with PD after a follow-up of three months and six months, compared to patients with PD who will not receive a structured medication review during follow-up. Disease-specific quality of life will be measured, using the Parkinson's Disease Questionnaire-39 (PDQ-39) (37).

2.2 Secondary Objectives (Hypothesis)

The secondary objectives of the study are measurements of activities in daily life and physical disability, mobility and motor symptoms, non-motor symptoms, cost-effectiveness and health state, and personal carers' quality of life, by comparing the results of PD patients who receive a medication review with PD patients who will not receive a medication review.

- Effects on activities in daily life and the level of physical disability will be measured, using the AMC Linear Disability Scale (ALDS) (38).
- Effects on non-motor symptoms will be measured, using the Non Motor Symptoms Questionnaire (NMSQuest) (39).
- Cost-effectiveness and the experience of health state will be measured, using the EuroQOL-5 Dimensions (EQ-5D) and the Visual Analogue Scale (VAS) (40) (41).
- Effects on quality of life for personal or home caregivers of patients with PD will be measured, using the PDQ carer questionnaire (42).

3. STUDY DESIGN

The study will be designed as a randomized controlled trial (RCT) with the aim to assess whether a structured medication review in primary care improves medication adherence and leads to better quality of life in patients with PD after a follow-up of three months and six months, compared to patients with PD who will not receive a structured medication review during follow-up.

As intervention, community pharmacists will perform the structured medication reviews as one-time assessment at the start of the study within the intervention group. Half of the randomly assigned patients will receive this structured medication review, while the other half will not receive a medication review during follow up and receives usual care.

Based on inclusion criteria and exclusion criteria, potential eligible patients will be identified from appointment schedules at the neurology department of Medisch Spectrum Twente hospital (Enschede) and from existing database files for patients with PD within the region of Enschede. These patients with PD will be contacted about the study. Information shall be sent if they are interested, after which patients will have the opportunity to ask questions and to sign an informed consent (IC) form at home. The randomization process may start if patients are included. After this, measurements at baseline will be done, and the intervention by community pharmacists can take place. The follow-up measurements will take place after three months and six months. The total duration of the study is expected to take two years, whereas the inclusion of patients might take twelve months, presumably between June 2013 and June 2014. The expectation is that after the final measurements, still three months are necessary for analysing and processing the results to determine whether there is a significant difference in medication adherence and quality of life between the intervention group and the control group.

A flow chart of the prospective process for each patient is shown in figure 1 at section 8.3 (Study Procedures).

4. STUDY POPULATION

4.1 Population (base)

Men or women with PD over eighteen years old will be recruited from appointment schedules at the neurology department of the Medisch Spectrum Twente (MST) hospital (Enschede) and from existing database files within the region of Enschede. These patients need to express motor complications or non-motor symptoms due to the disease, and need to take four or more different medications daily at four or more intake moments to suppress these PD-related symptoms and to treat other comorbidities. Next to the anti-Parkinson medications, a variety of other drugs can be used by the population source, due to comorbidity (11). The likelihood that the planned number of patients (see section 4.4) can be recruited from the defined population is high: the strength of the study is that the medication review within the intervention group is an intervention that does not cause a burden on participants. This may lead to a relatively easy inclusion of patients with PD. Almost all pharmacists in the catchment area of the MST hospital agreed to participate in the study. Some of these pharmacists are already familiar with the execution of medication reviews, which is advantageous for the progress of the study, but thus far this is not always performed according to a clear protocol or during structural time periods.

4.2 Inclusion criteria

In order to be eligible to participate in the study, a subject must meet the following criteria:

- Diagnosed with PD according to the UK-brain banking criteria (43)
- ≥ Eighteen years of age
- ≥ Four different medications daily
- ≥ Four medication intake moments daily
- Expressing motor symptoms or non-motor symptoms
- Living (semi)-independent in the region of Enschede
- Be able to read and write the Dutch language

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Unable to administrate own medications, excluding PD patients with personal or family home caregivers
- Received a medication review within a year before the study

4.4 Sample size calculation

The primary objective of the study is to assess whether a structured medication review improves medication adherence and leads to better quality of life in patients with PD, which will be measured by the PDQ-39. Using this disease-specific questionnaire, a difference of four points is considered as a clinically relevant difference (44). The expectation is that during the study a difference of six points will occur after the intervention. In a previous study, the standard deviation was 15 (44). This standard deviation will be used to make a preliminary calculation of the sample size. A significance of 5% and a power of 80% will be used, which means that a sample size of 198 patients with PD is required to provide a reliable answer. Therefore, two groups of 99 subjects should be included in the study. However, the actual effect of a medication review is unknown and also the standard deviation may be different. For this reason, we would like to propose to make an interim analysis after the inclusion of 2*25 patients and three months of follow-up as an estimate of the final results to determine the final sample size.

