CLINICAL MEDICATION REVIEW:

ONE STEP BEYOND

Computer rules or personal goals?

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For reasons of consistency within this thesis, some terms have been standardised throughout the text. As a consequence the text may differ in this respect from the articles that have been published.

Clinical medication review: one step beyond

Computer rules or personal goals?

Medicatiebeoordeling: een stap vooruit

Beslisregels of persoonlijke doelen?

(met een samenvatting in het Nederlands)

PROEFSCHRIFT

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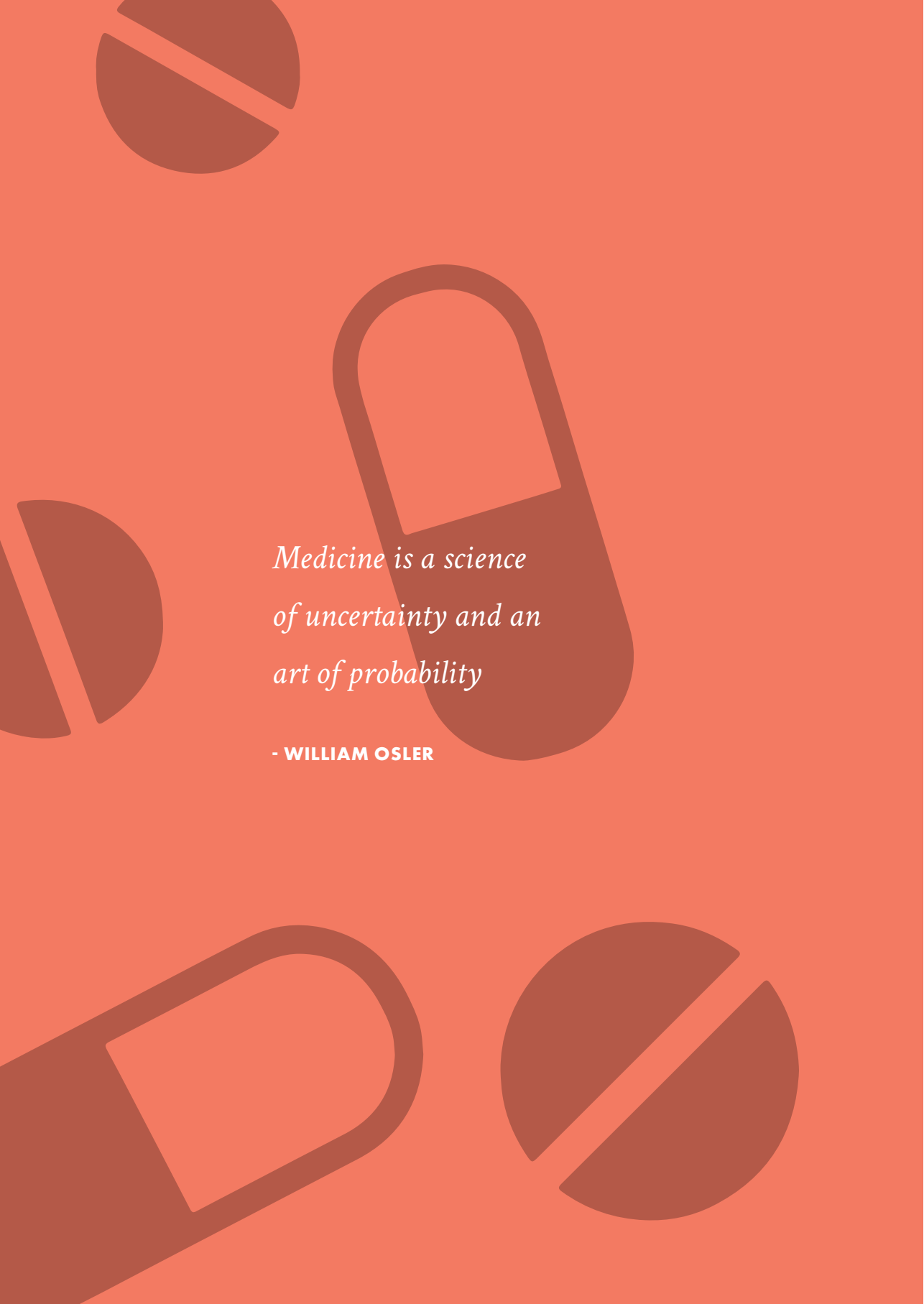
Medicine is a science
of uncertainty and an
art of probability
- WILLIAM OSLER

CHAPTER 1

General introduction

INTRODUCTION

The impact of the ageing society on the sustainability of the current healthcare system is one of the major challenges of the next decades. In the Netherlands, the number of frail older people will grow to one million in 2030 [1]. The rapid increase in the number of older people, especially the oldest old, leads to an increase in the demand for care for these groups. Almost half of the healthcare costs are spent for care for older people and these costs will even rise with 37% until 2030 [2]. To keep healthcare costs affordable, the number of beds in care homes for older persons is being reduced. Older persons are expected to live longer independently at home. This is in line with the new perspective presented by the Dutch health council in 2009. Care for older people should be focused on self-reliance and prevention of limitations in functioning [3]. The Dutch health council suggested that improved quality of life, by maintaining independence, self-care, autonomy and participation in society could be combined with reduced healthcare consumption [4]. This is a major challenge because many older persons suffer from multimorbidity and are dependent of medication.

Multimorbidity is strongly associated with polypharmacy. Almost two-thirds of the persons aged 65 years and older has multimorbidity and one fifth of these persons has polypharmacy and uses five or more chronic drugs [5,6]. Although preventive medication may increase life expectancy and may contribute to improved health, medication use also has his drawbacks. Due to age-related changes in pharmacokinetics and pharmacodynamics, older persons are at increased risk of drug-related problems (DRPs) [7,8]. DRPs often lead to adverse events and drug-related hospital admissions [9-11]. At least five percent of hospital admissions are drug-related and almost half of them could be avoided [10].

Because of the positive and negative consequences of polypharmacy, medication use in older people needs secure management; optimising treatment effects and harms. One strategy that has been recommended to minimize the risk for adverse events and drug-related hospital admissions is a medication review [12]. Reducing drug-related harms could ultimately improve the quality of life and independence of older people. On population level this could reduce drug costs and lower the economic burden.

Clinical medication review

There is no uniform definition of medication review. Literature describes a wide variety of approaches ranging from a prescription review (which is basically an evaluation of the list of prescribed medicines) to a clinical medication review (CMR) with the availability of all clinical data and an extensive patient interview [13,14]. Medication reviews may be performed both in primary care, nursing homes and in hospitals [15-21]. This thesis focuses on the CMR performed in primary care, where both patient, general practitioner (GP) and community

pharmacist are involved. Primary care seems the obvious place to improve effective and safe use of medicines, because the vast majority of medication prescriptions is initiated or repeated in general practice.

Clinical medication review is a structured critical examination of a patient's medicines with the objective of reaching an agreement with the patient about treatment, optimising the impact of medicines, minimizing the number of DRPs and reducing medication waste [13]. In the Netherlands, a CMR consists of five different steps as described in the multidisciplinary guideline 'Polypharmacy in the Elderly' which is shown in **Figure 1** [22,23]. Currently in the Netherlands, CMRs are recommended by the healthcare inspectorate and reimbursed by health insurance companies. However, questions still remain how CMR should be implemented on large scale, which patients should receive a CMR, what the effects of CMR are on clinical and economic outcomes, and what the most appropriate outcomes are to show effects of CMR. This thesis will focus on these aspects of CMR.

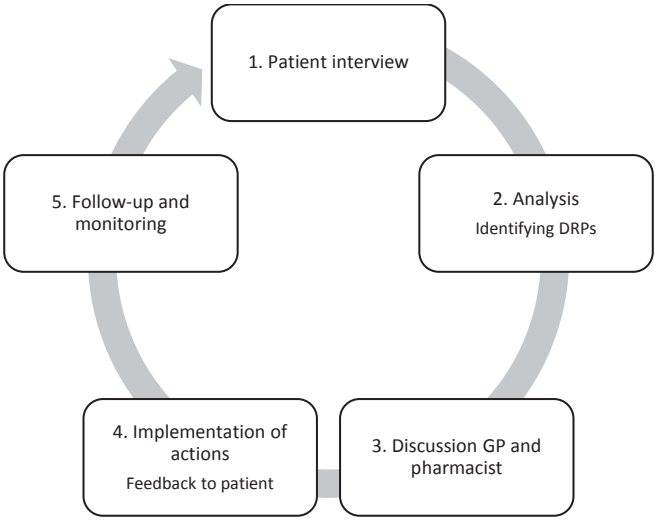

FIGURE 1: Stepwise approach of a CMR according to multidisciplinary guideline 'Polypharmacy in the Elderly' [22]

The CMR starts with a patient interview in step 1, performed by the community pharmacist either at the patient's home, in the general practice or in the pharmacy [15,24-26]. All medication in use including; usage, effectiveness, potential side effects, adherence, over-the-counter medication and patient's beliefs and experiences about medication are discussed in a face-to-face interview. A patient interview contributes significantly to the identification of

DRPs and DRPs identified during the interview are classified as most relevant by patients [27-29]. Studies with a focus on the patient interview are needed to investigate if this type of intervention could improve patient relevant outcomes.

After the patient interview, the pharmacist identifies all potential DRPs in step 2 and proposes recommendations to solve these DRPs. Both medical data (clinical indications and laboratory values), drug dispensing data and patient data are used. Implicit and explicit criteria have been described to identify and report DRPs. Implicit criteria, such as the Medication Appropriateness Index, consist of a structural assessment and professional judgment of the patient's medicines and are therefore useful but time consuming [30]. Explicit criteria consist of lists with inappropriate medications and prescribing omissions in in older people, such as the Beers-criteria and 'Screening Tool of Older Persons Prescriptions' (STOPP) and 'Screening Tool to Alert doctors to Right Treatment' (START) criteria [31-34]. The Dutch multidisciplinary guideline combines an implicit method with a Dutch version of the STOPP- and START-criteria [22,35]. To increase the efficiency in the detection of DRPs in order to facilitate the medication review process, explicit criteria could be incorporated into clinical decision support systems (CDSS) [36-38]. Studies are needed to determine whether incorporation of explicit criteria in a CDSS improve the efficiency and quality of the CMR process.

In step 3, DRPs and recommendations for actions are discussed between the GP (or other physicians when necessary) and pharmacist, preferably in a face-to-face meeting [39,40] All actions aimed to solve DRPs are formulated into a pharmaceutical care plan, including which actions will be implemented when and by whom. This pharmaceutical care plan is proposed to the patient in step 4. Patient, GP and pharmacist decide together which actions, e.g. drug changes, will be implemented. Studies in different settings have shown broad ranges of implementation rates for recommendations following DRPs, ranging from 17-86%. Improved collaboration between GP and pharmacist has been shown to increase the implementation rate of recommendations [40-42]. Finally, during the follow-up in step 5, the GP or pharmacist evaluate all agreed actions with the patient to investigate if the DRPs are actually resolved. When necessary, adjustments in the pharmaceutical care plan can be made and new actions will be planned.

Eligible patients for CMR

In most studies investigating CMR, eligible patients were community-dwelling older persons (defined as an age of ≥65 years) with polypharmacy (defined as use of ≥5 chronic drugs). It is questionable whether these current selection criteria for CMR identify patients who are most likely to benefit from a CMR, because this is a very heterogeneous group ranging from relatively healthy people with only one chronic condition to the vulnerable oldest old

with multimorbidity. Moreover, it is almost impossible to offer a time consuming CMR to all patients aged 65 years and older using five or more chronic drugs in this ageing society. Studies investigating a more tailored patient group or addition of other selection criteria to the current criteria are needed to investigate which patients will benefit the most from a CMR and to make the eligible patient group manageable for healthcare providers.

Risk factors that are associated with DRPs according to the literature and in guidelines are: non-adherence, decreased cognitive function, renal impairment, four or more co-morbidities, increased risk of falling and living alone [10,22]. These risk-factors could be used as selection criteria for patients who are eligible to receive a CMR. However these factors are not always readily available in daily practice in healthcare information systems. Other options that have been investigated as selection criteria for medication review are patients receiving their drugs via multidose drug dispensing, multiple intake moments for medication per day, reduced health literacy, dexterity problems or impaired sight, confused mental state, vision or hearing impairment and questionnaires about functional decline [19,45,46,58,59,65,66].

Effects of CMR

Many studies have investigated the effects of CMR on DRPs and have shown that CMR identifies and solves DRPs, such as suboptimal therapy and overtreatment [24,25,43-47]. Aiming to solve these DRPs, CMRs cause both initiation, cessation and other changes to the drug therapy regimen [45-48]. Medication review improves adherence to prescribing guidelines [48-50]. Finally medication review improves patients' drug knowledge and adherence to medication [18,42,48,51,52]. Some studies have shown effects of medication reviews on other intermediate outcomes, such as laboratory values, such as a reduction of LDL-cholesterol, blood pressure and HbA1c [18,19,24].

Although DRPs have been related to preventable drug-related hospital admissions [10], there is very limited evidence for an effect of medication review on clinical outcomes such as hospitalisations, morbidity and mortality [16,18,52-56]. Because outcomes such as hospitalisations and mortality are rare, studies in primary care need inclusion of large numbers of patients and should have long follow-up to have sufficient power to see an effect on these outcomes. Studies have investigated effects of medication review on healthcare consumption such as hospitalization, emergency department contacts or GP visits, outpatient visits or admittance to residential homes but these effects are limited [16,18-20,46,55]. More prevalent clinical outcomes in older people are pain and falls for example. Some studies have shown that medication review can reduce pain and falls in older persons living in care homes [44,49,57].

Several studies have investigated the effects of medication review on health-related quality of life (HR-QoL), but the effects on HR-QoL are limited [25,26,43,46,58,59]. As far as we know only one study has shown that a CMR could improve HR-QoL measured with EQ-5D and EQ-VAS [60]. Cost-effectiveness studies are sparse and effects on healthcare costs are inconclusive. Some studies found positive effects of medication review on total healthcare costs and one study proved CMR to be cost effective [19,46,60-62]. There is limited reimbursement for pharmacists for cognitive pharmacy services such as CMR, which could be a barrier to implement this intervention in daily practice [41,63].

Because of the heterogeneous patient groups, settings, interventions, and research designs, it is difficult to conclude how effective a CMR is for patients and for the society. Studies recommend that more patient-reported outcomes and potentially a core outcome set for CMR are needed [15,64].

Objective

The expected increase in older patients with polypharmacy in the upcoming years, makes it necessary to investigate if the eligible patient group for CMR can be narrowed or if tools and checklists can support the efficiency and quality of the CMR process. Moreover, additional evidence is needed to determine the benefits of CMR, both on population level (to manage an expected increase in healthcare costs) and on patient level (to improve older persons' wellbeing and to stimulate them to live longer independently in good health). Previous studies have shown effects of CMR on process- and intermediate-outcomes, but effects on clinical and economic outcomes are limited. Studies on clinical outcomes such as hospital admissions and mortality are difficult to perform and are expensive because large numbers of patients and a long follow-up period is needed. Health-related quality of life is an alternative clinical outcome, that can be measured in every patient, but unfortunately HR-QoL is not very sensitive to change. Improving the patient-centeredness of CMR may increase the likelihood of an effect on HR-QoL. To show improvement on older persons' health, functioning and wellbeing, also additional patient-reported outcomes may be necessary.

Therefore, the objective of this thesis is to generate evidence that may contribute to further optimisation of CMR in daily clinical practice. We will investigate whether CMR can be optimised in terms of efficiency, e.g. by the use of checklists with explicit and automated criteria, i.e. "computer rules", and by investigating the most appropriate selection criteria for a CMR. Moreover, we will investigate if a more patient-centred approach using "personal goals" during a CMR could improve HR-QoL and reduce healthcare costs. Finally, we will investigate new patient-reported outcomes to explore if these outcomes are useful in measuring the effects of a CMR. In the end we will try to answer three questions about: 1)

the most appropriate selection criteria for a CMR, 2) the best way to perform a CMR and 3) the most appropriate outcomes to measure the effects of a CMR. Targeting all these aspects (**Figure 2**) may optimise the benefit of CMR for older patients and an ageing society.

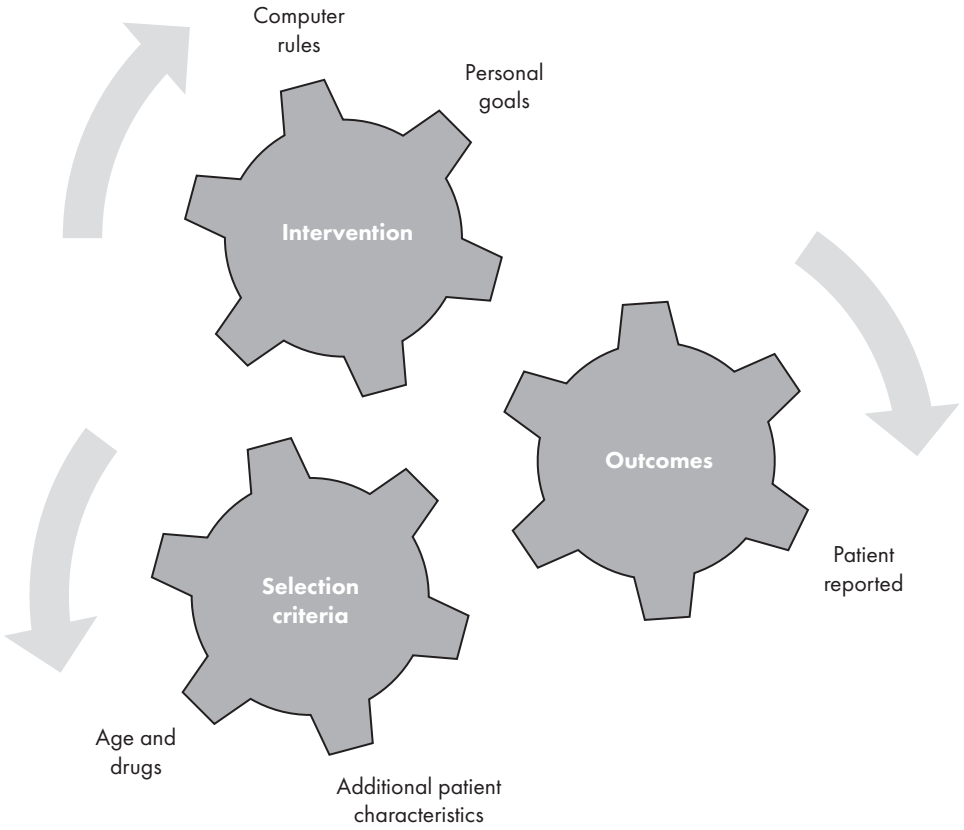

FIGURE 2: Aspects of CMR that will be addressed in this thesis

OUTLINE OF THE THESIS

This thesis consists of three parts. In part 1 we investigated whether efficiency of CMR could be improved by adding tools to support the identification of DRPs. This part presents two studies investigating the addition of explicit criteria to the CMR process. First, we performed a retrospective analysis of the applicability of STOPP/START criteria on the identification of DRPs during a CMR **(Chapter 2)**. Second, an extensive list with explicit criteria was incorporated into a CDSS and we performed a pre-post analysis of identified DRPs and performed interventions during a CMR **(Chapter 3)**.

