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ORIGINAL ARTICLE

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Cost-utility and cost-effectiveness analysis of a clinical medication review focused on personal goals in older persons with polypharmacy compared to usual care: Economic evaluation of the DREAMeR study

Sanne Verdoorn[1,2] | Jeroen van de Pol[1] | Anke M. Hövels[1] | Henk-Frans Kwint[2] | Jeanet W. Blom[3] | Jacobijn Gussekloo[3,4] | Marcel L. Bouvy[1,2]

[1]Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, The Netherlands

[2]SIR Institute for Pharmacy Practice and Policy, Leiden, The Netherlands

[3]Department of Public Health and Primary Care, Leiden University Medical Center, Leiden, The Netherlands

[4]Department of Internal Medicine, section Gerontology and Geriatrics, Leiden University Medical Center, Leiden, The Netherlands

Correspondence
Sanne Verdoorn, Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, the Netherlands, SIR Institute for Pharmacy Practice and Policy. Leiden, the Netherlands.
Email: s.verdoorn@apotheekhoogland.nl

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Aims: The ageing society may lead to increasing healthcare expenditure. A clinical medication review (CMR) could potentially reduce costs. The aim of this study is to perform a cost-utility and cost-effectiveness analysis from a societal perspective of a patient-centred CMR.

Methods: A trial-based cost-utility and cost-effectiveness analysis was performed as part of the DREAMeR study, a pragmatic controlled trial that randomised patients aged ≥70 years using at least seven drugs to either CMR or usual care. Over six months, healthcare consumption and drug use were collected to estimate costs, and effects were collected in terms of quality-adjusted life years (QALYs) measured with EQ-5D-5 L and EQ-VAS and as reduced health-related complaints with impact on patients' daily lives.

Results: The total mean costs per patient (n = 588) over six months were €4,189 ± 6,596 for the control group (n = 294) and €4,008 ± 6,678 for the intervention group (n = 294), including estimated intervention costs of €199 ± 67, which resulted in a mean incremental total cost savings of €181 for the intervention group compared to the control group. Compared to the control group, for the intervention group, the mean incremental QALYs over six months were: −0.00217 measured with EQ-5D and 0.003 measured with EQ-VAS. The incremental effect of reduced health-related complaints with impact was −0.34. There was a likelihood of >90% that the intervention was cost-saving.

Conclusions: The benefits of a patient-centred CMR were inconsistent with no benefits on HR-QoL measured with EQ-5D-5 L and small benefits on HR-QoL measured with EQ-VAS and health-related complaints with impact on patients' daily lives. Additionally, a CMR could potentially be cost saving from a societal perspective.

KEYWORDS
clinical medication review, cost-effectiveness, older persons, polypharmacy, primary care, randomised controlled trial

Sanne Verdoorn and Jeroen van de Pol are equal contributions. Marcel L. Bouvy is the Principal investigator.

1 | INTRODUCTION

In most developed countries the number of older people with multimorbidity and chronic medication use is expected to continue to rise in the coming decades.[1] The chronic use of multiple drugs may lead to drug-related problems (DRPs) and inappropriate prescribing.[2,3] This may have a large impact on healthcare expenditure and is a major challenge for the upcoming years.[4–8] To reduce DRPs and to prevent people from medication-related hospital admissions, guidelines recommend a regular review of medication use by clinical medication reviews (CMR).[9] A CMR is 'a structured critical examination of patient's medicines with the objective of reaching an agreement with the patient about treatment, optimising the impact of medicines, minimising the number of DRPs and reducing waste'.[10] It has a multidisciplinary approach and the patient, physician and pharmacist are involved.

There is abundant evidence on the effectiveness of CMRs regarding the reduction of DRPs. Moreover, several studies have shown positive effects on intermediate outcomes, such as LDL-cholesterol, HbA1c or hypertension. The evidence for effects on more clinically relevant outcomes, such as pain-scores, falls, hospital admissions, health-related quality of life (HR-QoL) and on cost savings is limited.[11–19] A CMR may reduce healthcare expenditures, but a CMR itself is labour intensive and could therefore contribute to a further rise in healthcare costs. For studies to measure the cost-effectiveness of CMR, they should ideally measure HR-QoL and estimate quality-adjusted life years (QALYs).[20] However, many interventions that are performed during CMR are unlikely to improve HR-QoL for the short term (e.g. starting statins or acetylsalicylic acid as primary or secondary prevention will not increase HR-QoL on a time horizon of six months).