5. TREATMENT OF SUBJECTS

5.1 Investigational treatment

As intervention, community pharmacists will perform the structured medication reviews as one-time assessment at the start of the study within the intervention group. This means that half of the patients will receive this structured medication review, while the other half will not receive a structured medication review during follow up and receives usual care. After the randomization, pharmacists will receive a message of the researcher to prevent that patients in the control group receive a medication review.

The evaluation will be used to facilitate the use of anti-Parkinson and non-Parkinson medications and to minimize side effects or drug-drug interactions, which may lead to a simplified dosing of prescribed medicines, reduced complexity of medication schedules, and improved adherence (31). The community pharmacists can collaborate with the patients' GP to create a modified schedule. First, this will be communicated to the GPs: they will receive an information letter about the study and the regional newsletter 'Tussen de lijnen' will be used, which is functioning as a connection between GPs and medical specialists. Furthermore, the community pharmacists may consult the treating neurologist of the MST hospital for PD-related questions about medications. If it appears in some cases that it is necessary and appropriate to consult other specialists (such as internists and cardiologists), this opportunity can be realized.

The community pharmacists are also already able to retrieve laboratory results of blood values to underpin their choices with regard to medication adjustments. If laboratory results are not up-to-date, possibly a new blood sample needs to be taken. This can be considered as regular care. Once the review is done, a report about adjustments in the medication regimen must be written to the current healthcare providers of the patient. Furthermore, the new medication regimen should be discussed with the patient and an explanation about the use of (new) medicines should be given. It means that the pharmacist will inform the patient about the results of the structured medication review. Therefore, it is necessary that the patient will be consulted at the pharmacy. In case of no or only a few little changes in the medication regime, the pharmacist may decide to call the patient to explain the changes. Within four months, pharmacists will call the patients to evaluate the adjustments.

The community pharmacists are offered a training regarding the study protocol, the documentation, and the execution of a structured medication review (33). This training will be a master class in April and is provided by the neurologist and a pharmacist. To ensure

continuity of care and to facilitate collaboration between members of the healthcare team, creating a clear documentation is required, for which a protocol is chosen (24). This protocol is based on the action plan for medication assessment of the Multidisciplinary guideline Polypharmacy in the Elderly (26). It will ensure that every structured medication review is done in the same way, and will be explained during the training. The protocol foresees the possibility of consulting the GP, the neurologist, and other specialists if necessary. Community pharmacists see this study as a good opportunity to improve their tasks as pharmacists and to provide continuity of care in a systematic way.

A protocol for the structured medication review and documentation is added to appendix 1.

5.2 Use of co-intervention

Patients might receive help of personal or home caregivers to stick to their medication regimen, because the personal or home caregiver can be semi-responsible for an adequate medication adherence. Personal or home caregivers may also benefit from the study, because the burden of complicated medication schedules may be reduced: their tasks of reminding patients to take their medication and to help them with several intake moments may be simplified. To assess their experience and measure quality of life during this process, a questionnaire of the PDQ carer will be used (42).

5.3 Escape medication

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 primary objective of the study is to assess whether a structured medication review improves medication adherence and leads to better quality of life in patients with PD. Disease-specific quality of life will be measured, using the PDQ-39 (37). This validated and reliable instrument has 39 items and measures the eight domains of mobility, activities in daily living, emotional wellbeing, stigma, social support, cognitions, communication, and physical discomfort. PDQ-39 can be used to assess effectiveness of treatment, in which dimension scores are coded on a scale of 0 to 100: a higher score indicates lower quality of life (45). Using this questionnaire, it is possible to search for the minimum magnitude of change per dimension to evaluate change over time in PD. A difference of four points is considered as a clinically relevant difference, which indicates a minimally important difference within a domain. This is reached if a patient scores 'a little better' feeling (44).

8.1.2 Secondary study parameters/endpoints

The secondary objectives of the study are measurements of activities in daily life and physical disability, non-motor symptoms, cost-effectiveness and health status, and personal carers' quality of life, by comparing the results of PD patients who receive a medication review with PD patients who will not receive a medication review.