Part 2 presents the design, results and evaluation of the 'Drug use Reconsidered in the Elderly using goal Attainment scales during Medication Review' (DREAMeR) study. In this part we investigated whether the CMR could become more patient-centred and whether new patient-reported outcomes could evaluate the effects of CMR. **Chapter 4** describes the design of the DREAMeR study; a randomised controlled trial investigating the effects of CMR focusing on patient's health-related complaints, preferences and personal goals on health-related quality of life, health-related complaints and attainment of personal goals. In **Chapter 5** we report the clinical outcomes of this RCT and in **Chapter 6** we report the economic outcomes of this study.

Part 3 describes two in-depth analyses of the DREAMeR study. In **Chapter 7** we investigated whether older persons who received a CMR were able to set goals together with the community pharmacist and we evaluated with goal attainment scaling if these goals were attained after a CMR. In **Chapter 8** we explored whether the efficiency of CMR could be optimised by tailoring the eligible patient group for CMR by performing a subgroup analysis of the DREAMeR study.

Finally, the results of these studies are summarised, discussed and put into a broader perspective in **Chapter 9**.

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PART 1

Tools to support the identification of drug-related problems

CHAPTER 2

Majority of drug-related problems identified during medication review are not associated with STOPP/START criteria

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ABSTRACT

Background and objective

STOPP and START criteria identify potential inappropriate prescribing and potential prescribing omissions. It is unknown whether STOPP/START criteria identify all drug-related problems. This study aims to determine to what extent STOPP/START correspond to drug-related problems (DRPs) identified during a full clinical medication review (CMR).

Methods

In 13 Dutch community pharmacies, 457 community-dwelling patients aged ≥ 65 years and using ≥ 5 drugs, received a CMR. Community pharmacists identified potential DRPs and recommendations by implicit criteria. After completion, all identified DRPs and recommendations were compared with STOPP and START criteria by investigators.

Results

The total number of potential DRPs identified by community pharmacists was 1656 in 457 patients (mean 3.6 per patient). 81% of DRPs were not associated with STOPP/START criteria. The percentage of START criteria present in identified DRPs was higher than the percentage of STOPP criteria (13% vs. 5.7%, $p < 0.01$).

The implementation rate for recommendations associated with STOPP criteria was higher compared to recommendations associated with START criteria (56% vs. 39%, $p < 0.01$). Both implementation rates of STOPP and START recommendations were lower compared to recommendations not associated with STOPP /START criteria (66%, $p = 0.046$ and $p < 0.01$ respectively).

Discussion and conclusion

This study shows that the majority of drug-related problems of community-dwelling older patients was not associated with STOPP/START criteria. These findings suggest that application of STOPP/START criteria in CMR should preferably be combined with implicit criteria.

INTRODUCTION

Polypharmacy and inappropriate medication use by older people increase the risk of adverse drug reactions [1]. Inappropriate medications are defined as medications for which the potential risk outweighs the potential benefit [2]. Next to inappropriate medications, older patients with polypharmacy may also be susceptible to under-prescribing. Under-prescribing of medications refers to the omission of a drug when there is a clear indication and no contra-indication [3].

Several tools are available to evaluate inappropriate medication and prescribing omissions in older patients, including implicit and explicit criteria. Implicit criteria, like the Medication Appropriateness Index (MAI), consist of a structural assessment of the patient's medicines. They may rely on expert professional judgment for their application. Although implicit criteria have demonstrated their usefulness in detecting drug-related problems in several studies, the application may be rather time-consuming in practice [4-12]

Explicit criteria consist of lists of inappropriate medications and prescribing omissions in the elderly. The first explicit criteria published for potentially inappropriate medications were the Beers-criteria [2,13-15]. These are the most widely cited criteria for inappropriate medications, but the applicability outside the U.S. is limited due to differences in types of drugs and guidelines [16-18]. In 2008, two sets of European-based criteria (STOPP and START) were formulated to address the perceived deficiencies of Beers' criteria and prescribing omissions as well [19]. STOPP (Screening Tool of Older Persons' Prescriptions) contains a list of 65 potentially inappropriate medications or medication classes. START (Screening Tool to Alert doctors to Right Treatment) lists 22 potential prescribing omissions (PPOs) in patients with particular medical conditions [19].

Studies in older patients showed that STOPP criteria were more sensitive than Beers criteria in identifying potentially inappropriate medications [20-22]. However, there are no studies that compared the use of these explicit criteria with implicit criteria in the detection of drug related problems (DRPs). Therefore, the aim of our study was to determine the number and types of STOPP/START criteria present in identified DRPs and recommendations found by a CMR with implicit criteria.

METHODS

Study design and setting

In thirteen Dutch community pharmacies a list of all community-dwelling patients aged 65 years and older, using at least five oral prescription drugs in 2011 was compiled using the pharmacy information system. From this list the pharmacists took a convenience sample of patients to invite for a medication review. Pharmacies were located in both urban regions in the south-west of the Netherlands. Pharmacists received complete medical data from the general practitioners (GPs), including diagnoses and laboratory values, after agreement of the patient.

Clinical medication review

The patient's community pharmacist interviewed the patient about his drugs at home or in the pharmacy. Patient's concerns and experiences regarding drug therapy (in particular perception of the effectiveness and potential adverse effects), adherence issues, practical problems, understanding of their medication regimen and possible use of OTC (over the counter) medication were addressed during this interview. A pharmaceutical care plan was proposed by the community pharmacist using both the patient's medication records from the pharmacy, general practitioners (GP's) medical records and the data from the patient interview. Potential DRPs and associated recommendations were identified by implicit criteria based on a structural assessment of indication, effectiveness, safety and compliance by Hepler and Strand [7]. Recommendations were implemented after agreement between both the community pharmacist, the general practitioner and the patient. Follow-up of implemented recommendations was monitored by the community pharmacists.

Participating community pharmacists had experience in performing CMRs. Therefore, they received an accredited training course in CMR. The course educated in clinical guidelines, communication skills, identifying DRPs and designing pharmaceutical care plans. In addition, pharmacists participated in monthly web conference sessions moderated by a medication review expert. During these sessions, case-studies and treatment guidelines were discussed. Moreover all pharmacists were observed and received feedback on one medication review session.

Data classification

Drugs were classified using the Anatomical Therapeutic Chemical (ATC) Classification System (11th edition, 2008) formulated by the World Health Organization Collaborating Centre for Drug Statistics Methodology. Potential DRPs and recommendations were classified according to the D.O.C.U.M.E.N.T. system by the community pharmacists [12,23-25].

Application of START/STOPP criteria

After completion of the CMRs, the anonymised results were sent to the investigators. The database with the results consisted of registered DRP's, ATC-codes of the drugs associated with the DRPs and interventions, recommendations and free text boxes with reasons to change a drug (e.g. start ACE-inhibitor because of heart failure), Based on these results, STOPP and START criteria were retrospectively and independently applied by two investigators (H.K. and S.V.). Differences were discussed until consensus was reached. A 10% sample of the DRPs was taken and also reviewed by two other investigators (A.F. and M.B.). For the application of the STOPP/START criteria, the first version of the STOPP/START criteria was used [19]. Two adaptations of the original criteria were made to make the criteria fit the current Dutch guideline [8]. The STOPP-criteria: "aspirin or NSAIDs without an proton pump inhibitor" and "opiates without laxatives" were modified to START criteria [8].

Outcome measures

The primary outcomes were number, type and implementation rate of STOPP and START criteria applicable to identified DRPs and associated recommendations during the CMRs. The implementation rate was defined as the percentage of recommendations that was fully or partly implemented according to the community pharmacist.

Statistical analysis

All implementation rates of recommendations were analysed on an intention-to-treat basis. Descriptive statistics were used for basic characteristics. Pearson chi-square tests were used for each categorical variable. A p-value < 0.05 was considered statistically significant. All data were analysed using Microsoft Access and Excel 2010 (Microsoft Corporation, Redmond, WA, USA) and SPSS version 20.0 (SPSS Inc., Chicago, IL, USA).

Ethics

Medication reviews are provided as an enhanced service for older people with polypharmacy by pharmacists and GPs in the Netherlands. In order to protect the patient's privacy, all data were anonymized by the community pharmacists using a randomly assigned unique number. The researchers only received the anonymized written care plans of the medication reviews. In addition they received anonymized drug dispensing records for each patient. Because this study was performed retrospectively and used anonymised patient data, no ethical approval was required according to current Dutch guidelines.

RESULTS

Descriptive statistics

Twenty-one community pharmacists in 13 pharmacies collaborated with 65 GPs in this study. The pharmacists conducted 533 patient interviews. Clinical medication reviews were performed for 461 of 533 patients. 72 patients were excluded because their medication reviews were not fully completed. Of the 461 patients, another four patients were excluded during follow-up because of death or hospital admission. Finally 457 patients were included for analysis. The median age was 77 years (interquartile range: 73-81) and 60% were women (**Table 1**). The most commonly prescribed drug classes were "Antithrombotic agents" (69%) and "Agents acting on the Renin-Angiotensin System" (68%).

STOPP and START criteria among identified DRPs

A total of 1656 potential DRPs were identified (mean 3.6 per patient) (**Table 2**). 81% of DRPs were not associated with either STOPP or START criteria. The percentage of START criteria present in identified DRPs was higher than the percentage of STOPP criteria (13% vs. 5.7%, $p < 0.01$).

TABLE 1: Baseline characteristics of participants (≥ 65 years and ≥ 5 drugs)

Characteristic		n = 457
Sociodemographic		
Sex, female		60%
Age, median (IQR), years		77 (73-81)
Number of drugs in use, (SD)		8.7 (3.2)
Most prescribed drug classes (ATC)		
B01A	Antithrombotics	69%
C09	Agents acting on the Renin-Angiotensin System	68%
C10A	Lipid Modifying agents	59%
C07A	Beta blockers	57%
A02B	Drugs for peptic ulcer and GORD	57%
A10	Drugs used in diabetes	33%
C03C	High-ceiling diuretics	31%
C08C	Selective calcium channel blockers	27%
C03A	Low-ceiling diuretics, thiazides	24%
R03	Drugs for obstructive airway diseases	22%
N05BA/ N05CD	Benzodiazepine derivatives	22%

Abbreviations: ATC = Anatomical Therapeutic Chemical Classification System, IQR = interquartile range; SD = standard deviation

TABLE 2. Classification of identified DRPs by STOPP and START criteria

		Not identified by STOPP/START		Identified by STOPP		Identified by START	
DRP type and subtype	**n**	**n**	**(%)#**	**n**	**(%)#**	**n**	**(%)#**
D(rug selection)	303	239	(79)	59	(19)	5	(2)
Duplication	20	3[a]	(15)	17	(85)	-	-
Drug interaction	11	10	(91)	1	(9)	-	-
Contra-indication apparent	16	7	(44)	7	(44)	2	(12)
No indication apparent	256	219	(86)	34	(13)	3	(1)
O(ver or underdose)	200	199	(99)	1	(1)	-	-
Prescribed dosage too high	64	63	(99)	1	(1)	-	-
Prescribed dosage too low	52	52	(100)	-	-	-	-
Incorrect or unclear dosing instructions	84	84	(100)	-	-	-	-
C(ompliance)	142	139	(98)	1	(1)	2	(1)
Taking too little	72	69	(96)	1	(1)	2	(3)
Taking too much	8	8	(100)	-	-	-	-
Difficulty using dosage form	62	62	(100)	-	-	-	-
U(ndertreated)	507	289	(57)	13	(3)	205	(40)
Condition undertreated	380	215	(57)	12	(3)	153	(40)
Condition untreated	127	74	(58)	1	(1)	52	(41)
M(onitoring)	222	221	(99)	-	-	1	(1)
Laboratory monitoring	152	152	(100)	-	-	-	-
Non-laboratory monitoring	70	69	(99)	-	-	1	(1)
E(ducation or information)	62	62	(100)	-	-	-	-
Disease management or advice	62	62	(100)	-	-	-	-
N(on-clinical)	55	54	(98)	1	(2)		
Other	55	54	(98)	1	(2)		
T(oxicity)	165	145	(88)	19	(11)	1	(1)
Toxicity, allergic reaction or adverse effect present	165	145	(88)	19	(11)	1	(1)
Overall	1656	1348	(81)	94	(6)	214	(13)

Abbreviations: n = number; # % is the percentage within DRP type or subtype

[a:] These three DRPs were mistakenly coded duplicate medication by the pharmacists. DRPs were: 1) codeine and oxycodone (pseudo-duplicate); 2) allopurinol and colchicine (overtreatment), 3) two different dosages of doxazosine were in use simultaneously (dose too high)).

The majority of STOPP criteria was associated with DRP type "Drug Selection" (59/94, 63%) whereas START criteria were associated with DRP type "Undertreated" (205 /214, 96%). Both "Undertreatment" and "Drug selection" were more frequently identified in the absence of either STOPP or START criteria. Seventy-nine percent of the DRP type "Drug Selection" and 57% of the DRP type "Undertreated" did not comprise the criteria. The most common DRP type related with the recommendation to cease a drug was " No indication apparent" (186/338, 55%). The most common DRP type related with the recommendation to add a drug was an untreated symptom that emerged from the patient interview, e.g. pain, itching or shortness of breath (32/275, 12%).

Implementation rate of recommendations associated with STOPP/START criteria

Thirty-five percent of DRPs were associated with a recommendation to cease, replace or add a drug. The implementation rate for recommendations associated with STOPP criteria was higher compared to recommendations associated with START criteria (56% vs. 39%, p = 0.005). Both implementation rates of recommendations associated with STOPP and START criteria were lower compared to recommendations not associated with STOPP or START criteria (66%, p = 0.047 and p < 0.001 respectively, **Table 3**).

TABLE 3. Comparison of prevalence and implementation rate of recommendations to stop, add or replace a drug, associated with STOPP/START criteria and implicit criteria.

	No STOPP/START		STOPP		START		
Type of recommendation	**n**	**IR**	**n**	**IR**	**n**	**IR**	**p-value**
Cessation of drug	259	51%	79	58%	-	-	0.23
Addition of a drug	78	54%	-	-	197	38%	0.02
Replacement of drug	138	51%					
			15	47%	-	-	0.75
			-	-	17	53%	0.83
Other	873	75%	-	-	-	-	-
	1348	66%					
Total			94	56%	-	-	0.047
			-	-	214	39%	<0.001

Abbreviations: n = number; IR = implementation rate

STOPP criteria were applicable to 79 of 338 recommendations to cease a drug (23%). The implementation rate for STOPP criteria was not different compared to other recommendations to cease a drug (58% vs. 51 %, p = 0.23). START criteria were applicable to 197 of 275 recommendations to add a drug (72%). The implementation rate for the subgroup START criteria recommendations was lower compared to other recommendations to add a drug (38 vs. 54%, p = 0.02) (**Table 3**).

Prevalence and types of STOPP/START criteria

STOPP criteria were present in 80 patients (17%). Sixty-nine patients had one potentially inappropriate drug and 11 had more than one. START criteria were present in 163 patients (36%). One-hundred-twenty-two patients had one potential prescribing omission and 41 had more than one. Nine types of STOPP criteria accounted for 82% of the total and 25 of the 65 available types of STOPP criteria were present. The most prevalent STOPP criteria were duplicate drug classes (n=19, 20%), benzodiazepines (n=12, 13%) and vasodilator drugs (n=12, 13%) (*Supplementary Table S1*). Ten START criteria accounted for 89% of the total and 18 of the 22 available START criteria were present. The most common START criteria were calcium and vitamin D in osteoporosis (n=58, 27%), statins in coronary, cerebral or peripheral vascular disease (N=31, 14%) and β-blockers in angina, acute MI or heart failure (n=20, 9%) (*Supplementary Table S2*).

DISCUSSION

This study shows that the majority (81%) of DRPs identified by pharmacists during a clinical medication review, was not associated with STOPP/START criteria. START criteria identified twice as much DRPs compared to STOPP criteria. In contrast, the implementation rate of recommendations originating from STOPP criteria was higher compared to recommendations originating from START criteria. However, recommendations not originating from STOPP/START criteria, h had a higher implementation rate than both STOPP and START criteria.