We expect that more specific attention to older patient's preferences, personal goals and complaints related to their health and medication during a CMR can potentially increase their HR-QoL. The 'Drug use Reconsidered in the Elderly using goal Attainment scales during Medication Review' (DREAMeR) study was designed based on these assumptions to assess the clinical and economic impact of a CMR for older persons (≥ 70 years) using at least seven drugs in primary care. The aim of this economic analysis is to perform a cost-utility and cost-effectiveness analysis from a societal perspective of this patient-centred CMR focused on patient's preferences, personal goals and complaints, compared to usual care.

2 | METHODS

2.1 | Design and setting

This study was a trial-based cost-effectiveness and cost-utility analysis of the DREAMeR study (Netherlands Trial Register; NTR5713, http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=5713). The design, conduct and reporting of this analysis adheres to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) and International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidelines.[20–22] The DREAMeR study was a pragmatic randomised controlled trial (RCT) performed in 35 community pharmacies of the franchise formula Service Apotheek and collaborating general practices in the Netherlands.[23] The target population comprised patients aged 70 years and over using seven or more chronic drugs. The selected pharmacists were accredited and experienced with CMRs. Pharmacists received a day of training before the start of the study, where they were instructed on all aspects of the study. The general practitioners (GPs) were informed by the pharmacists about the study. Participants were recruited by their community pharmacists. First, the pharmacists screened all their patients by the inclusion criteria. Then the pharmacists sent the lists with the selected patients to patients' GPs. The GPs judged the patients on the exclusion criteria. An anonymised list was then sent to the researcher to randomly assign 50 patients per pharmacy who would be invited first. These patients were subsequently invited by letter and/or telephone consultation by their pharmacist. Randomisation of participants to the intervention or control group was carried out at patient level and performed after recruitment of the participants. Block randomisation per pharmacy using a computer-generated list of random numbers was applied by the researcher to obtain equal numbers of persons per pharmacy per group. A block consisted of the number of patients who agreed to participate in a pharmacy. The study design, study protocol, procedure and informed consent were approved by the Medical Ethics Committee of the University Medical Centre of Utrecht (protocol number 15/737). Participation was voluntary and all participants have signed informed consent. The full study protocol of this RCT has been published elsewhere.[23]

2.2 | Intervention and comparator

The intervention was a CMR with a patient-centred approach, focused on patient's preferences, personal goals and health-related complaints. The CMRs were performed according to a structured method described in the Dutch multidisciplinary guideline 'Polypharmacy in the elderly'.[9] Before the start of the CMR, questionnaires were completed about health-related complaints which could be used as input for the pharmacist. In addition, proposing personal goals together with patients was new in this study. The pharmacist discussed all aspects (e.g. effectiveness, safety and practical issues) of the drugs in use. Subsequently the pharmacist discussed the personal goals, preferences and other DRPs with the GP during a personal conversation. Recommendations were proposed in a pharmaceutical care plan, which was then discussed with the patient. Actions that both the patient, GP and pharmacist agreed upon were implemented gradually and two follow-up moments were scheduled (within approximately three months) to evaluate the attainment of goals and the agreed-upon actions. The pharmaceutical care plan was adjusted when needed. Patients in the control group received usual care and were scheduled to receive a CMR after the study had finished (postponed intervention).

2.3 | Effects

The primary outcome measures in the DREAMeR study were HR-QoL and the number of health-related complaints per patient with moderate to severe impact on the patient's daily life. Health-related quality of life was measured with the Dutch version of the EQ-5D-5 L and EQ-VAS.[24] These outcome measures were collected through written questionnaires at baseline, 3 months and 6 months. Questionnaires were sent to patients by the pharmacists, but completed independently by the patients. If in need of assistance, patients could obtain help from an independent research assistant. All questionnaires were recorded in duplicate by two independent research assistants to enable checks on registration mistakes. The EQ-5D-5 L describes health status in terms of five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Scores on these five domains were used to estimate health utility values with the use of the Dutch EQ-5D-5 L tariff, which ranges from −0.329 (less than death) to 1 (indicating best possible health status).[25] In addition, the EQ-VAS was used to measure a person's health status with scores ranging from 0–100, in which 0 indicates the worst and 100 indicates the best possible health status. In this economic analysis, the effects were determined with QALYs. The QALYs were calculated with the health utility values from the EQ-5D-5 L and EQ-VAS using linear interpolation between time points. Within the time horizon of the study (6 months), the maximum number of QALYs that a patient could gain was 0.5.