- Activities in daily life and physical disability

The effects on activities in daily life and the level of physical disability will be measured, using the ALDS. The disease-specific and validated questionnaire exists of 26 questions that allow us to quantify functional status, which is seen as an important determinant of patients' quality of life (46). Using this questionnaire, functional status is expressed by the ability to perform activities of daily life: each item in the ALDS describes an activity with four response options. A higher score indicates less physical disabilities, and a difference of four points is considered as a clinically relevant difference (38).

- Non-motor symptoms

The effects on non-motor symptoms will be measured, using the NMSQuest. The disease-specific questionnaire exists of 30 yes (one point) or no (zero points) questions and presents a range of problems that may occur in patients with PD during the past month. A higher score indicates more non-motor symptoms (47). The NMSQuest recognizes that non-movement difficulties often occur in PD, which can have great impact on (quality of)

life. This means that the questionnaire is a useful screening tool to draw attention to the presence of non-motor symptoms and to initiate further investigation (39).

- Cost-effectiveness and health status
Cost-effectiveness and the experience of health status will be measured, using the EQ-5D and the VAS. The EQ-5D is a validated, reliable, and generic instrument to measure quality of life. The questionnaire can be useful in patients with PD and comprises five questions on mobility, self-care, pain / discomfort, usual activities, and psychological status with three possible answers. A higher score indicates a better health status (40).

Using this questionnaire, also cost-effectiveness can be analyzed by measuring utilities. A higher score indicates a lower experience of utilities, which can be used to measure Quality Adjusted Life Years (QALYs). To calculate these QALYs and to make a comparison in cost- effectiveness between the (medication review) intervention by community pharmacists and other interventions in patients with PD, costs need to be taken into account. Possible costs incurred during this study are medication costs, hospitalization costs, outpatient visit costs, home care costs and the costs for the execution of medication reviews. In addition, the VAS can be used for patients with PD to score their experience of health state on a certain day, ranging from 0 (worst experience) to 100 (best experience) (41). This instrument is designed to present a rating scale with minimum constraints to the respondent: it is easy to use, provides reproducible results and is applicable in several practice settings.

- Personal carers' quality of life
The effects on quality of life for personal or home caregivers of patients with PD will be measured, using the PDQ carer questionnaire. This validated and reliable instrument has 29 items and measures the four domains of social and personal activities, anxiety and depression, self-care, and stress. A higher score indicates more impact on the personal or home caregiver (42).

8.1.3 Other study parameters
The following parameters will be registered during the study:
- Date of study participation
- Gender
- Date of birth
- Stage of PD, according to the Hoehn and Yahr scale (HY) (48)
- Comorbidities

8.2 Randomization, blinding and treatment allocation

The randomization process only may start when the hospital receives an IC form of a participant and if a patient meets all the criteria as described in section 4, so that the patient is eligible to participate in the study. After the inclusion of patients, a blocked randomization will be performed with block sizes four and eight. Subsequently, the patients assigned to the intervention group will receive the structured medication review, while the other half will not receive a structured medication review during follow up and receives usual care. The randomization list will be managed by the researcher who does not know the patients.

8.3 Study procedures

The aim of the study is to assess whether a structured medication review in primary care improves medication adherence and leads to better quality of life in patients with PD, compared to patients with PD who will not receive a structured medication review. As intervention, community pharmacists will perform the structured medication reviews as one- time assessment at the start of the study within the intervention group, which is possible after the inclusion and randomization of patients with PD.

Based on inclusion criteria and exclusion criteria (see section 4), potential eligible patients will be identified from appointment schedules and existing database files for patients with PD. While using these databases to identify patients, the investigator is obliged to follow medical confidentially rules. The potential eligible patients will be contacted by telephone about the study and will be asked if they are interested to participate. If this is the case, more information shall be sent by postal mail, which includes a patient information letter with an explanation about the present study, experimental subject information for the caregivers, two IC forms, one for the patient and one for the caregivers, and a standard brochure about medical scientific research. It means that also the personal or home caregiver of the patient with PD will be approached to participate in the study, because the effects of the intervention on their quality of life can be measured. Subsequently, patients and their personal or home caregivers will have the opportunity to ask questions and to sign an IC form at home within one week.

The randomization process may start if patients are included. After this, measurements at baseline will be done, and the intervention by community pharmacists can take place. This means that the patient (and their personal or home caregiver if possible) needs to fill in several questionnaires before the intervention may take place (see section 8.1.1 and 8.1.2). Participants need to complete these questionnaires by themselves, but they might receive help from their personal or home caregiver as long as they do not affect the answers.