The majority of DRPs (65%) identified during medication review is not associated with recommendations to cease, replace or add a drug and could therefore not be detected with STOPP/START-criteria. Furthermore, only half of the recommendations to cease or add a drug is associated with STOPP/START criteria in this study. In particular, only 23% of all recommendations to cease a drug comprised a STOPP criterion. The most important reason to cease a drug was no indication apparent for a drug. The majority of DRPs can therefore only be detected by a structural assessment of the patient's medicines and diagnoses using

the implicit criteria. These findings underline the importance of using implicit criteria for medication review and education of the community pharmacist to develop the required medication review skills to use them [26]

START criteria were applicable to 36% of patients which was considerably higher than in the study of Ryan et al. (23%) [27]. Eighteen of 22 criteria accounted for the prescribing omissions in our study while this was 15 in the study of Ryan [27]. The high prevalence of START criteria in our study together with the high proportion of recommendations to add a drug associated with START criteria suggests a good practical applicability of this tool for older patients with polypharmacy in primary care. Other reasons to add a drug were mainly based on the complaints of the patient that emerged from the interview. These problems are diverse and could not easily be converted into a START criterion.

The implementation rate of recommendations associated with STOPP was comparable to other recommendations to cease a drug. On the contrary, recommendations to add a new drug based on START were less frequently implemented compared to other recommendations to add a drug. Especially, recommendations to add cardiovascular drugs (e.g. statins, ACE inhibitors and beta-blockers) were poorly implemented. It is likely that GPs are cautious to change cardiovascular treatment of patients who are concurrently seeing a specialist. Furthermore, non-acceptance may be caused by the fact that patients previously experienced adverse effects on these drugs. Although these adverse effects are probably not always that serious that rechallenge is unacceptable, patients will often be reluctant to restart such drugs. Finally, GPs may be reluctant to add preventive drugs in the oldest old, because risk factors such as high cholesterol levels and hypertension for those patients may not be related to mortality [28,29]. On the contrary, addition of proton pump inhibitors and, to a lesser extent, calcium and vitamin D had high implementation rates. These drugs are characterized by a direct effect or by the absence of serious adverse effects.

Strengths and limitations

Our study had several strengths. First of all, the elaborate description of DRPs and recommendations by the pharmacists enabled retrospective identification of STOPP/START criteria. Second, we used data from routinely performed medication reviews involving a high number of community pharmacists, GPs and patients. The results are therefore likely to be representative for daily clinical practice in primary care.

There were some limitations to this study. First, we could not directly apply the STOPP/START criteria because the researchers, unlike the pharmacists, did not have access to medical records (diagnoses and laboratory values). Therefore the study design did not allow for a direct comparison of a strategy purely based on STOPP/START criteria and a strategy based

on implicit criteria. Although for a limited number of STOPP criteria clinical information is not required, access to the full clinical record is recommended for the majority of STOPP and START criteria [30].

Despite this, STOPP criteria in our study were applicable to 18% of the patients, which is slightly lower than the findings of Ryan et al. in a comparable primary care population [27]. In our study 25 of 65 STOPP criteria were used, which is comparable to the study of Ryan et al. using 28 STOPP criteria [27,30].

Second, the pharmacists who performed the CMRs did not have specific training in the application of STOPP and START criteria. However, the pharmacists were considered to have sufficient knowledge of the guidelines underlying these explicit criteria, based on the training programme and monthly web conferences. Still it is likely that applying the STOPP/START criteria on the medication data of the original population selected for medication review would also have identified some DRPs that now have been missed by the pharmacist. Third, the implementation rate of recommendations was based on self-report by the community pharmacists and not on measurement of medication changes in dispensing records. Finally, by including only patients taking five or more medications, bias could be introduced by potential underestimation of prescribing omissions as detected by START criteria.

Although STOPP/START criteria were present in a minority of all DRPs identified, especially START criteria do seem applicable as a screening tool for medication review in primary care. It has been suggested to incorporate STOPP and START in existing information systems in primary care [27]. Such automated systems could facilitate medication review, but cannot replace a systematic approach using implicit criteria. Finally, explicit criteria will remain susceptible to changes, which is shown by the recently published second version of the STOPP/START criteria [31]. Future research should further establish the applicability of STOPP/START criteria in CMR by incorporation of these checklists into the intervention.

CONCLUSION

This study shows a higher prevalence of START criteria compared to STOPP criteria in identified DRPs of community-dwelling older patients, while STOPP criteria are implemented more frequently. Although STOPP/START criteria identify an important number of DRPs, the majority of DRPs identified during CMR was not associated with STOPP/START criteria. When used, START criteria may have a higher practical applicability compared to the extensive list of STOPP criteria for medication review in primary care. These findings suggest that health care providers cannot solely depend on the STOPP/START criteria to identify DRPs in primary care.

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SUPPLEMENTARY TABLE S1. Implementation rates of 10 most frequent potentially inappropriate medication according to STOPP criteria

Inappropriate medication	n	IR
Any duplicate drug class prescription	19	47%
Drugs that adversely affect fallers: Benzodiazepines	12	67%
Drugs that adversely affect fallers: Vasodilator drugs	12	50%
Long-term (i.e. >1 month), long-acting benzodiazepines	7	71%
Aspirin – not indicated	6	33%
Oestrogens without progestagen in patients with intact uterus	5	100%
NSAID with heart failure	5	80%
Long-term NSAID or colchicine for chronic treatment of gout - no contraindication to allopurinol	5	80%
Blockers and frequent hypoglycaemic episodes	3	67%
Long-term opiates in those with recurrent falls	2	50%

Abbreviations: n= number; IR = implementation rate

SUPPLEMENTARY TABLE S2. Implementation rates of 10 most frequent potential prescribing omissions according to START criteria

Omitted medication – medical condition	n	IR
Calcium and Vitamin D supplement- osteoporosis	58	57%
Statin therapy- history of coronary, cerebral or peripheral vascular disease	31	26%
βBlocker - angina, acute MI or heart failure	20	15%
Proton pump inhibitor - ASA (≤ 100mg) and >80 years, NSAID and >70 years or reflux[a]	19	79%
Bisphosphonates – corticosteroids or osteoporosis	16	13%
Statin therapy - diabetes mellitus	13	23%
ACE inhibitor - heart failure.	9	44%
Metformin - type 2 diabetes or metabolic syndrome	9	22%
ACE inhibitor or angiotensin receptor blocker - diabetes with nephropathy	8	50%
Antihypertensive therapy - systolic blood pressure >160 mmHg	8	25%

Abbreviations: n= number; IR = implementation rate; [a] This START criterion is an adapted version of the original STOPP criterion, as used in the Dutch guidelines [8]

CHAPTER 3

Drug-related problems identified during medication review before and after the introduction of a clinical decision support system

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ABSTRACT

Background and objective

To facilitate the identification of drug-related problems (DRPs) during medication review, several tools have been developed. Explicit criteria, such as Beers-criteria or STOPP (Screening Tool of Older Peoples' Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment) criteria can easily be integrated into a Clinical Decision Support System (CDSS). The aim of this study was to investigate the effect of adding a CDSS to medication review software on identifying and solving DRPs in daily pharmacy practice.

Methods

Pre-post analysis of clinical medication reviews (CMR) performed by 121 pharmacies in 2012 and 2013, before and after the introduction of CDSS into medication review software. Mean number of DRPs per patient, type of DRPs and their resolution rates were compared in the pharmacies pre- and post-CDSS using paired t-tests.

Results

In total, 9151 DRPs were identified in 3100 patients pre-CDSS and 15268 DRPs were identified in 4303 patients post-CDSS. The mean number of identified DRPs per patient (aggregated per pharmacy) was higher after the introduction of CDSS (3.2 vs. 3.6 $p < 0.01$). The resolution rate was lower post-CDSS (50% vs. 44%; $p < 0.01$), which overall resulted in 1.6 resolved DRPs per patient in both groups ($p = 0.93$). After introduction of CDSS, 41% of DRPs were detected by the CDSS. The resolution rate of DRPs generated by CDSS was lower than for DRPs identified without the help of CDSS (29% vs. 55%; $p < 0.01$). The two most prevalent DRP types were "Overtreatment" and "Suboptimal therapy" in both groups. The prevalence of "Overtreatment" was equal in both groups (mean DRPs per patient: 0.84 vs 0.77; $p = 0.22$) and "Suboptimal therapy" was more frequently identified post-CDSS (mean DRPs per patient: 0.54 vs 1.1; $p < 0.01$).

Conclusion

The introduction of CDSS to medication review software generated additional DRPs with a lower resolution rate. Structural assessment including a patient interview elicited the most relevant DRPs. Further development of CDSS with more specific alerts is needed to be clinical relevant.

INTRODUCTION

Older patients with polypharmacy are at risk for drug related problems (DRPs), such as overtreatment and suboptimal therapy [1]. A clinical medication review (CMR), consisting of a structured assessment of the pharmacotherapy including a patient interview, is an important instrument to identify and resolve DRPs [1-5]. This is a time consuming process [6]. Given the expected increase of older people with polypharmacy [7,8], the amount of medication reviews will increase substantially in the near future. Therefore, standardization and facilitation of the medication review process is needed [9].

To facilitate the identification of DRPs during medication review, several tools have been developed. These tools can be judgement based (implicit criteria) or criterion based (explicit criteria). An example of implicit criteria is the Medication Appropriateness Index [10,11]. Explicit criteria, such as the Beers criteria or 'Screening Tool of Older Persons Prescriptions' (STOPP) and 'Screening Tool to Alert doctors to Right Treatment' (START) criteria aim to identify inappropriate medication and prescribing omissions [12-14]. An advantage of explicit criteria is that they can be relatively easily integrated into clinical decision support systems (CDSS), whereas implicit criteria typically cannot. CDSS can be described as a computer program that generates alerts aimed at helping health care professionals to improve the quality and safety of pharmacotherapy including timely monitoring [15,16].

Most studies describing CDSS investigate only one type of alert; for example, alerts about reducing anticholinergic medication, improving antibiotic prescribing or use of medicines during pregnancy [16-18]. These alerts are usually designed to support physicians during prescribing [19,20]. Few studies have assessed CDSS in pharmacy practice to support pharmacists [9,21-25]. One study showed that the use of CDSS during medication review identified more potential DRPs than the pharmacists [21]. However, this study did not investigate the outcome of interventions aimed at resolving the identified DRPs. Another study suggested that only a minority of DRPs identified during medication review would have been found with explicit criteria. A limitation of this study was that the explicit criteria were applied retrospectively [26].

The aim of the study is to investigate the effect of adding a CDSS to medication review software on identifying and solving DRPs in daily pharmacy practice.

METHODS

Study design and setting

This study was a retrospective database study including a pre-post design. Data of CMRs were extracted from community pharmacies' databases and compared before and after the introduction of a CDSS into medication review software. The study was conducted at 121 Dutch community pharmacy franchisees of "Service Apotheek". Only pharmacies who performed at least five CMR before and after the introduction of the CDSS were included in the study. The pharmacies were located over the Netherlands in both rural and urban areas. Per pharmacy, one or more pharmacists performed the CMRs in community dwelling older patients. The pharmacists used medication review software to register DRPs and interventions during a medication review [3,27]. In 2013 a CDSS was incorporated into this software program. This CDSS consisted of 46 explicit criteria, which generated alerts to the pharmacist at the start of a CMR. All pharmacists previously received training in CMR as this is required by most health insurance companies to be reimbursed for CMR. A helpdesk was available in case pharmacists experienced difficulties with the CDSS.

Explicit criteria incorporated into the CDSS

An expert team drafted a preliminary list of clinical rules, based on national prescribing guidelines, Beers, STOPP/START criteria, but also on other relevant themes in polypharmacy such as inconvenience of use or economic efficiency [12,28,29]. Based on practical considerations, the developers of the CDSS incorporated 46 of these clinical rules into the CDSS in 2013 (*Supplementary Table S1*).

Clinical medication review

Patients aged ≥ 65 years using ≥5 chronic drugs were eligible for a CMR [6,11]. According to Dutch guidelines, a CMR should involve both pharmacist, general practitioner (GP) and patient [6]. First, the pharmacist collected both clinical and drug dispensing data from the patient. Then the pharmacist interviewed the patient, identified DRPs and proposed recommendations (e.g. add or discontinue a drug) in a pharmaceutical care plan. The recommendations in this pharmaceutical care plan were discussed with the patient's GP. Agreed recommendations by the GP were discussed with the patient. After agreement of the patient, recommendations were implemented. After the introduction of the CDSS, the pharmacists followed the same procedure for CMR, with the exception that the CDSS also automatically generated potential DRPs at the start of the medication review process. The pharmacist could discuss these potential DRPs with the patient and GP during the CMR.

Data collection

Pharmacists were trained to document the results of the CMRs in the software program [3,27]. The following characteristics were documented: date of the CMR, name and ATC-code (Anatomical Therapeutic Chemical classification) of the drug(s) involved, DRP type, type of recommendation (e.g. recommendation to add a drug) proposed by the pharmacist and type of implemented recommendation (e.g. the drug was added). The medication review software program was linked to the pharmacy information system. In addition, anonymised dispensing records of all included patients, including age and gender, were available for a period of 12 months prior to the CMR date.

Data before CDSS-introduction were collected from January to August 2012. CDSS was introduced at January 2013. Data after introduction of CDSS were collected from January to August 2013.

Outcome measures

Primary outcome measures were the mean number of identified and resolved DRPs per patient aggregated per pharmacy before and after the implementation of CDSS. A DRP was considered resolved when the recommendation associated with the DRP was fully or partly implemented as documented by the pharmacists in the software program (e.g. dose reduction when complete discontinuation was proposed). Secondary outcome measures were: type of DRPs, type of implemented recommendations and prevalence of the potential DRPs generated by CDSS. The classification of DRPs was adapted from Hepler and Strand and is described in the national guidelines [3,6,30].

Data analysis

Duplicate DRPs, incomplete registrations and incomplete patient data were excluded from analysis. To validate the correct classification of DRPs by the pharmacists, a random sample of 100 records per DRP type was checked. The documented classification of DRPs was compared with the description in the free text box by two investigators (SV and HFK). Less than 10% of the classifications deviated from the free descriptions. This percentage was considered acceptable.

Statistical analysis

Descriptive statistics were used for basic characteristics. Frequencies and percentages were reported for categorical variables. Paired t-tests and related samples Wilcoxon signed rank tests were performed to compare differences between pre- and post-CDSS in the pharmacies, in demographics, mean number and type of identified and solved DRPs per patient and implemented recommendations between pre- and post-CDSS. All the results were aggregated

per pharmacy and compared on the pharmacy level pre and post-CDSS. The data were analysed using Microsoft Office Access, Excel Professional 2013 (Microsoft Corporation, Redmond, WA, USA) and IBM SPSS Statistics 22.0 (IBM Corporation, Armonk, NY, USA). A p-value < 0.05 was considered statistically significant.

Ethics

Because this was a retrospective analysis of routinely collected anonymised data, that could not be traced back to individual patients and pharmacies, ethical approval was not needed under the Dutch legislation.

RESULTS

Descriptive statistics

Clinical medication reviews were performed in 186 pharmacies both before and after the introduction of CDSS in medication review software (pre-CDSS and post-CDSS respectively). We excluded 65 pharmacies because they performed < 5 CMR, either pre- or post-CDSS. In the 121 included pharmacies, 3100 patients received a CMR pre-CDSS and 4303 patients post-CDSS. Pharmacies performed less CMRs pre-CDSS than post-CDSS (median 16 (IQR 9-36) vs. median 30 (IQR 18-49); $p < 0.01$). Patient characteristics aggregated per pharmacy are shown in **Table 1.**

Drug-related problems

In total 9151 DRPs were identified pre-CDSS and 15268 DRPs post-CDSS. The mean number of identified DRPs per patient (aggregated per pharmacy) increased after introduction of the CDSS (3.2 (SD = 1.1) vs. 3.6 (SD = 1.3); $p < 0.01$), while the proportion of resolved DRPs decreased (50% (SD = 18%) vs. 44% (SD = 15%); $p < 0.01$). This leads to an equal number of resolved DRPs before and after the introduction of CDSS (1.6 (SD = 0.82) vs. 1.6 (SD = 0.79); $p = 0.93$).

Type of drug-related problems

The two most prevalent type of DRPs before as well as after the introduction of CDSS were: "Overtreatment" and "Suboptimal therapy". The prevalence of "Overtreatment" was equal in both groups (0.84 (SD = 0.66) vs 0.77 (SD = 0.34); $p = 0.22$). Suboptimal therapy was identified more frequently after the introduction of CDSS (0.54 (SD = 0.38) vs 1.1 (SD = 0.44) per patient; $p < 0.01$). The mean number of resolved "Suboptimal therapy" issues per patient, was equal among both groups (0.20 (SD = 0.22) vs. 0.24 (SD = 0.22); $p = 0.15$). The other differences in type of DRPs are shown in **Table 2**.

TABLE 1: Baseline characteristics of participants aggregated per pharmacy before (pre-CDSS) and after the introduction of a CDSS (post-CDSS)

Characteristic		Pre-CDSS (n = 3100 patients)	Post-CDSS (n = 4303 patients)	p-value#
Sociodemographic				
Age, median (IQR), years		78 (75 – 82)	77 (75 – 80)	0.02
Number of drugs in use, median (IQR)		8 (7 – 9)	8 (7 – 8)	0.01
Sex, female		59%	53%	0.01
Most prescribed drug classes (ATC)		**Mean % of patients per pharmacy (SD)**	**Mean % of patients per pharmacy (SD)**	**p-value***
B01A	Antithrombotics	74 (14)	72 (11)	0.24
A02B	Drugs for peptic ulcer and GORD	68 (16)	65 (12)	0.16
C10A	Lipid modifying agents	63 (17)	68 (14)	0.01
C07A	Beta blockers	59 (15)	58 (12)	0.64
C09A	ACE inhibitors	35 (14)	39 (12)	0.02
A10B	Oral blood glucose lowering drugs	33 (17)	34 (14)	0.55
C03C	High-ceiling diuretics	30 (13)	25 (12)	< 0.01
C08C	Selective calcium channel blockers	29 (16)	31 (10)	0.29
A06A	Laxatives	27 (15)	25 (12)	0.40
C09C	Angiotensin II antagonists	24 (11)	24 (8.5)	0.67

Abbreviations: IQR = interquartile range, CDSS = clinical decision support system; ATC = Anatomical Therapeutical Chemical classification; GORD = gastro-oesophageal reflux disease
n = 121 pharmacies; # related samples Wilcoxon signed rank test; * = paired t-test

Type of implemented recommendations

The mean number of ceased drugs per patient decreased after introduction of the CDSS (0.40 (SD = 0.40) vs. 0.31 (SD = 0.23); $p < 0.01$), while the mean number of added drugs per patient increased (0.19 (SD = 0.16) vs. 0.25 (SD= 0.18); $p < 0.01$). Post-CDSS more recommendations led to "no intervention" (1.1 (SD = 0.80) vs. 1.4 (SD = 0.80); $p < 0.01$). The other differences in types of implemented recommendations are shown in **Table 3**.

