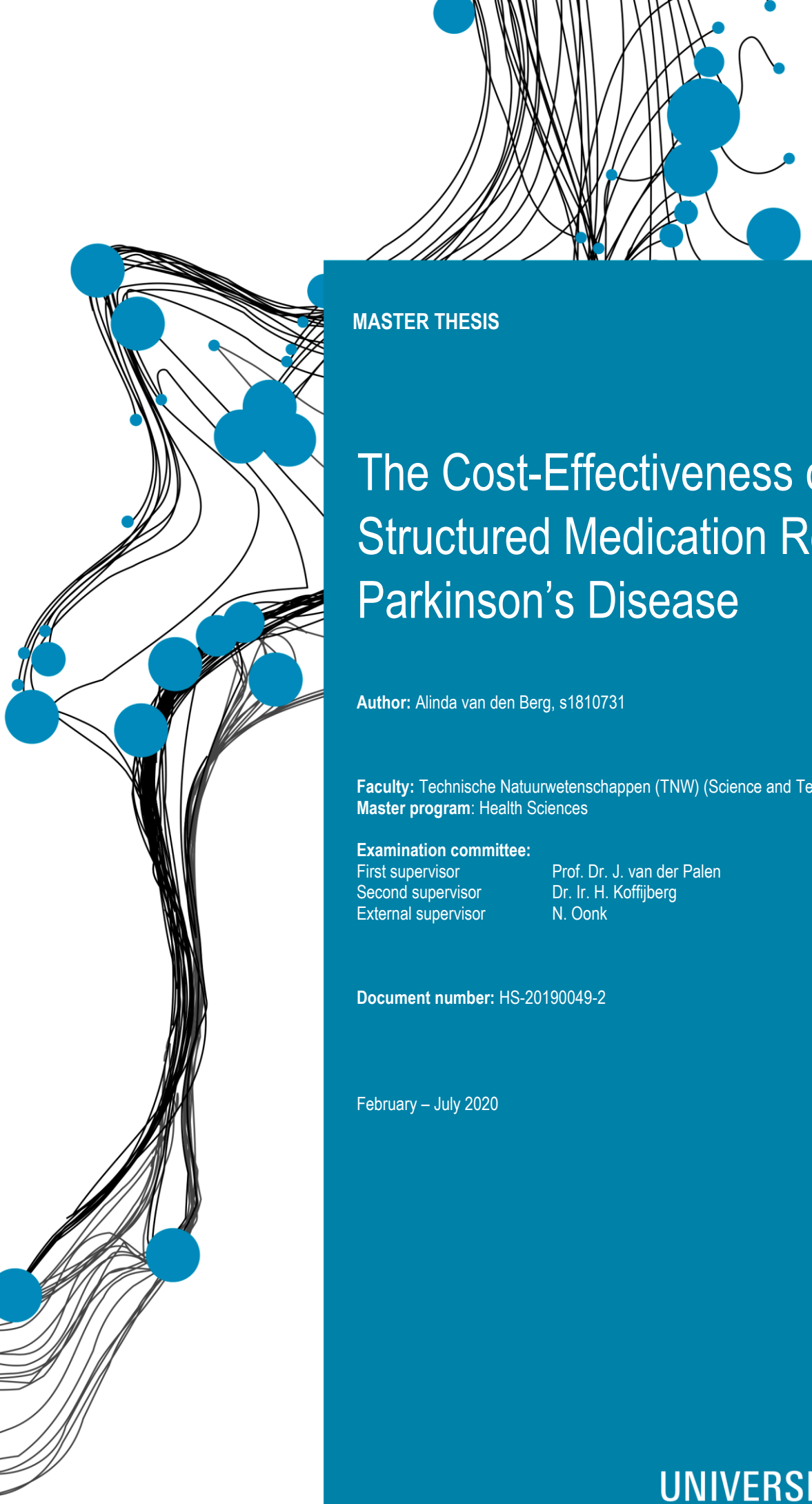

MASTER THESIS

The Cost-Effectiveness of a Structured Medication Review in Parkinson's Disease

Author: Alinda van den Berg, s1810731

Faculty: Technische Natuurwetenschappen (TNW) (Science and Technology)
Master program: Health Sciences

Examination committee:

First supervisor	Prof. Dr. J. van der Palen
Second supervisor	Dr. Ir. H. Koffijberg
External supervisor	N. Oonk

Document number: HS-20190049-2

February – July 2020

UNIVERSITY OF TWENTE.