2.4 | Health-related complaints

Health-related complaints were measured with a written questionnaire[23] and were based on the most common complaints in older people and the most common side effects of drugs.[23,26] Twelve complaints, e.g. pain, dizziness and stomach problems, were registered. The severity of these complaints was measured on a visual analogue scale (VAS), with a range from 0 to 10, and influence on a patient's daily life with a 5-point Likert scale. To add clinical relevance, a health-related complaint with moderate to severe impact on patient's daily life was defined as the following: a severity score with VAS ≥ 5 and influence on daily life of moderate, severe or extreme (≥ 3 points on a 5-point Likert scale).[27] Effectiveness was determined as the number of reduced health-related complaints with impact per patient 6 months after the study period.

2.5 | Costs

2.5.1 | Identification

This study evaluated costs from a societal perspective. Healthcare costs were divided into direct costs and indirect costs. Direct healthcare costs included healthcare consumption and drug costs measured in the RCT. Indirect healthcare costs included informal care maximised to 16 hours per day. Productivity costs were not included given that all patients were expected to be retired as they are all older than 70 years.

2.5.2 | Measurement

Healthcare consumption was measured with the Dutch Medical Consumption (iMTA) Questionnaire including an extra question about informal care through telephone assessments performed by independent study assistants at baseline and 3 and 6 months after the start date.[28] Data were collected at each time point about the previous 3 months. Total healthcare costs were divided into six different categories: (1) drugs; (2) primary care, including GP, practice nurse, physiotherapist and other visits; (3) secondary care, including emergency department visits, hospital admissions and visits to physicians at outpatient clinics; (4) institutional care, including day visits and admissions to rehabilitation clinics, psychiatric wards and nursing homes; (5) home care, including housekeeping and nursing; and (6) informal care. Informal care was measured by asking patients the amount of time they had received informal care for the past 3 months. Drug dispensing records were collected from the pharmacy information systems to calculate drug costs during the study period of 6 months. To measure the time spent for the CMR, all pharmacists were asked to record the average time spent for every step of the medication review process, including patient interview, DRP analysis, conversation with GP and follow-up and monitoring. In addition, the time spent by the pharmacy technician during the CMR process was recorded.

2.5.3 | Valuation

Healthcare utilisation was valued according to guidelines for economic evaluation in healthcare in the Netherlands.[29] Informal care was valued according to iMTA (Medical Technology Assessment) at €14 per hour (2014 prices) and was indexed to 2017 prices. The amount of time for informal care was maximised at 16 hours per day. Drug costs were presented in 2017 euros. Prices from previous years were updated according to the Dutch consumer price index.[30] The costs of the intervention were calculated by multiplying the time spent by the pharmacist, pharmacy technician and GP with the average wage of these healthcare providers based on an earlier report presenting costs associated with a CMR.[31]

2.5.4 | Analysis

Descriptive statistics were used to describe patient characteristics. Costs were calculated over the 6 month period. To account for missing data in effects and costs (e.g. due to patients not being reachable), the method of multiple imputations was used to generate ten imputed data sets with predictive mean matching, assuming that the data were missing at random.

The effectiveness of the intervention was expressed in estimators that are important for patients' daily lives, namely HR-QoL and health-related complaints with an impact on patient's daily life. Results of the cost-effectiveness analysis were expressed in terms of the incremental cost effectiveness ratio (ICER) 6 months after the intervention. These ICERs were calculated for all three outcomes: (1) costs/QALY measured with EQ-5D health utility values, (2) costs/QALY measured with EQ-VAS scores, and (3) costs/reduced complaint with impact.

The total costs included drug costs, all healthcare costs including informal care and intervention costs, calculated over 6 months from the start date of the study. In order to analyse the uncertainty of the ICER results, we performed a probabilistic sensitivity analysis (PSA) with 1000 replications with gamma distributions for all costs and health-related complaints with impact, a normal distribution for health utility values and a beta distribution for EQ-VAS scores. The resulting 1000 replicates were plotted on the cost-effectiveness plane and used to construct a cost-effectiveness acceptability curve. The graphical presentation of the cost-effectiveness is presented as the difference in costs on the vertical axis and the difference in effects on the horizontal axis. Deterministic sensitivity analyses (DSA) were conducted for all different cost parameters to test the robustness of the analyses. Estimates for all different types of costs in both groups were varied between their 95% confidence intervals to assess the confidence. The resulting ranges of costs are presented in a tornado plot. Base case analysis shows unadjusted values. An additional analysis, in which data were adjusted for baseline costs and utility simple linear regression, is presented in the supplementary methods.

The data were analysed using IBM SPSS Statistics 24.0 (IBM Corporation, Armonk, NY, USA) and Microsoft Office Excel and Access 2013 (Microsoft Corporation, Redmond, WA, USA).