Post-CDSS

Post-CDSS, 41% of all potential DRPs were detected by the CDSS and 59% were identified by structural assessment by the pharmacists during the CMR. Only 29% (SD = 17%) of potential DRPs detected by CDSS were resolved compared to 55% (SD = 20%) of DRPs identified by pharmacists ($p < 0.01$).

TABLE 2: Prevalence and implementation rate of various DRP types pre- and post-CDSS

	Pre-CDSS (n = 3100 patients)		Post-CDSS (n = 4303 patients)		p-value*	
DRP type per patient aggregated per pharmacy	**DRPs identified (mean, SD)**	**% resolved**	**DRPs identified (mean, SD)**	**% resolved**	**DRPs identified**	**% resolved**
Overtreatment	0.84 (0.68)	43%	0.77 (0.34)	45%	0.22	0.53
Suboptimal therapy	0.54 (0.38)	38%	1.1 (0.44)	23%	<0.01	0.15
Contra indication	0.28 (0.40)	43%	0.28 (0.40)	45%	0.97	0.85
Drug not effective	0.27 (0.28)	51%	0.22 (0.20)	46%	0.027	0.033
Adverse effect	0.27 (0.24)	58%	0.27 (0.21)	57%	0.85	0.96
Drug interaction	0.22 (0.32)	63%	0.06 (0.09)	44%	<0.01	< 0.01
Inconvenience of use	0.18 (0.18)	70%	0.32 (0.23)	54%	< 0.01	< 0.01
Non-compliance	0.16 (0.19)	71%	0.12 (0.13)	76%	0.017	0.10
Dose too low	0.16 (0.17)	47%	0.13 (0.09)	35%	0.071	0.012
Dose too high	0.16 (0.18)	60%	0.06 (0.06)	53%	< 0.01	< 0.01
Miscellaneous	0.13 (0.27)	44%	0.28 (0.33)	35%	< 0.01	< 0.01
Inappropriate dosage form	0.03 (0.06)	53%	0.07 (0.07)	64%	< 0.01	< 0.01

Abbreviations: DRP = drug related problem; CDSS = clinical decision support system; * paired t-test
n = 121 pharmacies. Numbers are aggregated per pharmacy

TABLE 3: Differences in type of implemented recommendations pre- vs. post-CDSS

Type of implemented recommendation per patient	Pre-CDSS (n = 3100 patients)	Post-CDSS (n = 4303 patients)	p-value*
Drug changes			
Drug added	0.19	0.25	<0.01
Drug ceased	0.40	0.31	<0.01
Drug replaced	0.18	0.15	0.23
Dosage (regimen) changed	0.26	0.22	0.18
Dosage form changed	0.03	0.04	0.083
Other interventions			
Performed monitoring	0.39	0.54	<0.01
Information/advice provided	0.48	0.50	0.71
Synchronisation of all drugs	0.06	0.10	0.019
Other	0.15	0.09	0.033
No intervention	1.1	1.4	<0.01

Abbreviations: CDSS = clinical decision support system; * paired t-test
n = 121 pharmacies. Numbers are aggregated per pharmacy

Table 4 shows the 10 most prevalent alerts based on explicit criteria generated by the CDSS. The most prevalent alert was "Cardiovascular disease without a statin", which is related to the DRP type: "Suboptimal therapy". The implementation rate of the associated recommendation to add a statin was 23%. The alert in the CDSS with the lowest implementation rate was "Absence of antiplatelet therapy in cardiovascular disease" (14%) and the alert with the highest implementation rate was: "Lack of vitamin D in osteoporosis" (71%).

TABLE 4: Top 10 most prevalent potential DRPs generated by the CDSS

Top	Description alert of the CDSS (Potential DRP type)	Prevalence in total number of DRPs (n = 15268 DRPs)		Percentage resolved
		n	%	
1	Cardiovascular disease without a statin (Suboptimal therapy)	669	4.4%	23%
2	Concomitant use of three or more antihypertensives (Overtreatment)	647	4.2%	24%
3	Absence of antiplatelet therapy in cardiovascular disease (Suboptimal therapy)	594	3.9%	14%
4	Inconvenience of use of ACE-inhibitor: once-daily alternative or combination available (Inconvenience of use)	490	3.2%	32%
5	Inappropriate use of inhaled corticosteroids in COPD (Overtreatment)	457	3.0%	26%
6	Concomitant use of two or more antithrombotics (Overtreatment)	397	2.6%	52%
7	Use of aerosol without a spacer (Inappropriate dosage form)	390	2.6%	53%
8	Loop-diuretics as first-line treatment of hypertension (Suboptimal therapy)	324	2.1%	31%
9	Lack of vitamin D in osteoporosis (Suboptimal therapy)	298	2.0%	71%
10	Heart failure without an ACE-inhibitor (Suboptimal therapy)	289	1.9%	17%

Abbreviations: CDSS = clinical decision support system; DRP = drug-related problem; ACE = angiotensin converting enzyme

DISCUSSION

This study demonstrated that the mean number of identified DRPs increased after the addition of a CDSS to medication review software. On the contrary, the implementation rate of the recommendations associated with the DRPs decreased resulting in an equal number of resolved DRPs before and after the introduction of the CDSS.

Our finding, that a CDSS leads to the identification of more potential but less relevant DRPs, is comparable to other studies. A study of Curtain et al. also showed that a CDSS detected more DRPs than a structural assessment by the pharmacist [21]. A previous study found that only a minority of the DRPs were associated with explicit criteria and a lower resolution rate of these DRPs (26). A limitation of that study was that the investigators applied explicit criteria retrospectively. Our current study investigated the applicability of explicit criteria incorporated into software, by pharmacists during CMRs in daily pharmacy practice.

Several reasons for the low implementation rate and limited effectiveness of CDSS alerts have been described in the literature. Some studies have suggested low specificity and alert fatigue as the main reasons for the limited effectiveness of CDSS alerts [16,22]. There are several comparable explanations for the low resolution rate of DRPs generated by the CDSS in this study. One reason could be that the alerts were not specific enough, such as for example the clinical rule that aims to detect heart failure not yet treated with an ACE-inhibitor. This clinical rule is triggered by the presence of a diuretic without concomitant use of an ACE-inhibitor in the drug dispensing records. Probably many patients identified by this clinical rule will use diuretics for other indications. In this case the diagnosis heart failure is derived from the use of a drug (diuretic) and this often leads to false assumptions. It would be better to incorporate a heart failure diagnosis in the system that generates the clinical rule. Another reason that clinical rules often do not lead to drug changes may be that patients are intolerant for the suggested medication. The percentage of implemented recommendations for the alert of the explicit criterion: “Cardiovascular disease without a statin” was very low, namely 23%. Many patients have already discontinued using statins because of myopathy. In general alerts are based on algorithms derived from guidelines developed for use on population level, while CMRs are focused on the needs of individual patients [31].

Other studies have shown that pharmacists encounter barriers such as resistance to change, low consumer contact and lack of time [16,22]. In our study, low consumer contact and lack of time were no problem, because the CDSS was used during a CMR, where there is a multidisciplinary collaboration between pharmacist, GP and patient. Robertsen et al. also

described that a professional relationship between pharmacist and physician is essential for the benefit of CDSS [22]. In this setting, patient and GP are more inclined to cooperate with recommendations for drug changes.

Considering the DRPs that were identified by the pharmacists themselves during the CMR, the resolution rate of the DRPs was much higher. Fifty percent or more of these DRPs were resolved, both before and after the introduction of the CDSS. These DRPs were mainly derived by an implicit method of CMR, by a structural assessment and interview between the pharmacist and the patient. Overtreatment, suboptimal therapy, non-compliance and adverse effects are examples of DRPs that mostly derive from information from the patient interview [26]. The higher implementation rate of the recommendations associated with these DRPs could be explained by a higher relevance for the patient. Kwint et al. also showed that DRPs identified during patient interviews were more frequently assigned a higher clinical relevance [32]. Also Roane et al. showed that consultation with a patient can lead to more appropriate recommendations [33].

Strengths and limitations

This study has several strengths. A major strength is the analysis of the large number of CMRs both before and after the introduction of CDSS. These CMRs represent the daily clinical practice of an average pharmacy in the Netherlands, which make the results likely to be more generalisable. A second strength is that this study is a direct comparison of medication review data before and after the implementation of a CDSS. Another strength is that we used a variety of clinical rules in the CDSS, that focussed both on inappropriate prescribing and suboptimal therapy, but also on other relevant practical aspects for older people with polypharmacy.

There were also some limitations to this study. The first limitation is the potential variability in classifications of the type of DRPs and interventions by the different pharmacists. However, we did check the encodings and we found that less than 10% deviated, which we found acceptable in such a large database. A second limitation is that the resolution of DRPs was based on the partly or full implementation of the associated recommendation registered by the pharmacists in the database. Implementations of medication changes were not checked by either analysis of drug dispensing records or by asking patients if the DRPs were solved. A third limitation is that the increase in number of identified DRPs may be associated with other factors than the addition of the CDSS, such as increased experience of pharmacists in performing CMR. However given the number of participating pharmacies (n = 121), we are of the opinion that the only factor that has changed in every pharmacy has been the introduction of the CDSS. Another limitation is that we only measured process outcomes, such as DRPs. Until now the association between DRPs and clinical outcomes has not been confirmed [4,5]. The increase in number of identified DRPs per patients is relatively small (approximately

12.5%). On a population level, however, this add thousands of DRPs. Although not every DRP will have clinical consequences for the patient, we are of the opinion that a proportion certainly will.

Finally, the last limitation is more linked to the CDSS itself. There was a lack of clinical information in the generation of specific alerts by the CDDS. The alerts in the CDSS were mainly based on drug dispensing records, because laboratory values and medical information are often unavailable in the pharmacy information system. This lack of clinical information influenced the implementation rate of the different alerts. This influence was reflected by a broad range in implementation rates between the different alerts in the top 10 potential DRPs identified by the CDSS. The implementation rates ranged from 14% (Absence of antiplatelet therapy in cardiovascular disease)" to 71% ("lack of vitamin D in osteoporosis)". For the first alert, more clinical information about the patient's history is needed to give a recommendation about whether an antithrombotic agent should be started. The second alert is based on the use of a bisphosphonate, which is used for osteoporosis and always requires additional supplementation with calcium and vitamin D [34]. Another explaining factor for the high implementation rate for this alert could be that there is little resistance to initiate vitamin D.

Our results have several implications for future use and studies of CDSS during CMRs. First, we saw that the current CDSS led to the detection of additional potential DRPs, but subsequently a low proportion of these DRPs were resolved. We suggest that the CDSS alerts should be more specific to have added value in detecting clinically relevant DRPs. More specific alerts could be generated by linking dispensing data with clinical diagnoses or laboratory values. Secondly, the aim of a CDSS is to perform a CMR more efficiently by facilitating the identification of potential DRPs. Future studies should include an analysis of the time spent on medication review with and without CDSS is needed to evaluate the added value of the CDSS. Besides that future studies should not only measure DRPs, but also more clinical and patient related outcomes to investigate the real benefits for the patients. Finally, we are of the opinion that a patient interview will always remain essential, because that interview identifies the health issues that are most relevant for the patient.

CONCLUSION

This study shows that the introduction of CDSS into medication review software identified more potential DRPs. However, DRPs identified by CDSS were less frequently resolved compared to DRPs identified by a CMR. Probably a structural assessment including a patient interview, facilitated by a CDSS, would identify the most relevant DRPs. Further development of CDSS with more specific alerts, linking dispensing and clinical information, could make the medication review process more efficient.

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APPENDIX

SUPPLEMENTARY TABLE S1: Overview of explicit criteria incorporated into the CDSS

Description	Type of potential DRP
Concomitant use of three or more antihypertensives	Overtreatment
Concomitant use of two or more antithrombotics	Overtreatment
Inappropriate use of inhaled corticosteroids in COPD	Overtreatment
Concomitant use of ACE-inhibitor and AT-2 antagonist	Overtreatment
Cardiovascular disease without use of a statin	Suboptimal therapy
Absence of antiplatelet therapy in cardiovascular disease	Suboptimal therapy
Loop-diuretics as first-line treatment of hypertension	Suboptimal therapy
Heartfailure without use of an ACE-inhibitor	Suboptimal therapy
Angina Pectoris without use of a statin	Suboptimal therapy
Absence of antiplatelet therapy in angina pectoris	Suboptimal therapy
Chronic heart failure without use of a beta blocker	Suboptimal therapy
Monotherapy with dipyridamole	Suboptimal therapy
Diabetes type 2 without use of a statin	Suboptimal therapy
Diabetes type 2 without use of an antihypertensive	Suboptimal therapy
Two or more short courses with oral corticosteroids per year in patients with asthma or COPD	Suboptimal therapy
Patients using antithrombotic without gastric protection	Suboptimal therapy
Use of opioids without laxatives	Suboptimal therapy
Patients aged 70 years or older using NSAIDs without gastric protection	Suboptimal therapy
Risk for peptic ulcers because of combined use of NSAID's, corticosteroids, anticoagulants, antithrombotics or spironolactone	Suboptimal therapy
Lack of vitamin D in osteoporosis	Suboptimal therapy
Use of non-selective beta blocker (except sotalol) in patients with diabetes	Contra-indication
Use of NSAIDs or salicylates in patients with asthma	Contra-indication
Use of cholinergic drugs in patients with asthma/COPD	Contra-indication
Use of nitrofurantoin in patients with renal impairment	Contra-indication
Use of betahistine/cinnarizine (Drug not recommended because of inadequate efficacy)	Drug not effective
Use of hydroquinine (seldom effective; only in muscle cramps not for restless legs; evaluate efficacy)	Drug not effective
Metformin and risk of reduced absorption of vitamin B12	Adverse effect
Use of glibenclamide in patients aged 70 years or older	Adverse effect
Use of codeine and an ACE-inhibitor	Adverse effect
Patients aged 65 years or older using cimetidine	Adverse effect

SUPPLEMENTARY TABLE S1: (Continued)

Description	Type of potential DRP
Patients aged 65 years or older using amitriptyline (Beers)	Adverse effect
Patients aged 65 years or older using long-acting benzodiazepines (Beers)	Adverse effect
Patients aged 65 years or older using promethazine (Beers)	Adverse effect
Use of oropharyngeal antifungals when using inhaled corticosteroids	Adverse effect
Phenytoin / phenobarbital and folate deficiency	Adverse effect
Interaction (es)omeprazole with clopidogrel	Drug Interaction
Concomitant use of a RAS inhibitor and another potassium enhancing agent	Drug Interaction
Inconvenience of use of ACE-inhibitor: once-daily alternative or combination available	Inconvenience of use
Inconvenience of use of verapamil twice daily: once-daily alternative or combination available	Inconvenience of use
Inconvenience of use of propranolol twice daily: once-daily alternative or combination available	Inconvenience of use
Dosage simvastatin too low	Dosage too low
Dispensing of methotrexate with incorrect dosage advice	Dosage too high
Use of aerosol without a (new) spacer	Inappropriate dosage form
Concomitant use of a powder inhaler and an aerosol	Inappropriate dosage form
Use of rosuvastatin as first-choice à cheaper alternative available	Economic efficiency
Use of rabeprazoleà cheaper alternative available	Economic efficiency

PART 2

Design and results of the DREAMeR study

'Drug use Reconsidered in the Elderly using goal Attainment scales during Medication Review'

CHAPTER 4

DREAMeR: Drug use Reconsidered in the Elderly using goal Attainment scales during Medication Review; study protocol of a randomised controlled trial

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BMC Geriatrics 2018;18:190

ABSTRACT

Background and objective

Clinical medication reviews (CMRs) are increasingly performed in older patients with polypharmacy. Studies have shown positive effects of CMR on process- and intermediate outcomes, such as drug-related problems (DRPs). Little effect has been shown on clinical outcomes, such as hospital admissions or health-related quality of life (HR-QoL). In particular, HR-QoL is related to the individual health-related goals and complaints of patients. The aim of this study is to investigate the effects of a CMR focused on personal goals on HR-QoL and health-related complaints in older patients with polypharmacy.

Methods

A randomised controlled trial will be performed in 35 Dutch community pharmacies aiming to include 630 patients aged 70 years and older using seven or more chronic drugs. Patients will be randomly assigned to control or intervention group by block-randomisation per pharmacy. Patients in the intervention group receive a CMR focussed on patients' preferences, personal goals and health-related complaints. With every goal, a goal attainment scale (GAS) will be proposed. Primary outcome measures are HR-QoL, measured with the EQ-5D-5L and EQ-VAS and the number of health-related complaints per patient measured with a written questionnaire, during a follow-up period of six months. Secondary outcomes are healthcare utilisation, number and type of drug changes, number and type of health-related goals, scores on GAS and number and type of DRPs and interventions.

Discussion

This study is expected to add evidence on the effects of a CMR on HR-QoL and health-related complaints in older patients with polypharmacy. New in this study is the use of personal goals measured with GAS and health-related complaints as patient-related outcome measures.