The Cost-Effectiveness of a Structured Medication Review in Parkinson's Disease

Oonk NGM[a], van den Berg AD[b], van der Palen J[c,d], Movig KLL[e], Dorresteijn LDA[a], Koffijberg H[f]

[a] *Department of Neurology, Medisch Spectrum Twente, Enschede, the Netherlands*
[b] *Department of Science and Technology, University of Twente, the Netherlands*
[c] *Department of Epidemiology, Medisch Spectrum Twente, Enschede, the Netherlands*
[d] *Department of Research Methodology, Measurement, and Data Analysis, University of Twente, Enschede, the Netherlands*
[e] *Department of Clinical Pharmacy, Medisch Spectrum Twente, Enschede, the Netherlands*
[f] *Department of Health Technology and Services Research, University of Twente, the Netherlands*

Abstract

Introduction: Parkinson's disease (PD) causes multiple motor and non-motor impairments. Most PD patients have complex medication regimens with multiple daily doses to control symptoms. A structured medication review (SMR) has shown to be valuable in improving therapy adherence and clinical outcomes in different care settings, but showed no significant improvement in quality of life in PD patients. The cost-effectiveness of an SMR in PD patients is yet still unknown. Therefore, the aim of this study is to determine the cost-effectiveness of performing an SMR in PD patients.

Methods: A cost-effectiveness analysis was performed based on a multicenter randomized controlled trial with 202 PD patients with polypharmacy. The intervention group received an SMR executed by a community pharmacist, whereas the control arm received usual care. The primary outcome of this study is the cost-effectiveness of performing an SMR in PD. The effect of the intervention was presented as incremental Quality Adjusted Life Years (QALYs), measured using the EQ-5D-5L questionnaire. Costs were determined based on real data. Missing data was imputed using multiple imputations techniques. Bootstrapping was used to estimate the uncertainty in all health and economic outcomes.

Results: The incremental QALYs of the intervention group compared to the control group was -0.008 (95%-CI -0.018 to 0.001) and incremental costs were €249 (95%-CI €-120 to €623). Bootstrapping showed that when adapting a willingness-to-pay threshold of €20,000/QALY and €80,000/QALY, the probability of SMRs being cost-effective was 9% and 12%, respectively.

Conclusion: An SMR in PD patients in primary care executed by community pharmacists shows no apparent benefit and is not cost-effective compared to usual care.

Keywords*: Parkinson's disease; therapy adherence; medication review; medication; cost-effectiveness.*

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disease (1) and the prevalence increases steadily with age (2). PD is associated with motor and non-motor impairment (3). The primary cause of these motor symptoms is the degeneration of dopaminergic nigrostriatal neurons. Non-motor symptoms, which impact quality of life severely, consist of a disturbed autonomic function, sleep disorders and neuropsychiatric symptoms. No treatment is available to stop progression of the disease, but drug treatment is available to control symptoms. Nonetheless, as the disease progresses the effect of the medication will decrease, side-effects might occur and a fluctuation in medication response can be present. To control this, more medication or higher doses can be necessary (3).

For this reason, most patients with PD have complex medication regimens with multiple daily doses (4). Study shows that polypharmacy -the use of multiple medications- results in low medication adherence (5). For PD patients, medication non-adherence is shown to vary between 10-67% (6). Non-adherence results in clinical consequences (7), such as sub-optimal

effect of the medication, more increases in drug dosage and substitution of medication. These changes can result in even lower medication adherence. Next to this, low medication adherence also results in an increase in healthcare costs (5).

A structured medication review (SMR) can be performed by a physician, nurse or pharmacist to improve medication adherence (4). It helps to identify problems in the medication regimen and improves the knowledge of patients and adherence to the medication regimen. The aim of an SMR thereby is to improve quality, safety and appropriate use of medicines(8).

The effect of performing SMRs has been studied in multiple healthcare settings and showed positive effects in reducing the amount of potentially inappropriate drugs (9) (10) (11) (12) and drug-related problems (12) (13) (14). Besides, it improved therapy adherence (13) and clinical outcomes (12) (15) (16). Regarding the effect of SMRs in PD patients, varying results were found. A pilot study (17), which investigated the effects of multiple pharmacist-led interventions in PD, showed potential positive effects of SMRs on medication adherence and quality of life. Besides, a recent study in the Netherlands analyzed whether SMRs could be helpful in improving medication adherence and subsequently quality of life and disease control in PD patients(18). This study showed no significant clinical effects. However, SMRs have proven to lower healthcare costs in a different healthcare setting (15). Therefore, SMRs may still be beneficial in terms of cost-effectiveness. Varying results were found on the cost-effectiveness of SMRs (19)(20)(21)(22). Therefore, the objective of this study was to perform a cost-effectiveness analysis of SMRs compared to usual care in PD patients and thereby contribute to the knowledge about improving medication adherence, quality of life and disease control in PD patients.

2. Methods

2.1 Study design

The study on which this cost-effectiveness analysis was based on, was designed as a multicenter randomized controlled trial with six months of follow-up among PD patients with polypharmacy. Patients were included via the neurology department of three different hospitals in the Netherlands (Medisch Spectrum Twente, Ziekenhuisgroep Twente and Isala) from June 2014 until December 2018. More details can be found in the published study protocol (23).

The study was conducted in agreement with the principles of the Declaration of Helsinki (24) and in accordance with the Medical Research Involving Human Subjects Act (25). The research protocol is registered in the Dutch clinical trial register (NL4360) and was approved by the Medical Ethical Review Board Twente, the Netherlands.