When the questionnaires are returned to the investigator, community pharmacists will perform the structured medication review in patients within the intervention group. The structured medication reviews used to determine improvements in medication adherence and quality of life in patients with PD are at the heart of the investigational treatment. These reviews are according to standards of the Nederlands Huisartsen Genootschap (NHG) and the multidisciplinary guidelines of polypharmacy in elderly people (see appendix 1), which enable us to investigate whether the intervention leads to better health-related clinical outcomes, compared to patients with PD who will not receive the intervention (24) (26).

During the execution of the structured medication review, the community pharmacists can collaborate with the patients' GP to create a modified medication schedule, and may consult the treating neurologist of the MST hospital for PD-related questions about medications. If it appears in some cases that it is necessary and appropriate to consult other specialists (such as internists and cardiologists), this opportunity can be realized. The community pharmacists are also already able to retrieve laboratory results of blood values to underpin their choices with regard to medication adjustments. If laboratory results are not up-to-date, possibly a new blood sample needs to be taken. This can be considered as regular care. Once the review is done, a report about adjustments in the medication regimen must be written to the current healthcare providers of the patient. Furthermore, the new medication regimen should be discussed to the patient and an explanation about the use of (new) medicines should be given. It means that the pharmacist will inform the patient about the results of the structured medication review. Therefore, it is necessary that the patient will be consulted at the pharmacy. In case of no or only a few little changes in the medication regime, the pharmacist may decide to call the patient to explain the changes. Within four months, pharmacists will call the patients to evaluate the adjustments.

The follow-up measurements will take place after three months and six months to measure what effects occur in the intervention group and the control group. It means that the participants need to complete the postal mailed questionnaires before the intervention once, and two times afterwards. Each participating patient will receive a code that will be saved in an Access database: the recorded data are only identifiably by the researcher.