INTRODUCTION

An ageing population and increased availability of evidence on the potentially beneficial effects of preventive medicine has led to a continuous increase in the number of older patients on chronic drug treatment. Especially in the last decades of life drug use is increasing fast [1]. More than one fifth of patients aged 65 years or older is using five or more medicines and almost one out of four older patients with polypharmacy has potential inappropriate medication [2,3]. The healthcare costs of inappropriate use of medicines are likely to be high, mainly due to drug-related hospital admissions [4,5]. Because of the changing health status in older people, the potential consequences of inappropriate medication and new insights in therapy, chronic medication use must be reviewed regularly [6,7].

Clinical medication reviews (CMRs) are increasingly performed over the last years [8-13]. In the Netherlands pharmacists and general practitioners (GPs) are expected to perform regular CMR in older patients according to the Healthcare inspectorate and national guidelines [7]. Many studies have shown effects of CMR on the quality of drug therapy, such as reducing drug-related problems (DRPs) and inappropriate prescribing [12,14-17]. In addition, studies have shown beneficial effects on disease specific outcomes, such as reducing LDL-cholesterol or HbA1c [15,18,19]. Moreover, studies suggest that CMR can improve more specific outcomes such as pain management and reduction of falls [9,20,21]. However, little effect has been shown on major clinical outcomes, such as morbidity, mortality, hospital admissions and health-related quality of life (HR-QoL) [6,8,20,22-25]. Only one study has shown that medication review with follow-up service improves HR-QoL and is likely to be cost effective [26]. However, the extent of time and the frequency of follow-up contacts in this study is not common for CMR. Therefore extrapolation of the study results is difficult.

According to recent systematic reviews, future studies investigating CMR should be high quality studies including high-risk patients and using relevant outcome measures. CMR should be more targeted on problems that patients experience themselves and outcome measures should be more patient-related [25,27]. Focusing on patient's preferences, health-related complaints and personal goals could be a way to improve patients' HR-QoL. Little is known about the incidence of health-related complaints in older people and to what extent these complaints are related to the HR-QoL of older patients. The only patient-reported complaints that have been studied yet are pain and falls [25,27,28]. The effect of CMR on other health-related complaints such as dizziness, tiredness or intestinal problems has not been studied.

One way of establishing a patient-centred approach in CMR is by setting personal goals. Attainment of goals can be evaluated by goal attainment scaling (GAS). This instrument is

used to measure progress on patient specific health-related goals. GAS has been previously used in rehabilitation care and is increasingly used for studies in (frail) older people [29,30]. However, this tool has never been used in CMR before. Goal setting in CMR can be used a part of a shared-decision making process to reach optimal therapy for patient's current situation, to prioritise the most important problems for the patient, with the aim to eventually improve patient's HR-QoL. An example of an expected health-related goal suggested by a patient during a CMR could be the wish to reduce pain. The severity of pain could be easily measured on the Visual Analogue Scale (VAS) and a GAS could be proposed. During the CMR the pain medication could be optimised to achieve this goal. Another expected goal of older people with polypharmacy could be the wish to use less medication. This could be an excellent opportunity for the pharmacist and GP to address "deprescribing" - the act of tapering, reducing or stopping a medication – and thereby balancing the benefits of the drug (e.g. long term effect) against the disadvantages (e.g. experienced adverse effects) [31]. Also in the perspective of reducing health-related complaints, which could be related to possible side effects of medication, "deprescribing" could be addressed. Current studies on this topic indicate that it is possible to discontinue (preventive) medication in older people and that reducing the number of medicines may decrease adverse events and improve quality of life [32,33]. The drawback of using GAS in a randomised controlled trial is that, as the application of GAS is part of the intervention, attainment of personal goals can only be measured in the intervention group. This study therefore chose HR-QoL as primary outcome as we expect attainment of personal goals will improve quality of life.

In the DREAMeR study we developed a patient-centred approach of CMR. The aim of this randomised controlled trial is to determine the effect of a CMR focusing on the patient's preferences, health-related complaints and personal goals related to their medication on patients' health-related quality of life and their health-related complaints.

METHODS

Study design and setting

The study is a randomised controlled trial performed in 35 community pharmacies spread throughout the Netherlands. The design, conduct, and reporting of the DREAMeR study will adhere to the Consolidation Standards of Reporting Trials (CONSORT) guidelines [34] and basic requirements from the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) [35]. The intervention consists of a CMR performed by a community pharmacist in collaboration with a general practitioner (GP). Participants in the control

group will be placed on a waiting-list; they receive a CMR after the study period (postponed intervention). Patients will be followed-up for six months. The flowchart of **Figure 1** provides a schematic overview of the study phases along with the participant flow at each study phase.

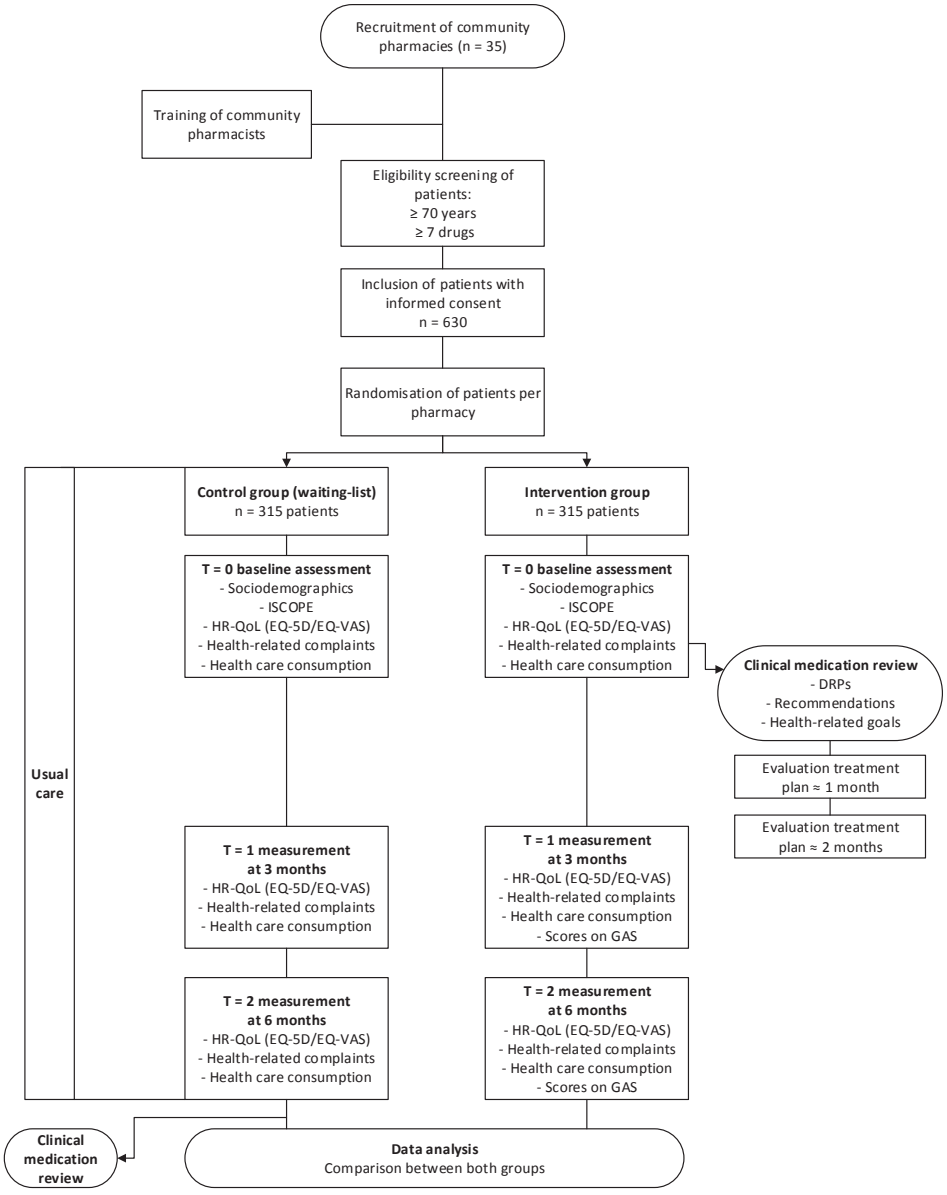

FIGURE 1: Study design DREAMeR study

Community pharmacists and general practitioners

The study was conducted at Dutch community pharmacy franchisees of "Service Apotheek". Participating community pharmacists must be accredited for CMR before start of the study and have performed at least 25 CMRs annually over the past three years. These accredited CMR courses consist of eight course days, video conferences and the obligation to present a portfolio with a number of medication reviews. Finally, the pharmacists should have agreement with at least one GP to join CMR. One or two community pharmacists will conduct the CMRs in each pharmacy. As one community pharmacy is possibly cooperating with several general practices, the pharmacist will collaborate with different GPs. All participating pharmacists must attend a training day prior to the study. During this training, the pharmacists will be instructed about every aspect of the study, such as registration, data collection, using GAS during CMRs and formulating SMART (specific, measurable, acceptable, realistic and time bound) goals together with patients. During the study, monthly web-conferences will be organised, where the pharmacists will present a CMR case with specific attention to the use of GAS.

Participants

The following inclusion and exclusion criteria are defined:

Inclusion criteria

- Community dwelling patients aged 70 years or older.
- Use of seven or more chronic oral drugs. Chronic use of at least one drug is defined as at least three dispensing moments for three months in the last 12 months.

Exclusion criteria

- An expected life expectancy shorter than six months.
- A hospital admission within one month before the inclusion date.
- A received CMR in the past 12 months.
- GP is not the primary caregiver (patients receiving repeat prescriptions solely from a specialist.

Recruitment

The participants will be recruited by their community pharmacists. We expect that in each pharmacy approximately 300-400 patients will be eligible for the study based on the age and number of drugs. We expect each pharmacy to include about 20-30 patients. With an expected response rate of 25%, community pharmacists will invite a total of 50-100 participants per pharmacy.

To avoid selection bias, the inclusion procedure consists of different steps. First, all patients are screened for the inclusion criteria by the pharmacist. Then, the pharmacist sends the lists with the selected patients to their GPs. The GPs judge the patients on the exclusion criteria and sends the list back to the pharmacist An anonymous but numbered list is sent by the pharmacist to the researcher to randomly assign 50 patients which will be invited first. Patients are then invited by letter and/or telephone consultation by their pharmacist.

Randomisation

Randomisation will be performed on patient level per pharmacy. To obtain equal numbers of patients in the intervention and the control group per pharmacy, we use block-randomisation. A block consists of the number of patients who agreed to participate in a pharmacy, usually about 20-30 patients. If an initial inclusion results in less than 20 patients, a second invitation round and block-randomisation will take place. The randomisation procedure will be executed using a computer generated list of random numbers.

Blinding

Participants, pharmacists and GPs cannot be blinded due to the nature of the intervention. All the results will be collected by the researcher in a database. This database will be handed to a statistician who will conduct a blinded analysis to prevent bias in the evaluation of the outcome measures.

Intervention

The CMR will be a comprehensive evaluation of patient's medicines, performed according to an implicit method described in the Dutch multidisciplinary guideline 'Polypharmacy in the elderly' [7]. This implicit method is called the 'Systematic Tool to Reduce Inappropriate Prescribing' (STRIP) method and consists of different five steps: 1) the CMR starts with a patient interview by the pharmacist. Prior to this interview, the patient completes the ISCOPE (Integrated Systematic Care for Older People) screening questionnaire, the EQ-5D questionnaire and the questionnaire 'common complaints in older people' (see outcome measures for explanation). These questionnaires can be used by the pharmacist during the interview. The pharmacist explores the perceived health complaints that may be related to the medication. All drugs in use (including over the counter drugs) by the patient will be discussed. Specific questions will be asked about the experiences of the patient with each drug. Explicit attention will be paid to the practical problems of drug use, effectiveness, adherence and possible side effects. The pharmacist and patient attempt to formulate personal health-related goals (GAS). These goals will concentrate on improving activities of daily living and health-related complaints. 2) After that, DRPs will be identified using all clinical data (laboratory values and diagnoses), medication data (drug dispensing records from the pharmacy) and

patient data from the interview. Recommendations will be formulated to solve these DRPs. Complete discontinuation or dose reduction of medication ("deprescribing") will be addressed when possible. 3) The pharmacist will discuss the DRPs and health-related goals with the GP. A pharmaceutical care plan will be formulated which include which actions will be carried out when and by whom. In this care plan all potential DRPs will be included, focused on patient's preferences and goals, but also on inappropriate prescribing and prescribing omissions. 4) This pharmaceutical care plan will be then discussed with the patient by the pharmacist or the GP and the actions will be implemented gradually. 5) Finally two follow-up moments will be scheduled (within approximately three months). The pharmacist and GP agree on how to perform the discussion of the pharmaceutical care plan with the patient and the follow-up and monitoring. Also the pharmacy technician or practice nurse could be involved in this process. If necessary, the pharmaceutical care plan will be adjusted in concordance with patient, pharmacist and GP. The implementation of the pharmaceutical care plan including follow-up is expected to be completed within approximately three months, depending on the type of interventions and DRPs.

Data collection

Measurements by means of paper questionnaires and telephone interviews will be carried out at baseline, and at three and six months. It is expected that some patients will experience difficulties completing the questionnaires. These patients may be supported by their family or their pharmacist could ask a research assistant to telephonically guide them through the questionnaire. Characteristics of medication and changes in medication will be assessed using drug dispensing data from the pharmacist. All process outcomes of the CMRs, will be collected using the Service Apotheek Medication Review Tool (SAMRT), a software program designed to record DRPs and interventions [12]. All demographic characteristics (sex, age, ethnicity, marital status), and number of drugs will be recorded at baseline. In addition the 'Integrated Systematic Care for Older People' (ISOPE) questionnaire will be completed at baseline [36,37]. This screening questionnaire contains questions on four domains of health: a functional, somatic (health and illness), mental and social domain. Individuals with problems on three as well as four domains are classified as having complex health problems [37].

Outcome measures

Primary outcome measures

The primary outcome measures are HR-QoL and the number of health-related complaints per patient. These outcome measures are collected at baseline, and at three and six months. HR-QoL will be determined by the EQ-5D-5L and EQ-VAS. The EQ-5D-5L has been shown to be valid and reliable in a variety of populations and patient groups [38]. Utilities will be calculated with the aid of EQ-5D tariff [39]. Quality-adjusted life years (QALYs) will be

calculated using linear interpolation between time points. Higher QALY scores indicate more improvement in HR-QoL. An additional cognition-question (EQ-6D) will be included in the questionnaire, but will not be used to calculate utilities and QALYs, as no tariff exists for the EQ-6D. [38]

The number and severity of health-related complaints will be assessed using a self-developed questionnaire which is based on common adverse effects of drugs and common complaints in older people previously identified in the ISCOPE study (see **Table 1** for all the complaints that will be measured) [40]. A complaint will be scored on severity with the VAS and on influence on daily life with a five-point Likert scale to determine the number of complaints with moderate to severe impact on patient's daily life (see example in **Figure 2**).

TABLE 1: Health-related complaints measured in the questionnaire

Type of health-related complaint
Pain
Itching
Dyspnoea
Problems with walking (mobility)
Dizziness
Sedation
Intestinal complaints (constipation/diarrhoea)
Gastric complaints (reflux or ulcer)
Forgetfulness
Fatigue
Dry mouth
Incontinence

Secondary outcome measures

Secondary outcome measures are healthcare consumption and number and type of drug changes. Healthcare consumption will be measured at baseline and at three and six months with the Dutch Medical Consumption (*i*MTA) Questionnaire including informal care [41]. Healthcare utilisation will be valued according to guidelines for economy evaluation in healthcare in the Netherlands [42]. Data about number and type of drugs in use will be derived from the drug dispensing records from the pharmacy information system over a period from

24 months before the start of the study until nine months after the start of the study. Use of OTC drugs is not always recorded in drug dispensing data because the majority is purchased outside the pharmacy in so called drugstores.

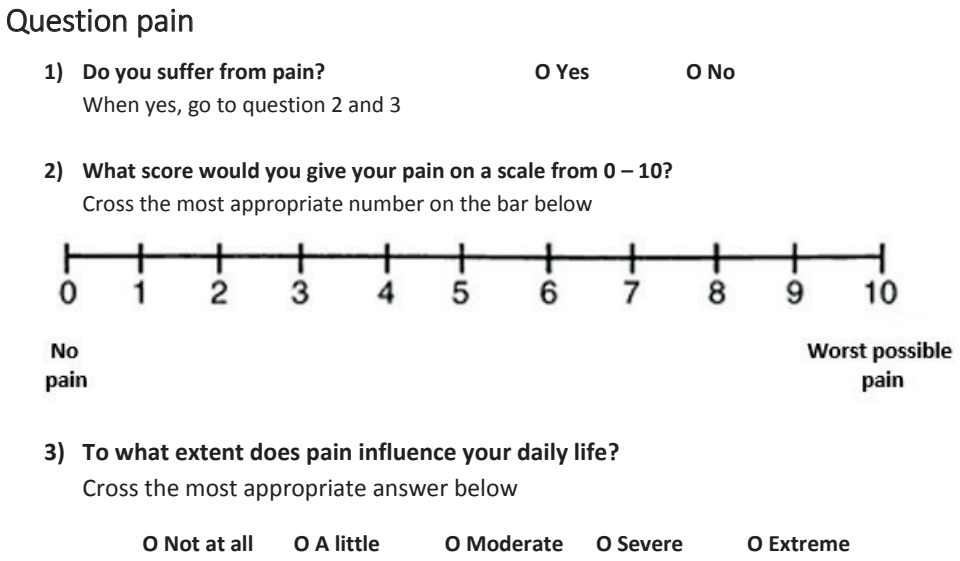

FIGURE 2: Example of question about the health-related complaint "pain"

Other secondary outcomes are process outcomes of the CMRs. The prevalence of number and type DRPs will be measured at baseline. DRPs will be classified accorded to an adapted version of Hepler and Strand which is described in the STRIP-method [7,43]. Also the interventions, such as drug changes, will be validated with the drug dispensing data. Different DRP-types and interventions are summarised in **Table 2**. Next to the interventions, the implementation rates will be calculated, defined as the percentage of the recommendations that are fully or partly accepted by GP and patient (e.g. dose change when cessation of drug was proposed).