2.2 Study population

Inclusion criteria were: (1) diagnosed with PD according to the UK-brain banking criteria (26); (2) ≥ eighteen years of age; (3) ≥ four different medications daily; (4) ≥ four medication intake moments daily; (5) expressing motor and non-motor symptoms; (6) living (semi)-independent in the region of Enschede, Almelo, Hengelo or Zwolle; (7) be able to read and write the Dutch language. Exclusion criteria were: (1) being unable to administer their own medication, e.g. when requiring assistance from medical home care. PD patients receiving help from personal or family caregivers were not excluded based on this criterion; (2) having received a medication review within a year prior to the study; (3) having received a Deep Brain Stimulator, continuous duodopa gastro-intestinal gel therapy or continuous apomorphine therapy within a year before the study or willing to receive this within three months. Based on a significance of 5% and a power of 80%, a sample size of 198 subjects was expected to be needed.

2.3 Intervention and control condition

In the intervention group, an SMR was performed as a one-time assessment by a community pharmacist. An SMR is defined as 'a structured, critical examination of a patients' 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' (12). Pharmacists were offered an accredited training regarding PD, drug treatment, the study protocol and execution of an SMR beforehand. The part regarding the execution of an SMR was based on the Dutch Systematic Tool to Reduce Inappropriate Prescribing (STRIP)-method (27), which is a standardized tool for pharmacists for executing SMRs in Dutch patients. Pharmacists had to record their modifications and recommendations and the amount of time that was invested in the SMR by both the pharmacist and the general practitioner (GP). The control group received care as usual (28) and did not receive an SMR during the six months of study participation.

2.3 Measurements

When informed consent was given by the patient, baseline measurement could take place. After this, patients were randomly assigned in a 1:1 ratio with a blinded blocked randomization with block sizes of four and eight. Inclusion was definite when baseline measurements were completed and, in case of the intervention group, the SMR was performed.

At baseline, three and six months follow-up participants had to fill in the following questionnaires regarding quality of life, disability, non-motor symptoms and health status: EuroQOL-5 Dimensions-5 Levels (EQ-5D-5L), Parkinson's Disease Questionnaire-39 (PDQ-39), Amsterdam Medical Center Linear Disability Scale (ALDS), Non-Motor Symptoms Questionnaire (NMS-Quest) and Visual Analogue Scale (VAS). Regarding baseline characteristics, severity of PD was derived from the Hoehn and Yahr score, which is a staging score that shows an estimate of clinical function in PD (29). Comorbidities were measured using the Rx-Risk comorbidity score, which is a score for the current comorbidities of a patient to predict costs of care and mortality (30).

The primary outcome of this study was the cost-effectiveness of performing an SMR in PD, presented as incremental effect in Quality Adjusted Life Years (QALYs) and as incremental costs of the intervention group compared to the control group (31).

2.3.1 QALYs

QALYs were calculated based on the EQ-5D-5L questionnaire, which is the preferred method for measuring health status according to the National Institute for Health and Care Excellence (32). It is a feasible and valid questionnaire to measure the quality of life of the patients with PD (33), focusing on the following five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The health profiles derived from the questionnaire were converted to utility scores, between 0 (state equivalent to death) and 1 (full health), using the Dutch tariff for the EQ-5D-5L (34). A negative number was possible, when the health state was worse than death (35).

To calculate the QALYs per patient for the follow-up period of six months, the area under the curve of the three utility scores (baseline, three and six months follow-up) was determined per patient.

2.3.2 Costs

Total costs per patient consisted of medication costs, hospital costs and, in case of the intervention group, the costs of performing the SMR. Costs for participants who got lost to follow-up were included when known.

Medication costs were derived at baseline and six months follow-up for each patient. The pharmacists provided for each patient a list of medications. With help of the Health Institute of the Netherlands (ZIN) website for the prices of all medications (36), the medication costs per day were calculated for each patient. In case no information on costs was available on this website, the prices of these drugs in the hospital system of Medisch Spectrum Twente were used. Medication costs for the follow-up period were calculated by multiplying the daily costs at six months follow-up by 183 days, which represents the follow-up period.

The hospital costs made by each patient during six months were collected based on actual costs. A distinction was made between hospitalization and outpatient costs.

The costs of performing the SMR were calculated based on the amount of time the pharmacist and GP needed to prepare for and perform the SMR. The amount of time was multiplied by the standard gross salary per month for a pharmacist and GP with ten years of experience (37). The costs for the accredited training of the pharmacists were not taken into account, since these were only offered in purpose of the study to inform pharmacists and standardize the execution of the SMR.

2.4 Analysis

Two different analysis were performed, a complete case analysis and a multiple imputed analysis. All outcome measures were presented based on multiple imputed data. The multiple imputed analysis was performed in IBM SPSS Statistics 26 to study the robustness of the findings. Missing data was imputed ten times. Predicting values for missing volumes that were needed to calculate costs were: baseline characteristics and data (randomization group, gender, age, disease duration, Hoehn and Yahr score, Rx-Risk score, number of daily medicines, number of daily intake moments, EQ-5D-5L score, medication costs) and follow-up data (number of medicines and medication costs at six months, EQ-5D-5L scores at three and six months, hospitalization costs, outpatient costs, number of hospitalization days). Predicting values for missing EQ-5D-5L scores were: the above-mentioned baseline characteristics, number of medicines at six months, number of hospitalization days, EQ-5D-5L scores at three and six months and PDQ-39 score at baseline, three and six months.