An overview of the prospective process for each patient during the study can be found on the following page in figure 1.
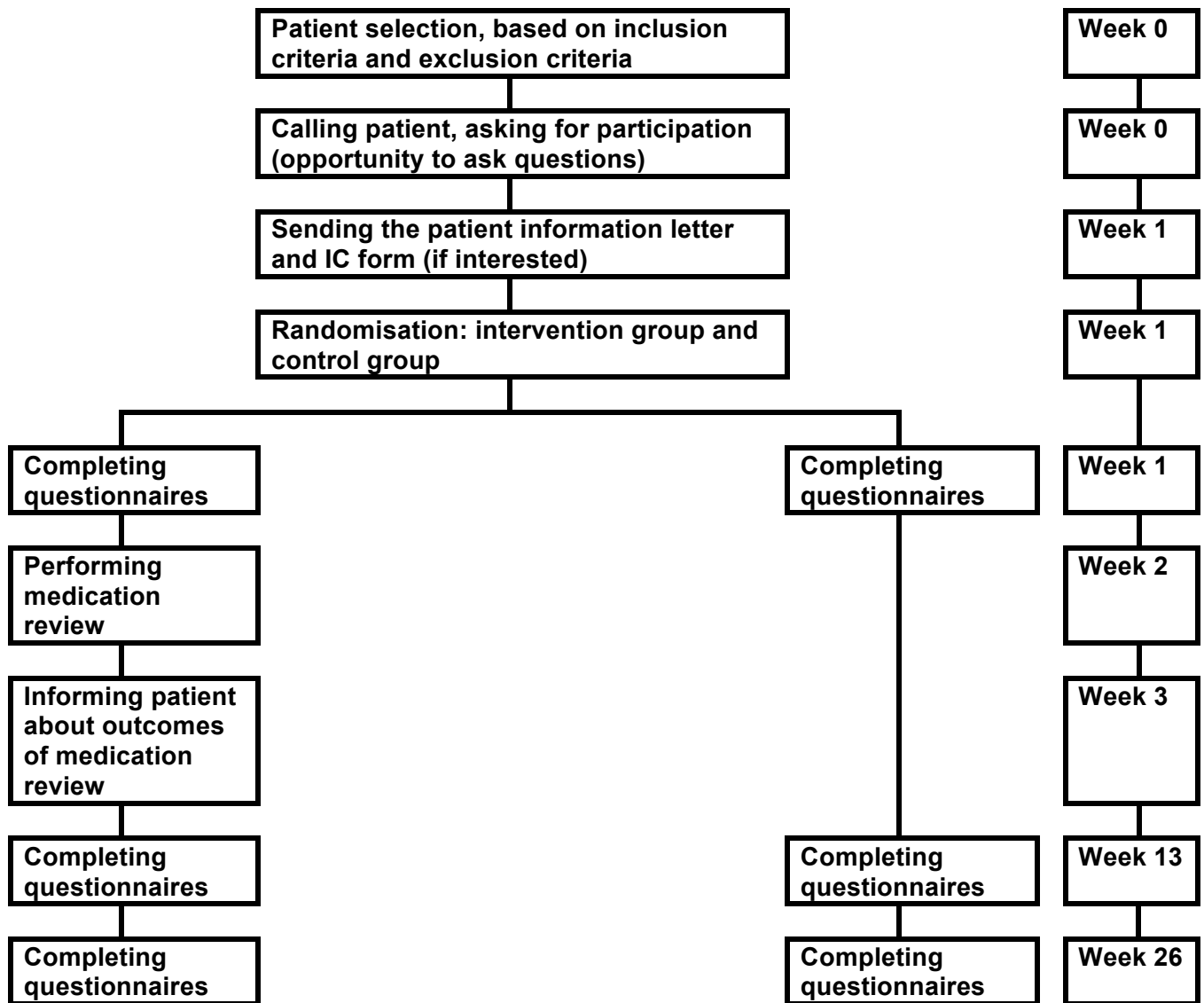
```
┌─────────────────────────────────┐        ┌──────────┐
│ Patient selection, based on     │        │ Week 0   │
│ inclusion criteria and          │        │          │
│ exclusion criteria              │        │          │
└─────────────────────────────────┘        └──────────┘
┌─────────────────────────────────┐        ┌──────────┐
│ Calling patient, asking for     │        │ Week 0   │
│ participation (opportunity to   │        │          │
│ ask questions)                  │        │          │
└─────────────────────────────────┘        └──────────┘
┌─────────────────────────────────┐        ┌──────────┐
│ Sending the patient information │        │ Week 1   │
│ letter and IC form              │        │          │
│ (if interested)                 │        │          │
└─────────────────────────────────┘        └──────────┘
┌─────────────────────────────────┐        ┌──────────┐
│ Randomisation: intervention     │        │ Week 1   │
│ group and control group         │        │          │
└─────────────────────────────────┘        └──────────┘

┌──────────────┐          ┌──────────────┐  ┌──────────┐
│ Completing   │          │ Completing   │  │ Week 1   │
│ questionnaires│         │ questionnaires│ │          │
└──────────────┘          └──────────────┘  └──────────┘
┌──────────────┐                             ┌──────────┐
│ Performing   │                             │ Week 2   │
│ medication   │                             │          │
│ review       │                             │          │
└──────────────┘                             └──────────┘
┌──────────────┐                             ┌──────────┐
│ Informing    │                             │ Week 3   │
│ patient      │                             │          │
│ about        │                             │          │
│ outcomes of  │                             │          │
│ medication   │                             │          │
│ review       │                             │          │
└──────────────┘                             └──────────┘
┌──────────────┐          ┌──────────────┐  ┌──────────┐
│ Completing   │          │ Completing   │  │ Week 13  │
│ questionnaires│         │ questionnaires│ │          │
└──────────────┘          └──────────────┘  └──────────┘
┌──────────────┐          ┌──────────────┐  ┌──────────┐
│ Completing   │          │ Completing   │  │ Week 26  │
│ questionnaires│         │ questionnaires│ │          │
└──────────────┘          └──────────────┘  └──────────┘
```

Figure 1: Flow chart of the prospective process for each patient during the study

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.

8.5 Replacement of individual subjects after withdrawal

After withdrawal, individual subjects will not be replaced.

8.6 Follow-up of subjects withdrawn from treatment

Subjects that withdraw from the study will be followed according to usual care.

8.7 Premature termination of the study

Premature termination of the study is not foreseen.

9. SAFETY REPORTING

9.1 Section 10 WMO event

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardize the subjects' health. 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. 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 at any dose:
- 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;
- Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardize the subject or may require an intervention to prevent one of the outcomes listed above.

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 15 days after the sponsor has first knowledge of the serious adverse events.

SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur not later than 7 days after the responsible investigator has

first knowledge of the adverse event. This is for a preliminary report with another 8 days for completion of the report.

Due to the disease status and the advanced age of patients with PD included in this study, adverse SAEs as hospitalization and death may occur. Unlikely is that these SAEs are associated with participation in the study. To cover this, a six monthly line listing is proposed to report SAEs.

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Not applicable.

9.3 Annual safety report

If the study will take longer than one year, an annual safety report will be submitted to the accredited METC. This can be combined with the annual progress report (see section 12.4).

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)

A DSMB will not be installed.