Health-related goals with GAS assessed by the pharmacist and the patient during the patient interview will be recorded in a separate database. At the start of the study a database with 50 health-related goals with GAS was composed to help the pharmacists with common examples. This list will be further expanded during the study based on the health-related goals people propose. GAS should be formulated SMART: specific, measurable, acceptable, realistic and

time-bound. The number and type of health-related goals will be assessed at baseline. The scores on the GAS (-3 to +2) will be assessed by telephonic interviews at three and six months. An example of a GAS can be found in **Figure 3**.

All outcomes will be assessed at patient level. An overview of all the outcome measures and instruments is shown in **Table 3.**

TABLE 2: Overview of different DRP and intervention types

DRP type	Intervention type
Overtreatment	Drug added
Drug not effective	Drug ceased
Suboptimal therapy	Drug replaced
(potential) Adverse effect	Dosage regimen changed
Dose too high or too low	Dosage form changed
Usage problem	Performed monitoring
Clinical relevant contra-indication or interaction	Information/advice provided
	Medication synchronised
	Other
	No Intervention

Problem	**Goal**	**Plan**	**Evaluation**
Pain	Reduce pain from VAS-score 6 to VAS-score 4	Start with painkillers; e.g. paracetamol in accurate dose	After 2-4 weeks

		Description	**Example**	**Score**
Was the goal achieved?	**Yes?**	A lot better than expected	No pain anymore or VAS-score < 3	+2
		A little more than expected	Pain VAS-score 3	+1
		As expected	Pain VAS-score 4	0
	No?	Partially achieved	Pain VAS-score 5	-1
		No change	Pain VAS-score 6	-2
		Got worse	Pain VAS-score >6	-3

FIGURE 3: Example goal attainment scale

TABLE 3: Overview outcome measures DREAMeR study

Parameters	Instrument or data source
Baseline assessment	
Sociodemographics	Data questionnaire
Complex health problems	ISCOPE screening questionnaire
Number and type of medication	Drug dispensing records pharmacy
Type of personal goals (intervention group)	Assessed by pharmacist and patient
Primary outcomes	
Health-related quality of life	EQ-5D-5L and EQ-VAS
Health-related complaints	Self-developed data questionnaire
Secondary outcomes	
Healthcare consumption	Dutch Medical Consumption (iMTA) Questionnaire
Number of changed drugs - Number of drugs added - Number of drugs ceased	Drug dispensing records pharmacy
Scores on goal attainment scales (intervention group)	Assessed by independent research assistants
Drug-Related Problems (intervention group)	Recorded in the SAMRT with encodings of table 2
Proposals and interventions of the pharmaceutical care plan (intervention group)	Recorded in the SAMRT with encodings of table 2

Abbreviations: ISCOPE = Integrated Systematic Care for Older People, EQ = EuroQol, VAS = Visual Analogue Scale, iMTA = Institute for Medical Technology Assessment; SAMRT = Service Apotheek Medication Review Tool

Sample size calculation

The sample size is based on an expected change on the EQ-5D health utility values of 0.05 ± 0.20 over six months. This difference is considered to be clinically relevant and feasible, based on previous studies in Spain and the Netherlands [15,26].

To achieve a statistically significant difference in the utility on the EQ-5D with alpha = 0.05 and beta = 0.20, a group size of 252 is sufficient. Allowing for a potential drop-out rate of 25%, a total number of 630 participants are needed (315 in each group).

This sample size is also expected to be sufficient for the second primary outcome measure: the number of health-related complaints per patient. Because comparative studies with this outcome measure are lacking, we have made some assumptions. If the study population

consists of 252 patients per group, a difference on the number of health-related complaints with approximately 0.5±2 with alpha = 0.05 and beta = 0.20 could be demonstrated. We expect that a patient has an average of two health-related complaints with moderate to severe impact on daily life, which may possibly be reduced by 25%. We consider this difference as feasible and clinically relevant. The number of complaints will be highly variable. Therefore we assume a standard deviation of two.

Statistical analysis

Descriptive statistics will be used for patient characteristics. Dropout and loss to follow-up will be described. Effect analyses will be performed according to both 'intention to treat' and 'per protocol' principles. Longitudinal differences in the primary outcomes between the two groups will be analysed with linear and logistic mixed model analyses. Intervention, time (baseline, and at three and six months), and the interaction between intervention and time will be used as fixed factors in the linear mixed model. Participant identification number will be included as a random effect to account for the dependence of repeated observations. Baseline characteristics can be integrated into the mixed model to control for confounding. Secondary outcomes are analysed analogously. Explorative subgroup analyses will be performed. In case of missing data, sensitivity analyses will be conducted to examine the influence of missing data on the study findings. p-Values ≤ 0.05 will be considered significant.

Economic evaluation

An economic evaluation will be added to investigate the additional costs per QALY. Costs will be measured from a societal perspective. Lost productivity costs will not be included since we expect that all patients will be over 65 years of age and therefore retired. Healthcare costs will be assessed using the Dutch Medical Consumption (*i*MTA) Questionnaire [41]. The costs of the intervention will be calculated by multiplying the time spent by the pharmacist with the average wage of a pharmacist. The time spent by the pharmacist is calculated by the average time writing per CMR for every pharmacy. All pharmacists will be asked to record the 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 and GP will be recorded. Drug spending will be derived from the pharmacy information system. Calculation of OTC drugs costs will not be possible, because purchase of OTC drugs is often not recorded in the pharmacy information systems. Quality Adjusted Life Years are used as the measure of effect. They are calculated using the Dutch tariff and the EQ-5D results from the trial. The incremental costs per QALY will be determined. Deterministic and probabilistic sensitivity analyses will be performed.

Process evaluation

Additionally quantitative (process documentation instruments) and qualitative (semi-structured interviews with pharmacists, patients and GPs) process evaluation will be conducted to identify possible barriers of implementation. The process evaluation involves assessing the extent to which the intervention is performed according to the protocol of the study and the opinion of the participants on the intervention.

Ethics

The study design, study protocol, procedure and informed consent are approved by the Medical Ethics Committee of the University Medical Centre of Utrecht (protocol number 15/737). Participation is voluntary and all participants will sign informed consent. The trial was registered in the Netherlands Trial Register number: NTR5713.

DISCUSSION

The DREAMeR study aims to determine the effects of a CMR on patient's HR-QoL and health-related complaints in older people with polypharmacy. What this study adds is the introduction of personal goals measured with goal attainment scales and number of health-related complaints as more patient-related outcome measures. The intervention is a CMR with a patient-centred approach, focusing on patient's preferences, health-related complaints and personal goals. The patients with a CMR are compared to patients in the control group who receive usual care and will receive a CMR after completion of the study.

The DREAMeR study was designed to elucidate the potential effects of CMR on clinical outcomes. Several reasons may contribute to the fact that clinical outcomes of CMR are still sparse despite a body of evidence on the effects on a reduction of DRPs. First, given the small baseline prevalence of hospitalisations and mortality very large sample sizes are needed to determine an effect of CMR on these outcomes. This would need budgets that are generally not available for pragmatic practice based studies. A second reason could be that selection criteria for eligible patients were not specific enough. Selection criteria for patients receiving CMR in studies were often set on patients aged 65 years or older using five or more drugs. Probably a large proportion of this sample of patients will have a high baseline HR-QoL and less medication to change, which makes it difficult to show an effect on HR-QoL. A third reason could be that the performed interventions during CMRs are very heterogeneous, from adding statins (preventive therapy) to adding painkillers (reducing complaints) and from monitoring renal functions (prevent harm from wrong dosage of ACE-inhibitors) to changing dosage regimens (to improve patient adherence). This could make it difficult to measure an effect on a generic outcome such as HR-QoL. Finally, it is possible that in previous studies not all

involved healthcare providers had sufficient experience with CMR, which makes it difficult to perform a good CMR with an effect for the patient. Specific guidelines for CMR have been developed, but compliance with these guidelines in daily practice is likely to be suboptimal.

Taken all these above mentioned hypotheses into account, we have designed the protocol for the DREAMeR study. Despite the fact that it is difficult to prove an effect of CMR on HR-QoL, we still chose the EQ-5D to be one of the primary outcome measures in this study. In our opinion, this is one of the most important outcome measures for older patients. Another advantage of measuring the EQ-5D is that it gives the opportunity to perform a cost-effectiveness analysis, which is needed for healthcare policies. We think that addressing the complaints and goals of patients in the DREAMeR study may translate in increased HR-QoL.

Other studies suggest the importance of more patient-related outcomes in CMR [25,27]. Therefore in this study a second primary outcome measure will be investigated next to the HR-QoL, defined as the number of health-related complaints with an impact on patient's daily life. Previous studies also suggest that CMR might be more beneficial for more specific patient groups. We aim to improve the patient selection with stricter selection criteria: patients aged 70 years or older and using seven or more chronic drugs. With these criteria, more frail patients with more complex diseases will be selected. These patients are potentially more likely to benefit from a medication review and more attention could be paid to the dilemma of "deprescribing" for patients who experience more negative than positive effects of drugs or patients who wish to use less medicines [44]. Until now it is not possible to select frail persons directly from pharmacy information systems. That is why we choose to increase age and number of drugs.

The wish for the reduction of severe complaints or the number of medicines, can be translated into goals. By proposing personal goals with the patient, the interventions in the pharmaceutical care plan can be prioritised. The most important issues for the patient will receive the most attention. Personal goals can be measured with GAS. Older community dwelling persons with complex problems are able to set personal goals using GAS according to one study [29]. GAS is a patient-centred outcome measure that cannot only demonstrate a change in health and function, but can also be scaled to allow for comparison of change within and between groups of older adults with distinct personalised goals [45-47]. The use of GAS makes it possible to aggregate the heterogeneous interventions during CMRs. This is a different approach compared to the usual process-outcomes that are measured in CMR. However, GAS is a new concept for both community pharmacists and GPs to work with. To support pharmacists with the application of GAS during a CMR, we offer a training day, monthly web conferences and a helpdesk service.

After the performance of the patient interview and the preparation of the pharmaceutical care plan in consultation with the GP and patient, specific attention will be paid to the follow-up of the interventions and monitoring of patients during the CMR. This may lead to a higher implementation rate of the interventions. [48].

Besides the use of more patient-related outcome measures and a patient-centred approach of CMR with specific attention to follow-up, the training, support and selection of the pharmacists is another strength of this study. We have selected pharmacists with previous experience and training in CMR and good collaboration with their GPs. We consider these conditions essential to perform a good CMR. However, we still provided extra training and monthly web conferences to ensure a good implementation of the study protocol and gain experience in working with GAS. Finally, a process-evaluation will give insight in the facilitators and barriers for implementation.

Although many have studies evaluated the effect of CMR on DRPs, we are of the opinion that the innovative approach chosen for CMR in this study will give us more insight into 'what really matters to the patient'.

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CHAPTER 5

Effects of a clinical medication review focused on personal goals, quality of life and complaints in older persons with polypharmacy; DREAMeR a randomised controlled trial

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Submitted

ABSTRACT

Background and objective

Clinical medication reviews (CMR) are increasingly performed in older persons with multimorbidity and polypharmacy to reduce drug-related problems. However, effects on clinical outcomes are limited. Little attention has been paid to patient's preferences and needs. The aim of this study was to investigate the effect of a patient-centred CMR, focused on personal goals, on health-related quality of life (HR-QoL) and health-related complaints.

Methods

This study was a randomised controlled trial performed in 35 community pharmacies and cooperating general practices in the Netherlands. Older persons (≥70 years) with polypharmacy (≥ seven chronic drugs) were randomly assigned to usual care or to receive a CMR. The primary outcomes were HR-QoL (assessed with EQ-5D-5L and EQ-VAS) and number of health-related complaints after three and six months. Complaints were measured as the total number of health-related complaints and number of health-related complaints with impact on daily life.

Results

Between April 2016 and February 2017, we recruited 629 persons (54% females, median age 79 years) and randomly assigned them to receive the intervention (n=315) or usual care (n=314). Over six months, compared with the control group, in the intervention group HR-QoL measured with EQ-VAS increased with 3.4 points (difference per 3 months: 1.7; 95% CI 0.47 to 2.9; p = 0.006), and the number of health-related complaints with impact on daily life decreased with 12% (difference per 3 months: -0.17; 95% CI -0.32 to -0.018; p = 0.029). There was no change between the intervention and control group for HR-QoL measured with EQ-5D-5L and total number of complaints.

Conclusion

In older persons with polypharmacy, CMR focused on personal goals increased quality of life measured with EQ-VAS and decreased the number of health-related complaints with impact on daily life, but did not improve quality of life measured with EQ-5D-5L.

INTRODUCTION

Clinical medication reviews (CMR) are increasingly performed and recommended by guidelines for older persons with multimorbidity and chronic medication use [1,2]. It is established that a CMR identifies and reduces drug-related problems (DRPs) and has positive effects on other intermediate outcomes, such as LDL-cholesterol or HbA1c [3-10]. However, the effect of CMR on clinical outcomes, e.g. hospital admissions and health-related quality of life (HR-QoL), is limited [5,6,11,12].

Several factors may contribute to the relative lack of positive evidence on clinical outcomes. First, the selection criteria for persons invited for medication review may have been too broad, e.g. that participants be aged ≥ 65 years and using ≥ 5 drugs [4,7,13,14]. A large proportion of these persons probably have a relatively good quality of life and a low probability for clinical events, such as hospital admissions. Preventing hospital (re)admissions is a very relevant goal of medication review, especially in high risk patients after a recent hospital stay [15]. However, in primary care, hospitalizations are rare and a focus on the general health problems of older persons may be more important. Furthermore, different types of medication reviews (e.g. treatment review or clinical medication review) are performed in different settings (e.g. primary care, nursing homes or hospital wards), implying that interventions performed during medication review are often heterogeneous [4,11,15-19]. For example, these interventions can vary from adding prophylactic medication (such as statins) to the start of symptomatic treatment (such as analgesics) and the discontinuation of medicines that cause side-effects (e.g. psychoactive drugs that cause dizziness or falling). This complicates measurement of an effect on a generic outcome, e.g. quality of life. Finally, earlier studies may have involved healthcare providers that lacked sufficient training and experience with a patient-centred CMR. Studies have recommended that future studies investigating CMR should include high-risk patients and use relevant patient-related outcome measures [5,6,20,21].

In the 'Drug use Reconsidered in the Elderly using goal Attainment scales during Medication Review' (DREAMeR) study, we developed a patient-centred approach of CMR in which the health-related complaints, preferences and personal goals of older people receive specific attention. The aim of the present randomised controlled trial (RCT) was to determine the effect of such a patient-centred approach in CMR on patients' health, fuctioning and wellbeing, including health-related quality of life and health-related complaints.

METHODS

Study design and setting

The DREAMeR study was a pragmatic RCT performed in 35 community pharmacies in the Netherlands comparing a CMR focused on personal goals with usual care. Between April 2016 and February 2017 patients were invited by the pharmacists to participate in this study and were followed for six months. 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. Participation was voluntary and all participants provided signed informed consent. The nature of the intervention made blinding impossible. The extensive study protocol has been published elsewhere [22].

Community pharmacists and general practitioners

Participating community pharmacists were accredited to perform CMR and had performed at least 25 CMRs annually over the past three years. The participating pharmacists received one day training about all aspects of the study, e.g. registration, data collection, communication skills, and goal setting in older persons during CMRs. Each pharmacist collaborated in the CMRs in this study with at least one general practitioner (GP); all GPs were informed by the pharmacists about the study. During the study, monthly web conferences were organised in which study progress and cases of the CMRs were discussed.

Participants

Persons were eligible if they were aged ≥ 70 years and used ≥ 7 chronic drugs. Exclusion criteria were: i) an expected life expectancy ≤ 6 months, ii) hospital admission within one month before the inclusion date, iii) having received a CMR in the past 12 months, and iv) receiving repeat prescriptions solely from a hospital specialist.

Intervention

Patients in the intervention group received a CMR review focused on personal goals. The Dutch multidisciplinary guideline 'Polypharmacy in the Elderly' was followed to perform these CMRs [2]. Full drug dispensing records and clinical records (disease history, and laboratory values) were available at the start of the CMR. The contribution of the patient was ensured by: using the questionnaires on health-related complaints at the start of the CMR as input for the pharmacist, and by proposing their personal health-related goals during the patient interview. A novel aspect of the present study was to propose goals during the patient

interview and evaluate them using goal attainment scaling (GAS). GAS is an individualised goal setting and measurement approach that is useful for patients with multiple, individualised health problems [23,24]. The process of CMR consisted of five different steps: 1) A patient interview performed by the community pharmacist, consisting of an extensive discussion of health-related complaints, patient's preferences, and all currently used drugs (including their effectiveness, usage, adherence, side-effects, and practical problems, and also for over-the-counter medication). At the end of the interview, all problems were summarised and one or more health-related goals were proposed. These goals could be related to patient's health-related complaints or other wishes related to medication and diseases and were (as far as possible) SMART formulated (i.e. specific, measurable, acceptable, realistic, and time-bound). 2) After the patient interview, all potential DRPs were summarised by the pharmacist and recommendations were proposed to attain goals and to solve DRPs. 3) The pharmacist had a face-to-face meeting with the patient's GP to discuss all health-related goals and other identified DRPs. They then proposed a pharmaceutical care plan including which actions should be carried out, as well as when and by whom. 4) The pharmaceutical care plan was then discussed with the patient to reach agreement about implementation. 5) Two follow-up moments were scheduled (within approximately three months), in which the pharmacist evaluated the agreed actions and the attainment of goals with the patient and, if necessary, adjusted the treatment plan in concordance with the GP. The CMR was expected to be completed within approximately three months, depending on the type of interventions. The scores on GAS at three and six months were independently collected by research assistants during telephonic interviews.