Non-parametric bootstrapping was used to resample the complete case data and the data completed with multiple imputations 5000 times to evaluate the uncertainty in all health and economic outcomes (31). This was done in Microsoft Excel, with the help of the Analysis Toolpak and Analysis Toolpak-VBA. Based on the bootstrap samples, the 95% confidence intervals (CIs) of all outcome measures were determined. Besides, the results were plotted on an incremental cost-effectiveness plane (38), which graphically shows the uncertainty in incremental costs and effects, and in a cost-effectiveness acceptability curve (39), in which the probability that SMRs are cost-effective was evaluated for willingness-to-pay threshold from €0/QALY to €200,000/QALY. In the Netherlands, this threshold ranges from €20,000/QALY to €80,000/QALY, depending on the burden of the disease (40).

An additional analysis was performed where hospital prices were standardized, since the prices for the same treatment differ among hospitals and this could have influenced the results.

3. Results

3.1 Flowchart and descriptive characteristics

A total of 240 participants were included in the study, of which 38 dropped out before baseline measurements could take place. This resulted in a definite inclusion of 202 participants, of which 34 were lost to follow-up. The flowchart is presented in Figure 1. From 50 included participants (25%) data was missing, which meant that 152 participants completed all measurements.

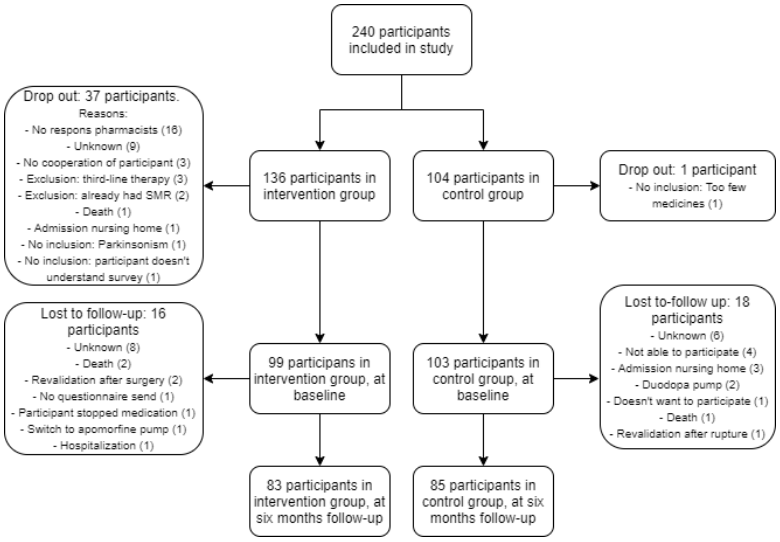

Figure 1. Flowchart of the study

The intervention and control group consisted of 99 and 103 participants, respectively. Baseline characteristics of the study population are presented in Table 1.

Table 1. Baseline characteristics of the study population

	Intervention group (n=99)	Control group (n=103)
Gender (%)		
- Male	55 (56%)	69 (67%)
- Female	44 (44%)	34 (33%)
Age (mean, (SD))	72.5 (8.2)	72.7 (7.0)
Disease duration in years (median, (IQR))	5.9 (3.0; 9.6)	6.3 (3.0; 9.1)
Hoehn and Yahr score (mean, (SD))	2.4 (0.73)	2.4 (0.86)
EQ-5D-5L score (mean, (SD))	0.67 (0.25)	0.67 (0.25)
Number of daily medications (mean, (SD))	7.3 (2.3)	7.4 (2.5)
Number of daily intake moments (median, (IQR))	5.0 (4.0; 6.0)	5.0 (4.0; 6.0)

3.2 Outcome measurements

3.2.1 QALYs

The mean utility score based on the EQ-5D-5L questionnaire in the intervention group was 0.67 at baseline and 0.64 at six months follow-up, which resulted in 0.32 QALYs during the six months follow-up period. For the control group the mean utility score was 0.67 to 0.68 respectively, which resulted in 0.33 QALYs during the six months follow-up period. The incremental QALYs were -0.008 (-0.018;0.001) for the intervention group compared to the control group (Table 2).

Table 2. Utility scores and QALYs for intervention and control group and incremental QALYs

	Intervention group, mean (SE)				Control group, mean (SE)				ΔI-C, mean (95%-CI)
	Baseline	3 months	6 months	QALYs	Baseline	3 months	6 months	QALYs	
EQ-5D-5L	0.67 (0.025)	0.64 (0.026)	0.64 (0.026)	0.32 (0.011)	0.67 (0.025)	0.66 (0.025)	0.67 (0.024)	0.33 (0.011)	-0.008 (-0.018;0.001)

3.2.2 Medication costs

The mean number of daily medications in the intervention group was 7.3 at baseline and 7.5 at six months follow-up. The mean daily costs were €4.21 and €4.17, respectively. For the control group the mean number of medications per day was 7.4 at baseline and 7.7 at six months follow-up. The mean costs were €4.58 and €4.69, respectively. Total medication costs during the six months follow-up were €96 (-164;-25) lower in the intervention group compared to the control group (Table 3).