3 | RESULTS

In total, 629 patients of the DREAMeR study were randomised into control (n = 314) or intervention (n = 315) groups. Over six months, the total drop-out rate was 6.7% in the intervention group and 6.4% in the control group (p = 0.88). Costs and effects could not be obtained for 41 participants, who were excluded from the results (see Figure 1). In total, 588 patients were analysed for this study (294 in both groups). Baseline demographics of the participants in both groups are shown in Table 1.

3.1 | Intervention

The CMR process was divided into different steps and the average time spent per step is shown in Table 2. The mean time (and standard

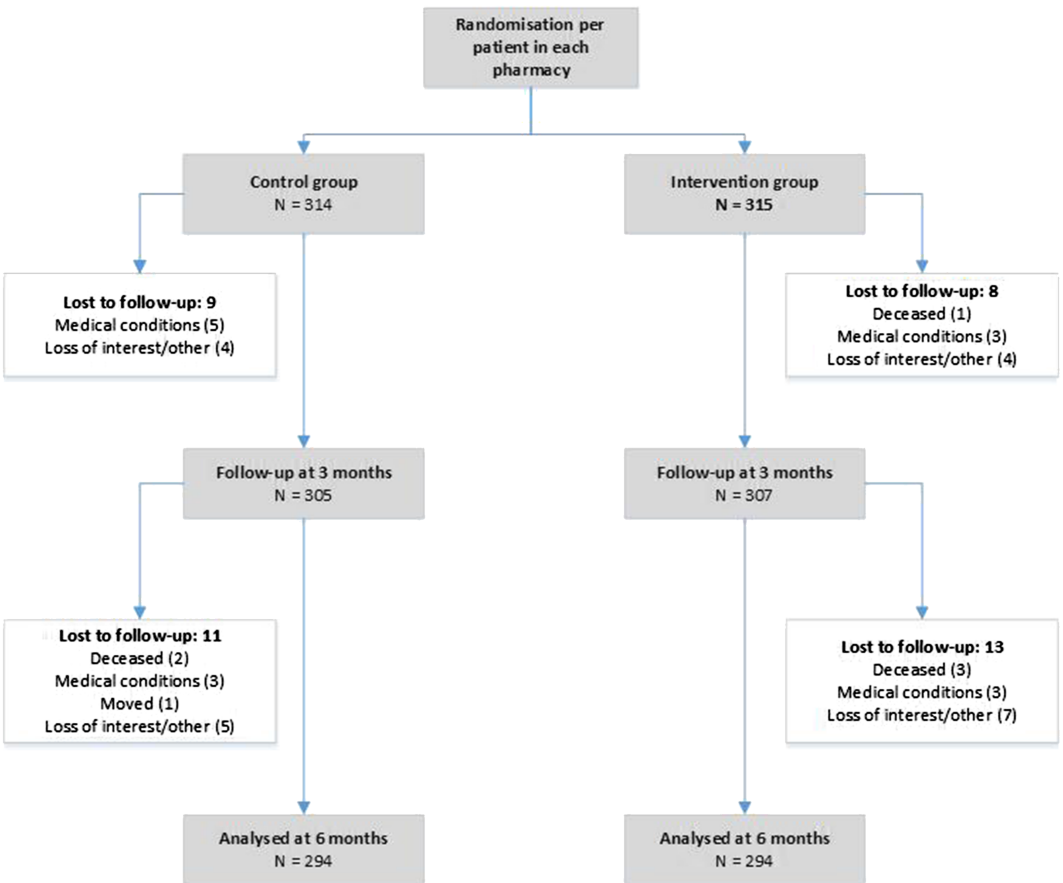

FIGURE 1 Study flowchart of the economic analysis of the DREAMeR study

TABLE 1 Characteristics of participants in the control and intervention groups

Characteristic	Control group (*n* = 294)	Intervention group (n = 294)
Age, median (IQR), years	78 (74–82)	79 (76–83)
Sex, female (%)	51%	56%
Ethnicity, European (%)	98%	97%
Living situation, alone (%)	38%	42%
Complex health problems[a] (%)	23%	25%
Number of drugs in use, median (IQR)	9.0 (7.5–10.5)	9.0 (7.5–10.5)
EQ-5D health utility values, mean (SD)	0.74 (0.18)	0.73 (0.18)
EQ-VAS scores, mean (SD)	70 (16)	69 (16)
Health-related complaints with impact, mean (SD)	2.6 (2.4)	2.7 (2.4)

IQR, interquartile range; SD, standard deviation; EQ, EuroQol; VAS, visual analogue scale.
[a]Complex health problems measured with ISCOPE-score (integrated systematic care for older people).