Usual care

The patients in the control group received usual care and were placed on a waiting list; all of them were offered a CMR after the end of the study (postponed intervention).

Outcome measures

The primary outcome measures were i) HR-QoL measured with the EuroQol EQ-5D-5L and the EQ-VAS (range 0 to 100), and ii) the number of health-related complaints. Health utility values (range -0.329 to 1) were calculated for EQ-5D-5L, indicating (less than) zero as death and 1 as best possible health status [25]. An additional cognition-question (EQ-6D) was included in the questionnaire, but was not used to calculate health utility values because, currently, no tariff exists for the EQ-6D [26]. Health-related complaints were divided into total complaints per patient (irrespective of the severity) and number of complaints per patient with a moderate to severe impact on daily life. A list with twelve complaints was measured based on the most commonly reported complaints in older people and the most common side-effects of drugs [27] (*see Chapter 4*). We assessed clinical relevance of the complaints, by

measuring severity and impact on patient's daily life. We defined a complaint with impact on daily life as one with a severity score of ≥ 5 on a Visual Analogue Scale (VAS; range 0-10) [28], and moderate, severe or extreme influence on daily life (i.e. ≥ 3 points on 5-point Likert scale).

Secondary outcome measures were i) number of prescribed drugs in use, ii) number of prescribed drugs added and ceased, and iii) severity of complaints measured with VAS scores (range 0-10). In the intervention group, process outcomes measured during the CMRs were number of health-related goals, attainment of goals measured with GAS, and number of DRPs per patient. Drug dispensing records were used to determine the number and type of drugs in use during each month. Finally, demographic information was collected, including the 'Integrated Systematic Care for Older People' (ISCOPE) screening questionnaire, to determine complex health problems in the participants [29].

Sample size

Calculation of a sample size was performed based on a change in health utility values of the EQ-5D from 0.05 with a standard deviation of 0.20 over six months; this difference was considered to be clinically relevant and feasible, based on previous studies [9,30]. This difference corresponded with a 5-point change in EQ-VAS. To achieve a statistically significant difference in the utility on the EQ-5D with alpha = 0.05 and beta = 0.20, a group size of 252 was sufficient. When correcting for a potential drop-out of 25%, a total of 630 patients was needed (i.e. 315 per group).

Statistical analysis

Descriptive statistics were used to describe patient characteristics. The analysis was based on intention-to-treat and effects of the intervention on outcome measures over six months were estimated using linear mixed model analyses. Intervention, time (baseline, and at three and six months), and the interaction between intervention and time were entered as fixed factors in the model. For effects on the number of drugs, the intervention, time (per month) and the interaction between intervention and time were entered as fixed factors in the model. Participant identification number was included as a random effect to account for the dependence of repeated observations. Adjustment for sex, age and pharmacy was made in the final models. Finally, a per protocol analysis was performed. Data were analysed using IBM SPSS Statistics 24.0 (IBM Corporation, Armonk, NY, USA). A p-value < 0.05 was considered statistically significant.

Ethics

The DREAMeR study was 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. All data were anonymised using a randomly assigned subject number.

RESULTS

Descriptive statistics

Of the 2290 invited patients, 707 (31%) consented to participate (**Figure 1**). Participants were recruited between April 2016 and February 2017; follow-up was performed up to August 2017. A total of 629 patients were randomised into the control (n=314) and intervention (n=315) group. Over six months, the total drop-out rate was 6.7% in the intervention group and 6.4% in the control group (p = .88). A total of 588 patients completed the study and complete data for the primary outcomes were available from 503 patients. All patients in the intervention group received the intended treatment. Since seven patients in the control group received a CMR before the end of the study, these patients were excluded from the per-protocol analysis. There patient characteristics for the intervention and control group are shown in **Table 1**. The number of participants per pharmacy ranged from 2-30 (per pharmacy: mean 18 (SD = 8)). A total of 43 community pharmacists (working in 35 community pharmacies) and 113 GPs participated in this study. The average time spent by the community pharmacists to completely perform a CMR was 107 (SD = 40) minutes.

Primary outcomes

Table 2 shows the unadjusted scores for primary outcomes at baseline and at three and six months. HR-QoL measured with the EQ-5D-5L showed no significant difference over time between the intervention and control group (β= -0.0011 per three months; 95% CI -0.012 to 0.010; p = 0.85; **Table 3**). HR-QoL measured with the EQ-VAS improved after six months with 3.4 points (β=1.7 per three months; 95% CI 0.47 to 2.9; p = 0.006; **Table 3**) in the intervention group compared to control group. Unadjusted regression scores showed similar results (data not shown). The scores on the six domains of the EQ-6D showed no differences between the two groups (*Supplementary Table S1*).

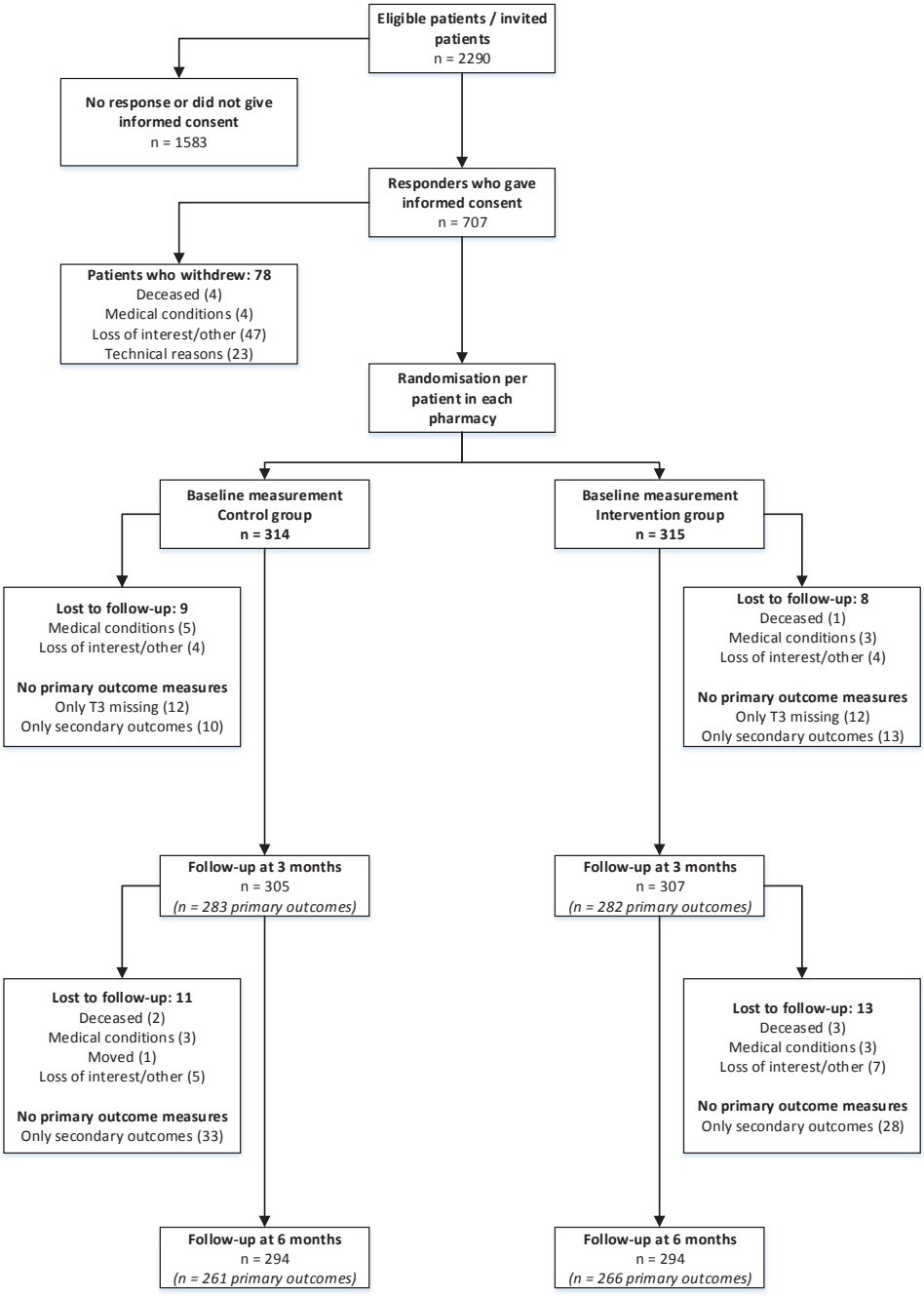

FIGURE 1: Flowchart of the study population

TABLE 1: Baseline characteristics of participants in the control and intervention group of the DREAMeR study

Characteristic		Control group (n = 314)	Intervention group (n = 315)
Sociodemographic			
Age, median (IQR), years		78 (74-82)	80 (76-83)
Sex, female		52%	56%
Ethnicity, European		98%	97%
Living situation, alone		37%	44%
Complex health problems†		24%	25%
Drug-related			
Number of drugs in use, median (IQR)		9.0 (7.5-10.5)	9.0 (7.5-10.5)
Multidose Drug Dispensing system use (%)		22%	27%
Most prescribed drug classes (ATC)			
A02B	Drugs for peptic ulcer and GORD	81%	83%
B01A	Antithrombotics	78%	79%
C10A	Lipid modifying agents	74%	71%
C07A	Beta blockers	70%	60%
C08C	Selective calcium channel blockers	38%	32%
A10B	Oral blood glucose lowering drugs	35%	31%
C09A	ACE inhibitors	38%	30%
C09C	Angiotensin II antagonists	30%	29%
A11C	Vitamin A and D	28%	25%
C03C	High-ceiling diuretics	23%	23%

Abbreviations: IQR = interquartile range; ATC = Anatomical Therapeutic Chemical classification; GORD = gastro-oesophageal reflux disease; †complex health problems measured with ISCOPE score (Integrated Systematic Care for Older People)

No differences were found in the total number of health-related complaints, irrespective of severity (β = -0.15 per three months; 95% CI -0.32 to 0.027; p = 0.099; **Table 3**). Compared to the control group, in the intervention group the number of complaints with impact on daily life decreased after six months with -0.34 complaints (β= -0.17 per three months; 95% CI -0.32 to -0.018; p = 0.029; **Table 3**), which is a reduction of 12% compared to baseline. Per-protocol analyses did not show different results compared to the intention-to-treat analyses (data not shown).

TABLE 2: Unadjusted scores for health-related quality of life and complaints over time in the control and intervention group

	Control group			Intervention group		
Outcome (mean, SD)	**Baseline (n=314)**	**T1 = 3 months (n=283)**	**T2 = 6 months (n=261)**	**Baseline (n=315)**	**T1 = 3 months (n=282)**	**T2 = 6 months (n=266)**
Health-related quality of life						
EQ-5D-5L, utility values	0.74 (0.18)	0.74 (0.17)	0.74 (0.18)	0.73 (0.18)	0.74 (0.18)	0.73 (0.20)
EQ-VAS	70 (16)	69 (16)	69 (15)	68 (16)	69 (17)	70 (16)
Health-related complaints						
Total complaints	5.5 (2.9)	5.3 (2.7)	5.3 (2.9)	5.9 (3.0)	5.6 (3.0)	5.5 (3.0)
Complaints with impact	2.6 (2.4)	2.5 (2.3)	2.5 (2.4)	2.8 (2.4)	2.5 (2.4)	2.4 (2.4)

Abbreviations: EQ-5D = EuroQol-5D; VAS = Visual Analogue Scale; SD = standard deviation
Definition complaint with impact = Severity VAS-score ≥5 and influence on daily life: moderate, severe, extreme

TABLE 3: Main outcomes of the linear mixed model analysis for intervention group compared to control group for health-related quality of life and complaints

	Group		Time		Group * Time	
Outcome	**β**	**95% CI**	**β**	**95% CI**	**β**	**95% CI**
Health-related quality of life						
EQ-5D-5L, utility values	+0.0073	-0.025 to 0.040	-0.0024	-0.010 to 0.0054	-0.0011	-0.012 to 0.010
EQ-VAS	-3.2*	-6.3 to -0.010	-1.0*	-1.9 to -0.17	+1.7**	0.47 to 2.9
Health-related complaints						
Total complaints	+0.30	-0.14 to 0.74	-0.041	-0.16 to 0.081	-0.15	-0.32 to 0.027
Complaints with impact	+0.11	-0.24 to 0.0.46	-0.0099	-0.12 to 0.098	-0.17*	-0.32 to -0.018

β coefficient and 95% CI for group (control vs. intervention group), time (per 3 months for HR-QoL and complaints and per month for drug use), group by time interaction (adjusted for age, sex, pharmacy)
*p<0.05, **p<0.01.
Abbreviations: CI = Confidence Interval; VAS = Visual Analogue Scale
Definition complaint with impact = severity VAS-score ≥5 and influence on daily life: moderate, severe, extreme
NB. The estimators in the column: "group * time" show the main difference in effects between the intervention group vs. control group per three months for HR-QoL and complaints

Secondary outcomes

Compared to the control group, in the intervention group the total number of drugs decreased with -0.32 drugs after six months (β= -0.054 per month; 95% CI -0.094 to -0.014; p = 0.008). A mean number of 1.7 drugs per patient was added in the intervention group compared to 1.4 drugs in the control group (p = 0.011); a mean number of 1.5 drugs was ceased in the intervention group compared to 1.0 in the control group (p < 0.01). Changes in drug use over time are shown in *Supplementary Figure S1*.

There was large variability in the prevalence and severity of the 12 complaints, with pain, mobility and fatigue being the most prevalent in both groups (*Supplementary Table S2*). No effects were found in frequencies and severities between the groups (*Supplementary Table S3*).

Process outcomes

At least one health-related goal was proposed in 283 patients in the intervention group (90%), with a mean of 1.4 per patient (SD = 0.52). Of the total number of 406 proposed goals, 350 were evaluated with GAS in 256 patients at three months (86%), and 347 goals in 247 patients at six months (86%). At three and six months, 37% and 43% of the goals were achieved, respectively. The mean number of DRPs per patient was 5.8 (SD 2.1); of these DRPs, 67% were solved and led to an intervention. Of all DRPs, 28% were related to a health-related goal.

DISCUSSION

The DREAMeR study shows that a CMR, focused on personal goals, improves quality of life measured with the EQ-VAS in older persons with polypharmacy and reduces the number of health-related complaints with moderate to severe impact on daily life. Concurrently, CMR decreased the number of prescribed drugs used. However, there was no effect on HR-QoL measured with the EQ-5D-5L and total number of complaints.

To our knowledge, this is one of the first studies to demonstrate a beneficial effect of CMR on HR-QoL measured with the EQ-VAS and to show an effect on the number of health-related complaints. Only one previous study has shown CMR to be effective on HR-QoL on both utility values and VAS-scores [30]; in that study, the medication reviews included six follow-up moments. Many earlier studies investigating CMR focused on prescribing guidelines and potential inappropriate prescribing, rather than patient goals [3,5,7,9,13,31,32]. Several studies suggested that patient interviews are important to find the most relevant DRPs [2,33-35].

In the DREAMeR study, the patient-centred approach of CMR improved relevant outcomes for older patients' lives such as the EQ-VAS and the number of complaints with impact on daily life. Despite the fact that the EQ-5D health utility values did not change, the more patient-relevant EQ-VAS did change, even though it was a small change of 3.4 points. Taken this in combination with the effect on complaints with impact on patient's life and a small reduction in the number of medicines in use, we consider this of clinical relevance for older patients' lives. It is a well-known problem that the patient experience is not always adequately represented in the responsiveness of the EQ-5D [36,37]. This indicates that patient-reported outcomes are important to show the benefits of this type of patient-centred care. Effects of a medication review on specific health-related complaints (such as pain), have been reported earlier [38], but no studies measured a range of 12 different complaints during medication review in primary care.

In addition to 'scientific evidence' and the 'experience of health care professionals', our patient-centred CMRs structurally adds 'patient's values and preferences' to complete the three main component of evidence based medicine. In this study, during the CMRs we specifically focused on patients' preferences, whereas many previous studies did not structurally involve this aspect. Shared decision-making involving the GP, pharmacist and patient needs a stepwise and individualised approach and goal setting [39,40]. In the present study, all these aspects were present during the CMRs. Goal setting during CMRs is important to prioritise the most important problems and motivate the patient for potential interventions, such as a change in drugs.

This study shows that both addition and discontinuation of drugs occurred more frequently in the intervention group. This demonstrates that, in older patients, a personalised approach is important, thereby balancing all potential harms and advantages to achieve optimal pharmacotherapy for an individual's current situation. In this study, the net effect was a slight decrease in the total number of drugs used; this is interesting as it is increasingly accepted that "deprescribing" in older persons with polypharmacy is a major challenge for the coming years [41-43].

Strengths and limitations

This study has several strengths. First, the novelty of the design was the combination of a complex intervention with personalised goal setting using patient-reported outcomes. Second, proposing personal goals during the medication reviews was new and effective in prioritising the most important problems for patients. Third, this was a pragmatic trial performed in daily pharmacy practice, which might enhance the generalisability of our results. Finally, we

included pharmacists with experience in CMR and established cooperation with GPs, and stipulated two follow-up contacts with patients by pharmacists and/or GPs. In this way, we included all the necessary elements for good CMRs [2,33,34].

Some limitations also need to be addressed. First, due to the nature of the intervention blinding was not feasible, which might have influenced the results of this trial. Second, there is a risk associated with proposing and measuring goals. For example, when unrealistic or unsolvable goals are proposed by the patient, this can lead to disappointment and a reduction in quality of life. Therefore, it is important to address a SMART formulation of goals. Finally, it is difficult to demonstrate which part of this complex intervention, (e.g. goal setting, extra attention to patients, reducing complaints, drug changes, etc.) has contributed to the effects that are found.