Table 3. Medication costs

	Intervention group, mean (SE)		Control group, mean (SE)		ΔI-C, mean (95%-CI)
	Baseline	6 months	Baseline	6 months	
Number of daily medications	7.3 (0.23)	7.5 (0.26)	7.4 (0.25)	7.7 (0.25)	-0.13 (-0.24;-0.03)
Daily medication costs	€4.21 (0.63)	€4.17 (0.42)	€4.58 (0.36)	€4.69 (0.46)	€-0.15 (-0.56;0.24)
Total medication costs		€763 (77)		€859 (85)	€-96 (-164;-25)

3.2.3 Hospital costs

The mean number of hospitalization days during the six months follow-up was 1.4 in the intervention group and 1.2 in the control group. Mean hospitalization costs were €1377 and €1296, respectively. The mean outpatient costs were €839 and €62, respectively. Mean total hospital costs were €291 (-65;639) higher in the intervention group compared to the control group (Table 4).

Table 4. Number of hospitalization days and hospital costs

	Intervention group, mean (SE)	Control group, mean (SE)	ΔI-C, mean (95%-CI)
Hospitalization days	1.4 (0.33)	1.2 (0.41)	0.2 (-0.1;0.5)
Hospitalization costs	€1377 (349)	€1296 (429)	€81 (-258;407)
Outpatient costs	€839 (104)	€628 (67)	€212 (135;286)
Total hospital costs	€2216 (372)	€1925 (453)	€291 (-65;639)

3.2.4 SMR costs

The mean time that pharmacists took to perform an SMR was 101 minutes (SE 5.76). With a gross salary of €4684 for a pharmacist, the mean costs were €45.54 (SE 2.60). The mean time that GPs took to perform an SMR was 16 (SE 1.58) minutes. With a gross salary of €5356 for a GP, the mean costs were €8.13 (SE 0.81). In total, the mean costs of performing an SMR were €53.67 (SE 2.97).

3.2.5 Total costs

The mean total costs were €3033 (SE 394) in the intervention group and €2784 (SE 483) in the control group, which was an increase in total costs in the intervention group of €249 (95%-CI €-128 to €614).

3.3 Cost-effectiveness analysis

3.3.1 Complete case analysis

For the complete case analysis ($n_{interventiongroup}$=73, $n_{controlgroup}$=79), the incremental QALYs the intervention group compared to the control group over six months follow-up of were -0.010 (95%-CI -0.044 to 0.023) and incremental costs were €222 (95%-CI €-716 to €1201).

3.3.2 Imputed data analysis

For the imputed data analysis ($n_{interventiongroup}$=99, $n_{controlgroup}$=103), the incremental QALYs of the intervention group compared to the control group over six months follow-up were -0.008 (95%-CI -0.018 to 0.001) and incremental costs were €249 (95%-CI €-120 to €623). Figure 2 shows the incremental cost-effectiveness plane and figure 3 shows the cost-effectiveness acceptability curve. The additional analysis, where prices for all treatments among the different hospitals were standardized, showed similar results.

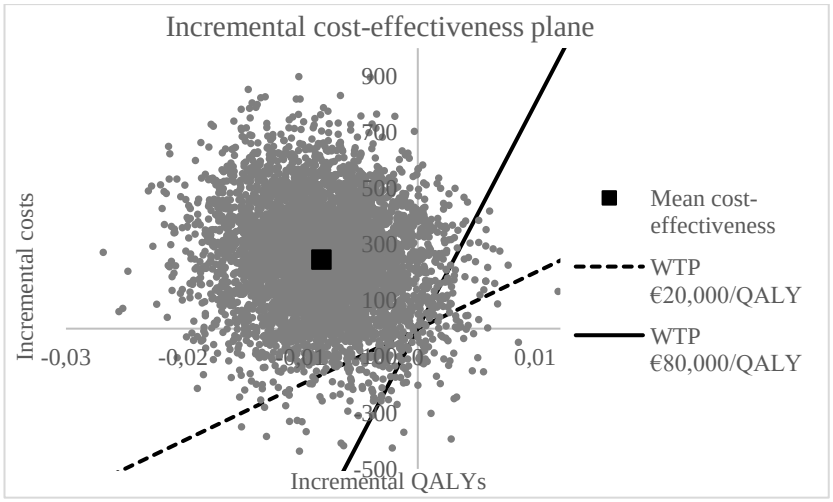

Figure 2. Incremental cost-effectiveness plane for an SMR compared to usual care. The incremental cost-effectiveness plane shows the impact of SMRs compared to usual care, on the difference in QALYs and costs. The willingness-to-pay thresholds of €20,000/QALY and €80,000/QALY are shown. The result is based on 5000 bootstrap samples generated from the multiple imputed data.