10. STATISTICAL ANALYSIS

To assess whether there is a significant difference between the intervention group and the control group in this quantitative research, categorical variables as well as continuous variables will be used to analyze the results. The categorical variables will be analyzed, using a Chi-square test (or Fisher's exact test) to process data that will be presented as numbers with percentages. The continuous variables will be analyzed, using t-tests (or Mann-Whitney test) to process data that will be presented as means with standard deviations (SD) in normal distributions or as medians with interquartile ranges (IQR) in non-normal distributions. For all continuous variables, a repeated measurement analysis will be done to deal with possible missing data.

The approach of modified intention-to-treat analysis will be used, which is based on the initial treatment assignment and not on the treatment eventually received. The reason for it is that there might be time between the randomization and the intervention. This means that participants in the intervention group need to receive the structured medication review after they completed the baseline questionnaires, and that participants in the control group need to complete the baseline questionnaire after randomization to include them in the study. Secondary, per protocol analysis can be done to measure the effects of participants who truly complete the entire trial according to the protocol. Only these participants will be counted towards the final results, because the participants who did not complete the trial according to the protocol may decrease the effects of the intervention and will therefore be excluded.

To determine whether there is a relation between the results over time, measurements will be repeated after three months and six months. The received data will be processed in SPSS version 21 and the quantitative outcomes will be presented in figures and tables. An interim analysis for the power calculation is planned after fifty patients have been included.

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (June 1964, as modified by the 64th World Medical Association, October 2013) and in accordance with the Medical Research involving Human Subjects Act (WMO).

11.2 Recruitment and consent

Potential eligible patients will be identified from appointment schedules and existing database files for patients with PD. While using these databases to identify patients, the investigator is obliged to follow medical confidentially rules. The potential eligible patients will be contacted by telephone about the study and will be asked if they are interested to participate. If this is the case, more information shall be sent by postal mail, which includes a patient information letter with an explanation about the present study, experimental subject information for the caregivers, two IC forms, one for the patient and one for the caregivers, and a standard brochure about medical scientific research. It means that also the personal or home caregiver of the patient with PD will be approached to participate in the study, because the effects of the intervention on their quality of life can be measured. Subsequently, patients and their personal or home caregivers will have the opportunity to ask questions and to sign an IC form at home within one week.

11.3 Objection by minors or incapacitated subjects

Not applicable.

11.4 Benefits and risks assessment, group relatedness

The proposed study is in line with two important issues of the Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie (KNMP) in 2014: 'Medication adherence' and 'Structured medication reviews' (49). This means that these issues are nationwide and current topics. The structured medication review is very unlikely to cause a burden or adverse events within the intervention group. PD patients are very suitable to conduct a structured medication review and to (presumably) improve medication adherence, because patients with PD usually have complicated medication schedules since various medications need to be taken at different doses and at different times of a day (11).

11.5 Compensation for injury

The participating hospital (the MST hospital) has liability insurances. Due to the risk-free nature of the study, a separate Insurance for Clinical Research in Humans is not deemed necessary.

11.6 Incentives

Once the review is done, the new medication regimen should be discussed to the patient and an explanation about the use of (new) medicines should be given. Therefore, it is necessary that the patient will be consulted at the pharmacy. All patients will receive compensation for travelling to their pharmacy once during the study.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

All patients included in the study will be given a subject code number: each participating patient will receive a code that will be saved in an Access database. The recorded data are only identifiably by the researcher. The subject code numbers will identify the subject, and all his / her documents. A subject identification code list can be used to link the data (as name, birth date, time included in the study etcetera) to an individual subject so that the investigator is able to trace data to the subject. The investigator will safeguard the code needed to retrieve the data. This coded data will be handled confidentially, which means that the handling of personal data will comply with the Dutch Personal Data Protection Act (in Dutch: De Wet Bescherming Persoonsgegevens, WBP).

12.2 Monitoring and Quality Assurance

Not applicable.

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

An annual progress report will be submitted to the accredited METC once a year. Information will be provided on the date of the inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events, other problems, and amendments.

12.5 End of study report

The investigator 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. In case the study is ended prematurely, the investigator 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 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

There are no limitations for the researcher concerning the public disclosure and the publication of the research data. The study will be published through a scientific article and will be registered at www.trialregister.nl

13. STRUCTURED RISK ANALYSIS

There are no risks involved for patients participating in the study. The intervention can be considered to be optimal regular care.

14. REFERENCES

1. Dauer W, et al. Parkinson's Disease: Mechanisms and Models. Neuron. 2003 September 11; 39(6): p. 889-909.

2. De Parkinson Vereniging. Onderzoeksrapporten. [Online]; 2013. Available from: *http://www.parkinson-vereniging.nl/onderzoek-en-ontwikkeling/onderzoeksnieuws/publieksenquete-2013/*.