TABLE 2 Overview of average time (in minutes) spent for the clinical medication review by pharmacist, pharmacy technician and general practitioner

Task	Pharmacist	Pharmacy technician	General practitioner
Preparation	13 ± 13	5 ± 7	
Patient interview	50 ± 18		
Discussion of pharmaceutical care plan	12 ± 8		12 ± 8
Implementation of actions	11 ± 6		
Follow-up and evaluation	16 ± 15		
Other[a]	5 ± 11	2 ± 5	
Total	107 ± 41	7 ± 12	12 ± 8

Notes: Average time spent in minutes (mean ± SD).
[a]Various items such as travel time or making appointments.
Potential additional time spent by the GP, besides the discussion with the pharmacist, was not recorded.

deviation [SD]) to perform a CMR was 107 ± 41 minutes for the community pharmacist, 7 ± 12 minutes for a pharmacy technician and 12 ± 8 minutes for the GP. The time for the GP was only recorded for the conversation with the pharmacist.

3.2 | Effects

Effects on primary outcomes are presented in Table 3 and extensively described in another paper.[32] Mean QALYs measured with EQ-5D per 6 months were 0.369 (0.355–0.377) and 0.367 (0.345–0.370) for respectively the control group and intervention group, resulting in an incremental QALY of −0.00217. Mean QALYs measured with EQ-VAS over 6 months were 0.345 (0.332–0.356) for the control group and 0.348 (0.335–0.362) for the intervention group, resulting in an incremental QALY of 0.003 Effectiveness measured as reduced health-related complaints with impact over 6 months was −0.04 complaints in the control group compared to −0.38 complaints per patient in the intervention group, resulting in an incremental effect of −0.34 complaints in the intervention group compared to the control group. Unadjusted scores for primary outcomes at baseline and at 3 and 6 months are presented in Supplementary Table S1.

3.3 | Costs

Table 3 summarises the different costs over the 6-month study period. The total mean healthcare costs per patient were €3,809 ± 6,678 in the intervention group compared to €4,189 ± 6,596 in the control group, resulting in incremental healthcare costs of −€380. Mean costs for all different cost categories at each time point for both groups are shown in Supplementary Table S2.

Combining the average time spent on a CMR and the updated 2017 hourly rates, the average costs of this CMR per patient would range between €145 and €203 for the community pharmacist, €6 and €8 for the pharmacy technician and €20 and €22 for the consultation with the GP,[30,31] which results in a mean intervention cost of €199 ± 67 for a CMR per patient. When adding the intervention costs to the total costs, the total mean costs per patient in the intervention group were €4,008 ± 6,678 compared to €4,189 ± 6,596 in the control group. This results in an incremental cost of −€181 for the intervention compared to usual care.

3.4 | Cost-utility analysis

To estimate the ICERs, we used the incremental costs and incremental effects (see Table 3). When HR-QoL measured with EQ-5D is the measure of effect, a loss of QALYs (−0.00217) is offset against cost savings (−€181) resulting in an ICER of €86.360. This can be interpreted as the compensation received in costs for a lost QALY. The CMR dominated usual care for the cost/utility analysis determined with EQ-VAS and cost/change in complaint with impact analysis, being both less costly and more effective.

3.5 | Probabilistic sensitivity analyses

Regarding the results from the cost-utility analysis, the CMR emerged as the dominant strategy for the EQ-VAS and health-related complaints with impact. Based on 1000 multiple replications, probabilistic sensitivity analyses (PSA) were performed and are presented in Figure 2. Figure 2A illustrates the ICER for costs/QALY measured

TABLE 3 Incremental effects and costs between control and intervention group over 6 months

Type of effects and costs	Control group (*n* = 294)	Intervention group (*n* = 294)	Incremental effects or costs
Effects			
QALYs (EQ-5D)	0.369 (0.355–0.377)	0.367 (0.345–0.370)	−0.00217
QALYs (EQ-VAS)	0.345 (0.332–0.356)	0.348 (0.335–0.362)	0.003
Reduced health-related complaints with impact	0.04	0.38	−0.34
Healthcare costs			
Drugs	€873 ± 822	€833 ± 888	−€40
Healthcare resources			
Primary care	€414 ± 558	€346 ± 453	−€68
Secondary care	€755 ± 1925	€700 ± 1997	−€55
Institutional care	€475 ± 3,507	€311 ± 3,655	−€164
Home care	€1,198 ± 2,821	€1,296 ± 2,923	€97
Informal care	€474 ± 2,126	€323 ± 1,542	−€150
Total healthcare costs	€4,189 ± 6,596	€3,809 ± 6,678	−€380
Intervention costs			
Clinical medication review	n.a.	€199 ± 67	€199
Total costs	€4,189 ± 6,596	€4,008 ± 6,687	−€181

QALY, quality-adjusted life years; EQ, EuroQol; VAS, visual analogue scale.
Note: QALYs are calculated as mean QALYs per patient over the study period of 6 months, with a maximum of 0.5.
[a]Costs are presented as mean cost per patient ± standard deviation.