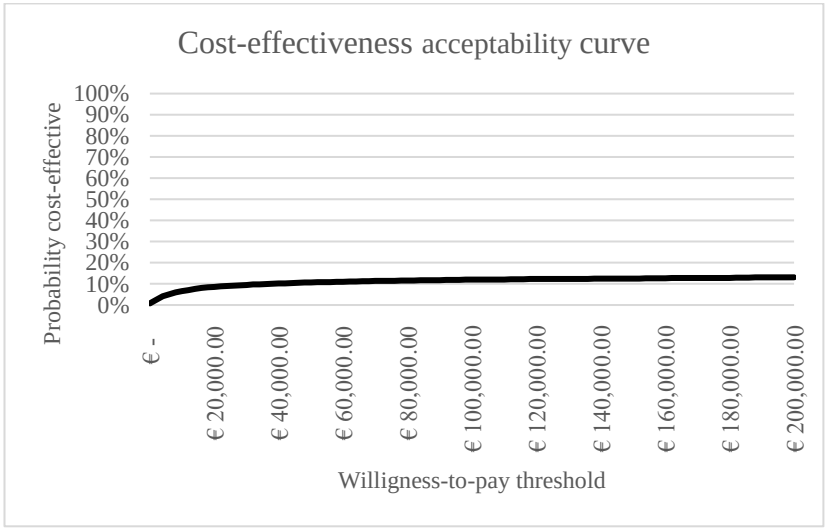

Figure 3. Cost-effectiveness acceptability curve at different willingness-to-pay levels for SMRs compared to usual care, based on 5000 bootstrap samples. The result is based on 5000 bootstrap samples generated from the multiple imputed data.

4. Discussion

4.1 Main findings

The results of the current study indicate that there is no apparent benefit of performing an SMR compared to usual care. This is predominantly based on the similar health outcomes (incremental QALYs of -0.008) and the extra costs of €249 in patients who had an SMR compared to patients with usual care. Thereby, the probability of SMRs being cost-effective was relatively low. When adapting a WTP-threshold of €20,000/QALY and of €80,000/QALY, the probability of SMRs being cost-effective is shown to be 9% and 12%, respectively. Besides, it is worth noting that incremental QALYs and incremental costs were similar for the complete case analysis.

Contrary to our expectations, the costs of the intervention were higher for patients who had an SMR. At first, performing the SMR itself leads to additional costs, but secondly, the increase in outpatient costs for SMR patients can also be a reason for the increasing costs. Regarding the effect of SMRs, one problem may have been that patients were not blinded. This might have led to lower health effects in patients who had an SMR. Patients might have had certain expectations about improvement of health after the SMR and the effect might have been disappointing, resulting in lower utility scores at three and six months follow-up. Blinding however is not possible with this intervention. Moreover, PD patients are in general older, more fragile patients for whom a change in medication regimen can be difficult to adapt to. Next to this, it is likely that there is little to be gained in the field of the medication regimen. In the Netherlands, patients with PD are regularly seen by a specialist, where the effect of the therapy is discussed and more frequently when medication is started or when clinical changes are experienced (28). Therefore, it is likely that the medication regimen of the PD patients is already nearly optimal and an SMR has little effect.

4.2 Relation to other studies

Our study is the first to evaluate the cost-effectiveness of a community pharmacist-led SMR in PD. Nevertheless, studies on the cost-effectiveness and health effects of SMRs exist in other healthcare settings. In terms of cost-effectiveness, results of previous studies were inconclusive. Whereas some studies imply a high probability of SMRs being cost-effective (19) (20), others found contrary results (21) (22). Van der Heijden et al. (22) showed a reduction of drug-related problems, but also an increase in healthcare usage and hospital admissions. The study also showed an increase in healthcare costs for the intervention group of €1654, however not significant. This in line with our study.

Besides, SMRs have proven to be effective in improving health outcomes (9) (10) (11) (12) (13) (14) (15) (16) (17), which is in contrast with our study. It is worth mentioning that most of these studies did not use clinical outcomes, but instead used the number of drug-related problems (12) (13) (14) or number of potentially inappropriate drugs (9) (10) (11) (12) to measure health effects. A few used questionnaire data as a secondary measurement (16) (17), but showed no significant differences in health status based on the questionnaires. This means that performing an SMR probably does not significantly change quality of life, but does have positive effects in reducing the number of drug-related problems and potentially inappropriate drugs. This may explain the difference in findings on effects of previous studies and our study. Therefore, it may be worth to study the (cost-) effectiveness of an SMR by using the amount of drug-related problems and potentially inappropriate drugs as outcome measures.