3. Parkinson J. An essay on the shaking palsy London: Whittingham and Rowland; 1817.

4. Jankovic J, et al. Handbook of Parkinson's Disease: Pathophysiology and clinical assessment of motor symptoms in Parkinson's disease. New York; 1992.

5. Chaudhuri KR, et al. Non-motor symptoms of Parkinson's disease: diagnosis and management. The Lancet Neurology. 2006 March; 5(3): p. 235-245.

6. Schulman LM, et al. Non-recognition of depression and other non-motor symptoms in Parkinson's disease. ELSEVIER. 2002 January; 8(3): p. 193-197.

7. Poewe W. Non-motor symptoms in Parkinson's disease. Special Issue: The Scientific and Clinical Basis for Future Therapies in Parkinson's Disease. European Journal of Neurology. 2008 April; 15(s1): p. 14-20.

8. Marsden CD, Parkes JD. 'On-off' effects in patients with Parkinson's Disease on chronic Levodopa therapy. The Lancet Neurology. 1976 February 7; 307(7954): p. 292-296.

9. Leoni O, al e. Drug prescribing patterns in Parkinson's disease: A pharmacoepidemiological survey in a cohort of ambulatory patients. Pharmacoepidemiology & Drug Safety. 2002; 11: p. 149-157.

10. Clarke CE. Has drug therapy changed the natural history of Parkinson's Disease? Journal of Neurology. 2010; 257(2): p. 262-267.

11. Aerts MB, et al. Stand van zaken - Onvoldoende therapietrouw bij ziekte van Parkinson. Nederlands Tijdschrift voor Geneeskunde. 2011; 155(21): p. 967.

12. Tarrants ML, et al. Drug therapies for Parkinson's disease: A database analysis of patient compliance and persistence. The American Journal of Geriatric Pharmacotherapy. 2010; 8(4): p. 374-383.

13. Grosset KA, et al. Medicine-taking behavior: Implications of suboptimal compliance in Parkinson's disease. Mov Disord. 2005; 20: p. 1397-1404.

14. Kulkarni AS, et al. Medication adherence and associated outcomes in medicare health maintenance organization-enrolled older adults with Parkinson's disease. Mov Disord. 2008; 23: p. 359-365.

15. Wei Y, et al. Antiparkinson Drug Use and Adherence in Medicare Part D Beneficiaries With Parkinson's Disease. ELSEVIER, Clinical Therapeutics. 2013 October; 35(10): p. 1513-1525.

16. Schachter M, et al. Deprenyl in the management of response fluctuations in patients with Parkinson's disease on levodopa. Journal of Neurology, Neurosurgery & Psychiatry. 1980 November; 43(11): p. 1016-1021.

17. Olanow CW, et al. An algorithm (decision tree) for the management of Parkinson's disease: Treatment guidelines. Neurology. 2001 June; 56(5): p. S1-S88.

18. Osterberg L, Blaschke T. Adherence to Medication. The New England Journal of Medicine. 2005; 353: p. 487-97.

19. Lawrence AD, et al. Compulsive use of dopamine replacement therapy in Parkinson's disease: reward systems gone awry? The Lancet Neurology. 2003 October; 2(10): p. 595-604.

20. Scheife RT, et al. Impact of Parkinson's disease and its pharmacologic treatment on quality of life and economic outcomes. American Journal of Health System Pharmacy. 2000; 57: p. 953-962.

21. Bainbridge JL, Ruscin, J.M. Challenges of treatment adherence in older patients with Parkinson's disease. Drugs & Aging. 2009; 26(2): p. 145-55.

22. Sabate E. Adherence to long-term therapies: Evidence for action. Geneva, Switzerland: WHO; 2003.

23. Davis KL, et al. Prevalence and cost of medication non-adherence in Parkinson's disease: evidence from administrative claims data. Mov Disord. 2010;25:p.474-80

24. KNMP, AccreDidact. Polyfarmacie. [Online]; 2013. Available from: *elearning.accredidact.nl/nascholingsartikel/t/2013_5_polyfarmacie#eindtoets*.

25. Lemmens LC, Weda, M. RIVM: Polyfarmacie bij kwetsbare ouderen. Inventarisatie van risico's en mogelijke interventiestrategieën. [Online]; 2013. Available from: *http://www.rivm.nl/dsresource?objectid=rivmp:213828&type=org&disposition=inline*.