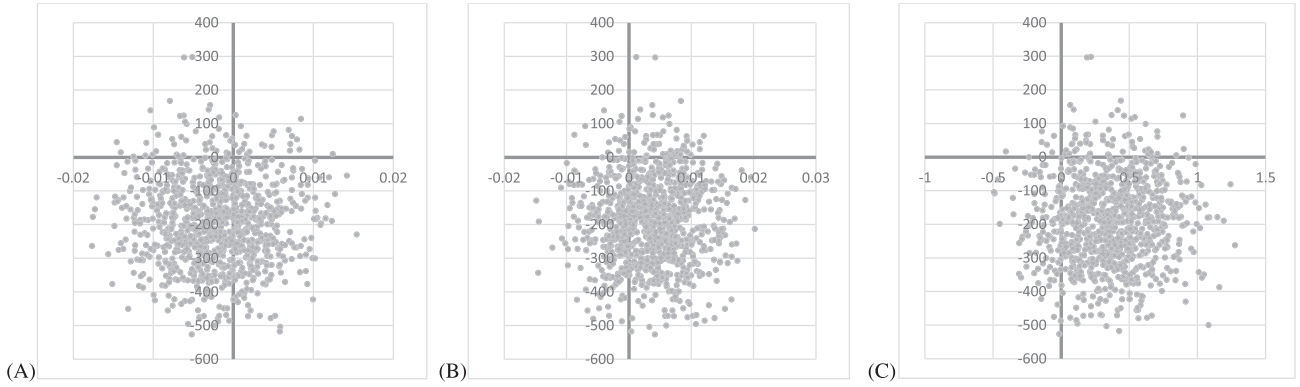

FIGURE 2 Cost-effectiveness plane for the incremental cost-effectiveness ratios (ICERs) determined as (A) costs/QALY measured with EQ-5D-5 L health utility values, (B) costs/QALY measured with EQ-VAS health utility values, and (C) costs/effects determined as reduced complaints with impact

with EQ-5D. Most of the simulations are located in the lower-left quadrant (59.9%) and in the lower-right quadrant (33.7%) of the cost-effectiveness plane, which results in a probability of 93.6% that a CMR is cost-saving and a probability of 63.7% of QALY loss. Figure 2B presents the ICER for costs/QALY measured with EQ-VAS; most of the simulations are located in the lower-right quadrant (69.2%) and in the lower-left quadrant (24.4%) of the cost-effectiveness plane, which results in a chance of 93.6% that a CMR is cost saving and a 26.1% of QALY loss (Figure 2B). Figure 2C offers the ICER for costs/reduced complaint with impact, showing a probability of 93.6% that a CMR is cost saving and a 90.1% probability of also giving a reduction in the number of severe complaints (Figure 2C). The acceptability curves are shown in Supplementary Figure S1.

3.6 | Deterministic sensitivity analyses

Results from the deterministic sensitivity analysis (DSA) are shown in Figure 3. A DSA determines the impact of uncertainty of individual cost parameters on the cost-saving or cost-introducing aspect of an intervention. Bars on the right-hand side show how uncertainty can increase the costs of an intervention and bars on the left-hand side show how uncertainty decreases the costs. The results show that the