4.3 Strengths and limitations

One strength of our study is that patients from three different hospitals and 82 different pharmacies were included, which supports the generalizability of the study. This generalizability is further supported by the number of patients included in the study. The aimed sample size of 198 was reached. Furthermore, randomization reduced the chance of selection bias. Standardization of the execution of the SMR was assured by training the pharmacists beforehand. This may also have positively affected the quality of the SMR by increasing the knowledge regarding PD, drug treatment and execution of an SMR. However, the training may also have influenced the cost-effectiveness results, since it is not standard when performing SMRs. In addition, one or more data on costs or EQ-5D-5L scores from 50 out of 202 (25%) patients were missing. To avoid bias, an imputed analysis was performed where missing data was imputed using multiple imputations. Besides, the follow-up period of six months may have been too short to observe the intervention's full effect. Zermansky and Silcock (20) suggests a period of at least one year to determine economic effects and a period of five to ten years to measure health effects. A period of five to ten years, however, may not be possible for patients with PD, since this is in general an old and fragile population. In addition, costs were not recorded for all participants at the same time, since data collection took five years in total. It is likely that usual care changed over the years, as well as medication and hospital prices. Therefore, prices for medication were standardized. Besides, an additional analysis was performed where hospital prices were standardized, but this showed similar results.

4.4 Implications

The results of our study indicate that SMRs executed by community pharmacists have no apparent benefit for PD patients. Taking into account both the pharmacist's effort and additional costs when performing an SMR in this current setting, the valuable time of a pharmacist could better be spent on more (cost-)effective interventions. Though, SMRs may not be apparently cost-effective in terms of improving quality of life, but can have other positive effects, such as reducing the number of drug-related problems. It may be worth for future studies to include these outcomes into the cost-effectiveness analysis. Besides, additional research can be performed on finding out if SMRs could be cost-effective in specific PD patients.

5. References

1. Schapira AHV. Chapter 71 - PARKINSON'S DISEASE. In: Neurology and Clinical Neuroscience. Elsevier; 2002. p. 927–60.
2. Pringsheim T, Jette N, Frolkis A, Steeves TDL. The prevalence of Parkinson's disease: A systematic review and meta-analysis. Mov Disord. 2014 Nov 1;29(13):1583–90.
3. Sveinbjornsdottir S. The clinical symptoms of Parkinson's disease. J Neurochem. 2016 Oct 1;139:318–24.
4. Richy FF, Pietri G, Moran KA, Senior E, Makaroff LE. Compliance with pharmacotherapy and direct healthcare costs in patients with parkinson's disease: A retrospective claims database analysis. Appl Health Econ Health Policy. 2013 Aug 7;11(4):395–406.
5. Aerts MB, van der Eijk M, Kramers K, Bloem BR. Insufficient medication compliance in Parkinson's disease. Ned Tijdschr Geneeskd. 2011;155:A3031.
6. Malek N, Grosset DG. Medication adherence in patients with Parkinson's disease. CNS Drugs. 2014 Oct 19;29(1):47–53.
7. Grosset D. Therapy adherence issues in Parkinson's disease. J Neurol Sci. 2010 Feb 15;289(1–2):115–8.
8. Blenkinsopp A, Bond C, Raynor DK. Medication reviews. Br J Clin Pharmacol. 2012 Oct 1;74(4):573–80.
9. Scheifes A, Egberts TCG, Stolker JJ, Nijman HLI, Heerdink ER. Structured Medication Review to Improve Pharmacotherapy in People with Intellectual Disability and Behavioural Problems. J Appl Res Intellect Disabil. 2016 Jul 1;29(4):346–55.
10. Hurmuz MZM, Janus SIM, van Manen JG. Changes in medicine prescription following a medication review in older high-risk patients with polypharmacy. Int J Clin Pharm. 2018 Apr 1;40(2):480–7.
11. Cooper JA, Cadogan CA, Patterson SM, Kerse N, Bradley MC, Ryan C, et al. Interventions to improve the appropriate use of polypharmacy in older people: a Cochrane systematic review. BMJ Open. 2015 Dec 9;5(12):e009235.
12. Clyne W, Blenkinsopp A, Seal R. A Guide to Medication Review [Internet]. 2008 [cited 2020 Mar 4]. Available from: http://www.cff.org.br/userfiles/52 - CLYNE W A guide to medication review 2008.pdf
13. Viswanathan M, Kahwati LC, Golin CE, Blalock SJ, Coker-Schwimmer E, Posey R, et al. Medication therapy management interventions in outpatient settings: A systematic review and meta-analysis. JAMA Intern Med. 2015 Jan 1;175(1):76–87.
14. Vinks THAM, Egberts TCG, De Lange TM, De Koning FHP. Pharmacist-based medication review reduces potential drug-related problems in the elderly: The SMOG controlled trial. Drugs and Aging. 2009 Aug 31;26(2):123–33.
15. Jokanovic N, Tan EC, Sudhakaran S, Kirkpatrick CM, Dooley MJ, Ryan-Atwood TE, et al. Pharmacist-led medication review in community settings: An overview of systematic reviews. Vol. 13, Research in Social and Administrative Pharmacy. Elsevier Inc.; 2017. p. 661–85.