26. Van Marum RJ, et al. Multidisciplinaire Richtlijn Polyfarmacie bij ouderen. Utrecht; 2012.

27. Montamat SC, Cusack, B. Overcoming problems with polypharmacy and drug misuse in the elderly. Clinics in Geriatric Medicine. 1992 February; 8(1): p. 143-58.

28. Stewart RB, et al. Polypharmacy in the Aged. Drugs & Aging. 1994 June; 4(6): p.449-61

29. Burke LE, et al. Compliance in Healthcare and Research. Armonk, NY: Furtura; 2001.

30. Van Dulmen S, et al. Patient adherence to medical treatment: a review of reviews. BMC Health Services Research. 2007 April 17; 7(55).

31. Shaw J, et al. Task Force on Medicines Partnership. The national Collaborative Medicines Management Service Program & the National prescribing Centre (NPC). Room for review. A guide to medication review. [Online]; 2002. Available from: *http://www.npc.nhs.uk/review_medicines/intro/resources/room_for_review.pdf*.

32. Geurts MM, et al. Medication review and reconciliation with cooperation between pharmacist and general practitioner and the benefit for the patient: a systematic review. British Journal of Clinical Pharmacology. 2012 January 13; 74(1): p. 16-33.

33. Leendertse AJ, et al. Preventing hospital admissions by reviewing medication (PHARM) in primary care: design of the cluster randomized, controlled, multi-centre PHARM-study. BMC Health Services Research. 2011; 11(4): p. 1-13.

34. Krska J, et al. Pharmacist–led medication review in patients over 65: a randomized, controlled trial in primary care. Oxford Journals, Age & Ageing. 2001; 30(3): p. 205-211.

35. Ahmad A, et al. Effect of medication review and cognitive behaviour treatment by community pharmacists of patients discharged from the hospital on drug related problems and compliance: design of a randomized controlled trial. BMC Public Health. 2010; 10(133): p. 1-10.

36. Bloem BR, et al. Multidisciplinaire richtlijn Ziekte van Parkinson. Alphen a/d Rijn; 2010.

37. Marinus J, et al. Health related quality of life in Parkinson's disease: a systematic review of disease specific instruments. Journal of Neurology, Neurosurgery & Psychiatry. 2002; 72: p. 241-248.

38. Holman R, et al. The Academic Medical Center Linear Disability Score (ALDS) item bank: item response theory analysis in a mixed patient population. Health and Quality of Life Outcomes. 2005; 3(1): p. 83.

39. Chaudhuri KR, et al. International multicenter pilot study of the first comprehensive self-completed non-motor symptoms questionnaire for Parkinson's Disease: The NMSQuest study. Mov Disord. 2006; 21(7): p. 916-923.

40. Schrag A, et al. The EQ-5D—a generic quality of life measure—is a useful instrument to measure quality of life in patients with Parkinson's disease. Journal of Neurology, Neurosurgery & Psychiatry. 2000; 69: p. 67-73.

41. Rabin R, et al. EQ-5D: a measure of health status from the EuroQol group. Ann Med. 2001; 33(5): p. 337-343.

42. Morley D, et al. The PDQ-Carer: Development and validation of a summary index score. ELSEVIER, Parkinsonism & Related Disorders. 2013; 19(4): p. 448-449.

43. Hughes AJ, et al. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. Journal of Neurology, Neurosurgery & Psychiatry. 1992; 55(3): p. 181-184.

44. Peto V, et al. Determining minimally important differences for the PDQ-39 Parkinson's Disease Questionnaire. Age and Ageing. 2001; 30: p. 299-302.

45. Schrag A, et al. What contributes to quality of life in patients with Parkinson's disease? Journal of Neurology, Neurosurgery & Psychiatry. 2000; 69(3): p. 308-312.

46. Lindeboom R, et al. Activities of daily living instruments in clinical neurology, optimizing scales for neurologic assessments. Journal of Neurology. 2003; 60: p. 738-742.

47. Hwynn N, et al. The Frequency of Non-motor Symptoms among Advanced Parkinson Patients May Depend on Instrument Used for Assessment. Parkinson's Disease. 2011 May 16.

48. Müller J, et al. Progression of Hoehn and Yahr stages in parkinsonian disorders: A clinicopathologic study. Journal of Neurology. 2000 September 26; 55(6): p. 888-891.

49. KNMP. KNMP Onderzoeksprogramma 2014. [Online]; 2014. Available from: *http://www.knmp.nl/over-de-knmp/wetenschappelijke-sectie-openbaar-apothekers-wso/knmp- onderzoeksprogramma-2014*.