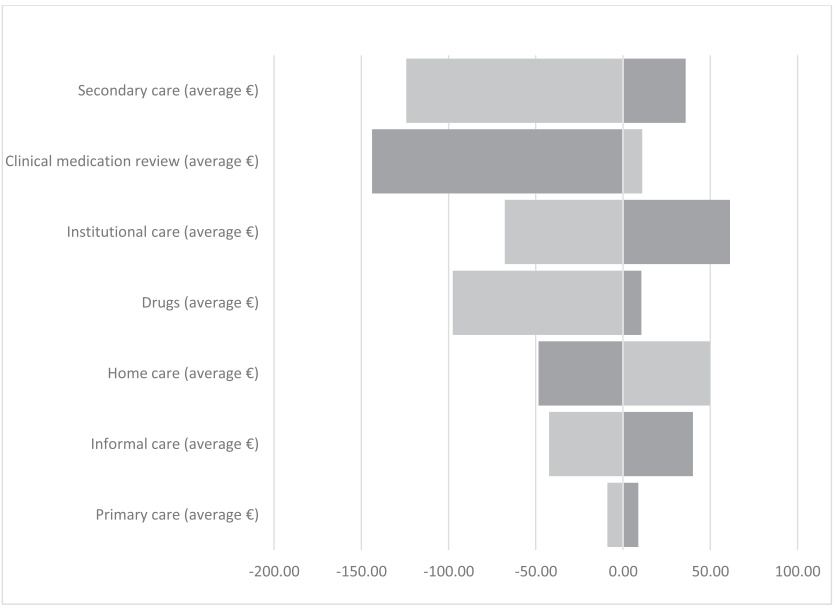

FIGURE 3 Tornado diagram describing the effects of uncertainty for the different cost categories

costs of the intervention, the costs of secondary care (including hospital admissions) and the costs of institutional care had the highest impact on the uncertainty of the ICER, but the CMR still results in cost savings because the ranges of all variables are lower than the incremental costs of −€181.

4 | DISCUSSION

This study shows that a CMR focusing on patient's preferences, goals and health-related complaints probably does not lead to an increase in costs from a societal perspective and could potentially be cost saving. The effect a CMR has on HR-QoL is less clear. HR-QoL measured with EQ-5D shows that a CMR could slightly reduce the quality of life. However, HR-QoL measured with EQ-VAS and health-related complaints with impact on daily life shows a slight to moderate improvement by increasing the quality of life and reducing the number of complaints with impact on daily life.

There is limited evidence for effects of CMR on clinical and economic outcomes.[14,33–35] The patient-centred approach applied during CMR in this study improved relevant outcomes for older patient's lives based on the EQ-VAS and the number of health-related complaints with impact on patients' daily lives. This could possibly be explained by the patient-centred and goal-oriented character of the CMRs performed in this study. The CMRs in this study focused mainly on the patient's preferences related to their medication and health, and could thereby improve their self-experienced quality of life, whereas other studies in medication review often focused on optimizing treatment according to guidelines.[14,33,34] The goals in the CMRs could be solved by drug changes performed during CMRs as shown by an in depth-analysis of the DREAMeR study.[36] Health utility values did not change significantly. This may be explained by the fact that the EQ-5D is less responsive compared to the EQ-VAS, especially when baseline values are high.[37,38] However, VAS is not a generally accepted way to measure utilities, due to the risk of end aversion bias. To negate end aversion bias, the possibility of conversion of VAS scores has been explored.[39] However, it was chosen not to convert VAS scores due to the fact that utilities measured with EQ-5D and EQ-VAS do not differ substantially, so the presence of end aversion bias seems very limited. Also, this study was conducted among patients aged ≥70 years and using at least seven drugs, which also reduced the chance of giving a VAS score of 100, and therefore introducing the risk of end aversion bias. VAS does, however, give some additional information on the (improved) health status experienced by the patient themselves and was therefore used to calculate utilities as well.

A previous study conducted in Spain illustrated that their medication review decreased costs, increased HR-QoL measured with both EQ-5D and EQ-VAS and was also seen as the dominant strategy over usual care.[19,40] The effects on HR-QoL were even higher than the effects in our study. Although this Spanish study was not explicitly designed as a patient-centred intervention, CMR in this study was accompanied with many follow-up contacts, which probably contributed to the patient-centredness of the study. Costs in the Spanish study were not directly comparable to the Dutch situation as these were not calculated from a societal perspective. A decrease in drug costs and hospital admissions was also demonstrated by Desborough et al., but they did not show effects on HR-QoL measured with EQ-5D.[41]

The average healthcare costs of the patients in this study are representative of the current Dutch situation for this age group.[42] A CMR could lead to small cost savings in healthcare compared to usual care and an average reduction of 0.5 in the number of drugs in use after 6 months.[32] Although the variation for each cost category was high in both groups, the results are strengthened by the sensitivity analyses, which show that the analysis is robust to variations in variables. The probability of cost savings in healthcare consumption is high (>90%) according to the cost-effectiveness planes of the ICERs.

The costs with the highest influence on the variability of the estimated cost savings were the intervention costs and the costs of institutional care and secondary care. Utilization of secondary care or institutional care can be expensive (e.g. one admission to a hospital or care home leads to large increases in healthcare costs) and therefore can also increase interpatient variability. However, even when the variation of these costs was performed, conclusions about cost savings were not influenced.