16. Krska J, Cromarty JA, Arris F, Jamieson D, Hansford D, Duffus PRS, et al. Pharmacist-led medication review in patients over 65: a randomized, controlled trial in primary care. Age Ageing. 2001;30(3):205–11.
17. Stuijt C, Karapinar-Çarkit F, van den Bemt B, van Laar T. Effect of Pharmacist-Led Interventions on (Non)Motor Symptoms, Medication-Related Problems, and Quality of Life in Parkinson Disease Patients. Clin Neuropharmacol. 2018 Jan 1;41(1):14–9.
18. Oonk NGM. -.
19. Jódar-Sánchez F, Malet-Larrea A, Martín JJ, García-Mochón L, Puerto López del Amo M, Martínez-Martínez F, et al. Cost-Utility Analysis of a Medication Review with Follow-Up Service for Older Adults with Polypharmacy in Community Pharmacies in Spain: The conSIGUE Program Key Points for Decision Makers. Pharmacoeconomics.
20. Zermansky AG, Silcock J. Is Medication Review by Primary-Care Pharmacists for Older People Cost Effective? A Narrative Review of the Literature, Focusing on Costs and Benefits.
21. Pacini M, Smith RD, Wilson ECF, Holland R. Home-based medication review in older people: Is it cost effective? Pharmacoeconomics. 2007 Sep 22;25(2):171–80.
22. Van Der Heijden AAWA, De Bruijne MC, Nijpels · Giel, Hugtenburg JG. Cost-effectiveness of a clinical medication review in vulnerable older patients at hospital discharge, a randomized controlled trial. Int J Clin Pharm. 2019;41(3):963–71.
23. Oonk NGM, Movig KLL, Munster EM, Koehorst-Ter Huurne K, van der Palen J, Dorresteijn LDA. The effect of a structured medication review on quality of life in Parkinson's disease: The study protocol. Contemp Clin Trials Commun. 2019 Mar 1;13.
24. General Assembly of the World Medical Association. World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects - PubMed. J Am Coll Dent. 2014;81(3):14–8.
25. Overheid. Regeling - Wet medisch-wetenschappelijk onderzoek met mensen - BWBR0009408 [Internet]. 2020 [cited 2020 Feb 20]. Available from: https://wetten.overheid.nl/BWBR0009408/2020-01-01
26. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: A clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry. 1992;55(3):181–4.
27. Verduijn M, Leendertse A, Moeselaar A, De Wit N, Van Marum R. Multidisciplinaire richtlijn Polyfarmacie bij ouderen. Huisarts Wet. 2013 Aug 22;56(8):414–9.
28. Specialisten FM. Optimale follow-upfrequentie bij ZvP - Richtlijn - Richtlijnendatabase [Internet]. 2010 [cited 2020 Jun 2]. Available from: https://richtlijnendatabase.nl/richtlijn/ziekte_van_parkinson/diagnosestelling_ziekte_van_parkinson/optimale_follow-upfrequentie_bij_zvp.html
29. Goetz CG, Poewe W, Rascol O, Sampaio C, Stebbins GT, Counsell C, et al. *Movement* Disorder Society Task Force report on the Hoehn and Yahr staging scale: Status and recommendations The *Movement* Disorder Society Task Force on rating scales for Parkinson's disease. Mov Disord. 2004 Sep 1;19(9):1020–8.
30. Vitry A, Wong SA, Roughead EE, Ramsay E, Barratt J. Validity of medication-based co-morbidity indices in the Australian elderly population. Aust N Z J Public Health. 2009 Apr 1;33(2):126–30.
31. Zorginstituut Nederland. Richtlijn voor het uitvoeren van economische evaluaties in de gezondheidszorg. 2016.
32. National Institute for Health and Care Excellence. Guide to the methods of technology Guide to the methods of technology appraisal 2013. Process and methods. 2013.
33. Schrag A, Selai C, Jahanshahi M, Quinn NP. 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.
34. Versteegh M, M. Vermeulen K, M. A. A. Evers S, de Wit GA, Prenger R, A. Stolk E. Dutch Tariff for the Five-Level Version of EQ-5D. Value Heal. 2016 Jun 1;19(4):343–52.
35. Neumann, P.J., Ganiats, T. G., Russell, L. B., Sanders, G. D., & Siegel JE. Cost-Effectiveness in Health and Medicine. Second. New York, USA: Oxford University Press;
36. Zorginstituut Nederland. Medicijnkosten [Internet]. 2020 [cited 2020 Feb 20]. Available from: https://www.medicijnkosten.nl/
37. Loonwijzer.nl. Salarischeck [Internet]. [cited 2020 Feb 20]. Available from: https://loonwijzer.nl/salaris/salarischeck#/
38. Black WC. The CE Plane: A Graphic Representation of Cost-Effectiveness. Med Decis Mak. 1990;10(3):212–4.
39. Fenwick E, O'Brien BJ, Briggs A. Cost-effectiveness acceptability curves - Facts, fallacies and frequently asked questions. Health Econ. 2004 May;13(5):405–15.
40. Brown H. Cost-effectiveness in practice. Geriatr Med. 2008;38(9):449.