The mean estimated cost for a CMR in this study was €199, which is comparable to the costs of €185 determined in an earlier report[31] and to the budget impact analysis presented in the current Dutch multidisciplinary guideline, which estimated costs for CMR between €136 and €303.[9] The average time spent by the pharmacists for the patient interview in our study (50 ± 18 minutes) was relatively high,[31] but this can be explained by the patient-centred approach with extra attention to the personal preferences, goals and health-related complaints of the patients. The GP spent at least an average of 12 ± 8 minutes on the CMR in this study, but this reflects only the discussion of the care plan with the pharmacist. There could have been potential other actions performed by the GP resulting from the CMR, that have been performed under standard GP care. Nevertheless, the total costs of primary care were lower in the intervention group compared to the control group.

In the current study, follow-up was limited to two moments, which is lower compared to the Spanish study. Increasing the number of follow-up moments could further increase the effectiveness of CMR, but would also increase costs associated it. Adequate training is needed to perform CMR, but most Dutch community pharmacists are already accredited to perform CMR. Therefore, training costs were not attributed to the total intervention costs. However, large implementation worldwide would also need budgets to train pharmacists to perform these patient-centred CMRs.

Because of the ageing society, with a rising number of older people with multimorbidity and polypharmacy, attention to maintain older people's health and concomitant containment of healthcare costs is essential. Goal-oriented patient care may improve the management of multimorbidity and polypharmacy.[43,44] When we extrapolate the results of this study to the whole country, there are around 300 000 persons aged 70 years and older using seven or more chronic drugs.[9] If we were to deliver this intervention to all eligible patients, this would cost around €60 million for the intervention, but concomitantly would lead to healthcare cost savings of around €114 million, resulting in a net benefit of €54 million over a period of six months.

4.1 | Strengths and limitations

There were several strengths of this study. First, this economic analysis is based on the data from a large pragmatic RCT performed in daily clinical practice, which increases the generalisability of the results. Second, because this analysis was trial based, we could use the actual costs and did not use rates or price agreements. Third, we measured a broader range of healthcare costs compared to most other studies, which results in a complete overview of effects compared to costs.

There were also several limitations of this study. First, due to the nature of the intervention, blinding was not feasible, which might have influenced the results of this trial. To minimise the risk of bias, all questionnaires were captured and recorded by independent research assistants. Control patients were offered a CMR after the end of the 6 months follow-up. Pharmacists are unlikely to have given extra attention to control patients, as they generally lacked time to perform additional reviews during the study period. However, it is possible that control patients could be triggered by participating in this study to consider obtaining advice about their medication, health problems or goals, but this would rather lead to an underestimation of the study results. Second, the healthcare consumption was measured by the medical consumption questionnaire by telephone interviews every 3 months. Although this is a validated method of collecting these data, it could have introduced recall bias as 3 months is a fairly long period of time. However, this bias is unlikely to be different between both groups. Also, drug dispensing records were obtained via the pharmacy information system of the community pharmacy. Medication dispensed outside this pharmacy, as well as over-the-counter drugs, could have been missed in the dataset. However, in the Netherlands, patients prefer to visit one pharmacy.[45] Finally, the follow-up period in this study was 6 months, so we do not know what the results are over a longer period.

5 | CONCLUSION

A CMR focused on patient's preferences, personal goals and health-related complaints slightly improved health-related quality of life measured with EQ-VAS and slightly reduced the number of health-related complaints with impact on patients' daily lives in older persons with polypharmacy, but had no effect on health-related quality of life measured with the EQ-5D-5 L. Additionally a CMR could potentially be cost-saving from a societal perspective.

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clinical medication reviews from the health insurance companies and a small administrative fee for mailings of questionnaires.

COMPETING INTERESTS

There are no competing interests to declare.

CONTRIBUTORS

S.V. conceptualized and designed the study, performed the data collection and data extraction, carried out analyses and interpretation of data, drafted the initial manuscript, and approved the final manuscript as submitted. J.P. conceptualized and designed the study, carried out analyses and interpretation of data, drafted the initial manuscript, and approved the final manuscript as submitted. A.H. conceptualized and designed the study, carried out analyses and interpretation of data, critically reviewed the initial manuscript, and approved the final manuscript as submitted. H.F.K. participated in study design and critically reviewed the manuscript and approved the final manuscript as submitted. J.B. participated in study design and critically reviewed the manuscript and approved the final manuscript as submitted. J.G. participated in study design and critically reviewed the manuscript and approved the final manuscript as submitted. M.L.B. conceptualized and designed the study, carried out interpretation of data, critically reviewed the initial manuscript, approved the final manuscript as submitted and is the principal investigator of this study.

DATA AVAILABILITY STATEMENT

Research data are not shared.

ORCID

Sanne Verdoorn https://orcid.org/0000-0002-6698-700X

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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