It could be questioned whether this type of CMRs could be implemented worldwide. CMRs are performed in different countries, but not always on this structural basis as in the Netherlands, due to limitations in remuneration, performance settings, lack of guidelines and limited effects [1,2,44-47]. As attention to goal oriented patient care and patient outcomes will become increasingly important in the management of multimorbidity and polypharmacy [12,48], implementation of patient-centred CMR is one of the steps to improve older patients' lives.

CONCLUSION

In older persons with polypharmacy, a clinical medication review focused on personal goals, improved health-related quality of life measured with EQ-VAS, reduced the number of health-related complaints with an impact on daily life and the number of drugs used, but did not improve health-related quality of life measured with EQ-5D.

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APPENDIX

SUPPLEMENTARY TABLE S1: Number of participants with problems on the six domains of the EQ-6D at baseline and at six months: comparison between control and intervention group

	Control group		Intervention group	
Outcome EQ-6 Domains	**Baseline (n=314)**	**At 6 months (n=261)**	**Baseline (n=315)**	**At 6 months (n=266)**
Mobility	76%	79%	77%	78%
Self-care	25%	27%	27%	26%
Daily activities	63%	66%	64%	69%
Pain/other complaints	79%	79%	77%	76%
Mood/anxiety	30%	27%	31%	32%
Cognition	52%	52%	59%	58%

NB. Percentage of patients with light to severe problems on each domain (score 2-5) compared to no problems (score 1).
The EQ-6D questionnaire contained six questions about six different health domains, but only five domains were used to calculate the health-utility values (cognition was excluded)

SUPPLEMENTARY TABLE S2: Baseline prevalence and severity measured with VAS-score of complaints, comparison between control and intervention group

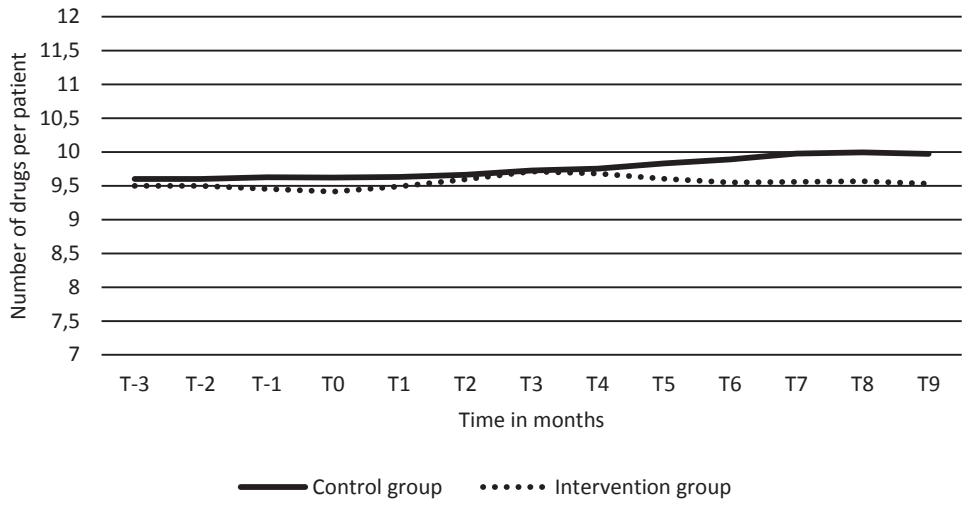
	Control group (n = 314)			Intervention group (n = 315)		
Type of health-related complaint	**Total complaints**	**Complaints with impact**	**VAS-score, mean (SD)**	**Total complaints**	**Complaints with impact**	**VAS-score, mean (SD)**
Pain	74%	43%	5.1 (2.1)	72%	41%	5.1 (2.2)
Itching	34%	14%	4.2 (2.2)	35%	11%	4.0 (2.3)
Dyspnoea	48%	25%	4.8 (2.2)	51%	23%	4.7 (2.1)
Mobility	77%	53%	5.7 (2.2)	78%	55%	5.9 (2.3)
Dizziness	35%	11%	3.6 (2.0)	43%	16%	4.1 (2.2)
Sedation	19%	6.4%	3.8 (2.0)	26%	7.9%	3.7 (2.1)
Intestinal problems	37%	17%	4.7 (2.2)	40%	20%	4.9 (2.2)
Stomach problems	23%	4.8%	3.5 (2.1)	23%	7.3%	3.9 (2.3)
Cognition	50%	8.6%	3.2 (1.8)	57%	11%	3.4 (2.1)
Fatigue	68%	40%	5.1 (2.2)	72%	44%	5.2 (2.1)
Dry mouth	43%	19%	4.6 (2.2)	46%	18%	4.6 (2.3)
Incontinence	38%	17%	4.5 (2.5)	43%	18%	4.6 (2.5)

NB. Data on <5% were missing; % of patients=number of patients with complaints compared to total number of patients at baseline.
Prevalence at baseline showed a significant difference between the groups for dizziness and sedation.
Definition of patient-relevant complaint = Severity VAS score ≥5 and influence on daily life: moderate, severe, extreme

SUPPLEMENTARY TABLE S3: Effects in severity measured with VAS scores over time: comparison between different health-related complaints.

Type of health-related complaint	Effects		
	β	p-value	95% CI
Pain	-0.075	0.43*	-0.26 to 0.11
Itching	-0.10	0.49	-0.40 to 0.20
Dyspnoea	-0.21	0.091	-0.45 to 0.033
Mobility	-0.086	0.34	-0.26 to 0.089
Dizziness	-0.27	0.077	-0.57 to 0.029
Sedation	-0.20	0.32	-0.61 to 0.20
Intestinal problems	-0.18	0.24	-0.47 to 0.12
Stomach problems	+0.022	0.90	-0.34 to 0.39
Cognition	-0.021	0.84	-0.23 to 0.19
Fatigue	-0.17	0.053	-0.34 to 0.0024
Dry mouth	-0.17	0.23	-0.44 to 0.11
Incontinence	+0.067	0.61	-0.19 to 0.33

NB. β coefficient and 95% CI group by time interaction (adjusted for age, sex, pharmacy)
*effect at 3 months is significant, but not at 6 months.
Abbreviations: CI = Confidence Interval; VAS = Visual Analogue Scale



SUPPLEMENTARY FIGURE S1: Mean number of drugs per patient over time for both groups.

NB. T0 = baseline

CHAPTER 6

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

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ABSTRACT

Background and objective

The number of older persons with polypharmacy is rising which may lead to increasing healthcare expenditure in the future. A clinical medication review (CMR) may reduce costs, but due to the labour intensiveness, could also further escalate healthcare costs. The aim of this study was to perform a cost-utility and cost-effectiveness analysis from a societal perspective of a CMR focused on personal goals.

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 ≥ 7 drugs to either a 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-5L and EQ-VAS and as reduced health-related complaints with impact on patients' daily lives.

Results

A total of 588 patients were analysed. The total mean costs per patient over six months were €4189 ± 6596 for control group (n = 294) and €4008 ± 6678 for intervention group (n = 294) including estimated interventions 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 control group, for the intervention group, the mean incremental QALYs over six months were the following: -0.00217 measured with EQ-5D and 0.00363 measured with EQ-VAS and the incremental effect of reduced health-related complaints with impact was -0.33. Probabilistic sensitivity analysis showed a likelihood of >90% that the intervention was cost saving. A CMR dominated usual care for the cost/QALYs measured with EQ-VAS and the cost/change in health-related complaints with impact.

Conclusion

A CMR is an attractive intervention for older patients with polypharmacy, due to a high probability of healthcare cost savings combined with a small beneficial effect on HR-QoL measured with EQ-VAS and health-related complaints.

INTRODUCTION

In most developed countries the number of older people with multimorbidity and chronic medication use is expected to continue rising in the next decennia [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 drug-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, minimizing 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 further rising of 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 CMRs 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 personal goals, compared to usual care.

METHODS

Study design and setting

This study was a trial-based cost-effectiveness and cost-utility analysis of the DREAMeR study. 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 Dutch community pharmacy franchisees of "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 the aspects of the study. The general practitioners (GPs) were informed by the pharmacists about the study. The DREAMeR study was 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. All data were anonymised using a randomly assigned subject number. The full study protocol of this RCT has been published elsewhere [23].

Intervention & 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 examined the personal goals, preferences and other DRPs to 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).

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-5L and EQ-VAS [24]. The EQ-5D-5L 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-5L 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-5L and EQ-VAS using linear interpolation between time points. Within the time horizon of the study (six months) the maximum number of QALYs that a patient could gain was 0.5.

Health-related complaints were measured with a written questionnaire 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 six months after the study period.

Costs

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 since all patients were expected to be retired being that they are all older than 70 years.

Measurement

Healthcare consumption was measured with the Dutch Medical Consumption (iMTA) Questionnaire including an extra question about informal care through telephonic assessments performed by independent study assistants at baseline and three and six months after the start

date. [28] Data were collected at each time point about the previous three 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. Drug dispensing records were collected from the pharmacy information systems to calculate drug costs during the study period of six months. To measure the time spent for the CMR, all pharmacists were asked to record the average time spent for every step of the CMR 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.

Valuation

Healthcare utilisation was valued according to guidelines for economic evaluation in healthcare in the Netherlands [29]. 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].

Analysis

Descriptive statistics were used to describe patient characteristics. Costs were calculated over the six months period. To account for missing data in effects and costs, the method of multiple imputations was used to generate 10 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. The EQ-VAS measurements were transformed to a utility scale using the power transformation 1 (VAS/100). Results of the cost-effectiveness analysis were expressed in terms of the incremental cost effectiveness ratio (ICER) six 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 six months after 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 probability 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.

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).

RESULTS

Descriptive statistics

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**.

Intervention

The CMR process was divided into different steps and the average time spent per step is shown in **Table 2**. The mean time to perform a CMR was 107 (SD = 41) minutes for the community pharmacist, 7 (SD = 12) minutes for a pharmacy technician and 12 (SD = 8) minutes for the GP. The time for the GP was only recorded for the conversation with the pharmacist.

Effects

Effects on primary outcomes are presented in **Table 3**. Mean QALYs measured with EQ-5D per six months were 0.369 and 0.367 for respectively the control group and intervention group, resulting in an incremental QALY of -0.00217. Mean QALYs measured with EQ-VAS over six months were 0.345 for control group and 0.348 for intervention group resulting in an incremental QALY of 0.00363. Effectiveness measured as reduced health-related complaints

with impact over six 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 three and six months are presented in *Chapter 5*.

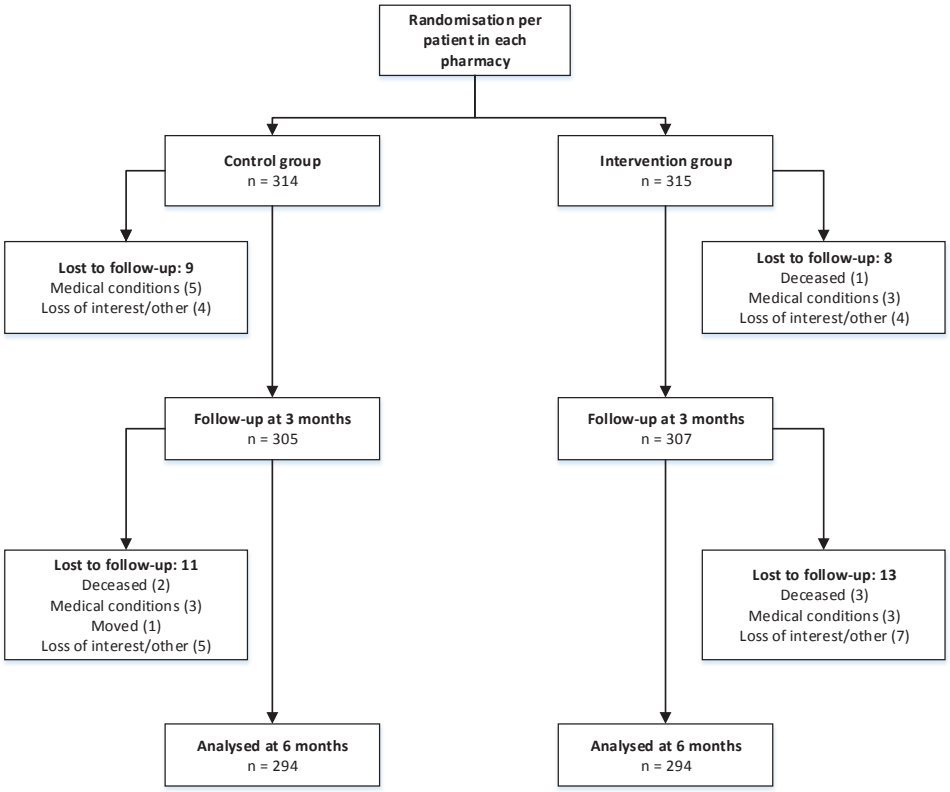

FIGURE 1: Flowchart of the study population

Costs

Table 3 summarises the different costs over the six months study period. The total mean healthcare costs per patient were €3809 ± 6678 in the intervention group compared to €4189 ± 6596 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 €4008 ± 6678 compared to €4189 ± 6596 in the control group. This results in an incremental cost of -€181 for the intervention compared to usual care.

TABLE 1: Baseline characteristics of participants in the control and intervention group

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*	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)

Abbreviations: IQR = interquartile range, SD= standard deviation, EQ=EuroQol, VAS=visual analogue scale;
* 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 pharmaceutical care plan	12 ± 8		12 ± 8
Implementation of actions	11 ± 6		
Follow-up and evaluation	16 ± 15		
Other*	5 ± 11	2 ± 5	
Total	107 ± 41	7 ± 12	12 ± 8

NB. Average time spent in minutes (mean ± SD).
Other* means 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.

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

Type of effects and costs	Control group (n = 294)	Intervention group (n = 294)	Incremental effects or costs
Effects			
QALYs (EQ-5D)	0.369	0.367	-0.00217
QALYs (EQ-VAS)	0.345	0.348	0.00363
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 ± 3507	€ 311 ± 3655	-€ 164
Home care	€ 1198 ± 2821	€ 1296 ± 2923	€ 97
Informal care	€ 474 ± 2126	€ 323 ± 1542	-€ 150
Total healthcare costs	€ 4189 ± 6596	€ 3809 ± 6678	-€ 380
Intervention costs			
Clinical medication review	n.a.	€199 ± 67	€ 199
Total costs	€ 4189 ± 6596	€ 4008 ± 6687	-€ 181

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

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 off set 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.

Deterministic and 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, PSAs were performed and are presented in **Figure 2**. Figure 2a illustrates the ICER for costs/QALY measured with EQ-5D. Most of the simulations are located in the lower-left quadrant (60%) and in the lower-right quadrant (34%) of the cost-effectiveness plane, which results in a chance of 94% that a CMR is cost saving. Figure 2b presents the

ICER for costs/QALY measured with EQ-VAS; most of the simulations are located in the lower-right quadrant (69%) and in the lower-left quadrant (25%) of the cost-effectiveness plane, which results in a chance of 94% that a CMR is cost saving (Figure 2b). Figure 2c offers the ICER for costs/reduced complaint with impact; most of the simulations are located in the lower-right quadrant (84%) and in the lower-left quadrant (9%) of the cost-effectiveness plane, which results in a chance of 93% that a CMR is cost saving (Figure 2c). The acceptability curves are shown in *Supplementary Figure S1.*

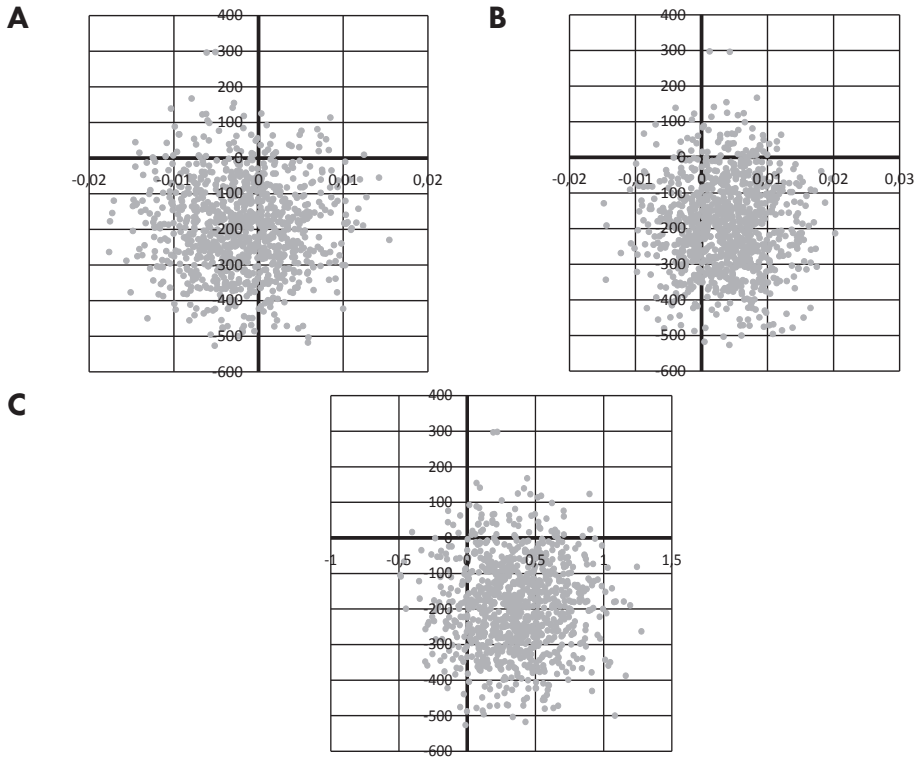

FIGURE 2A, B, C: Cost-effectiveness plane for the incremental cost-effectiveness ratios (ICERs) determined as a) costs/QALY measured with EQ-5D-5L health utility values, b) costs/QALY measured with EQ-VAS health utility values and c) costs/effects determined as reduced complaints with impact. The x-axis shows the incremental effects and the y-axis shows the incremental costs in euros. Abbreviation: QALY = quality-adjusted life year.

Results from the DSAs are shown in **Figure 3**. The results show that the 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.

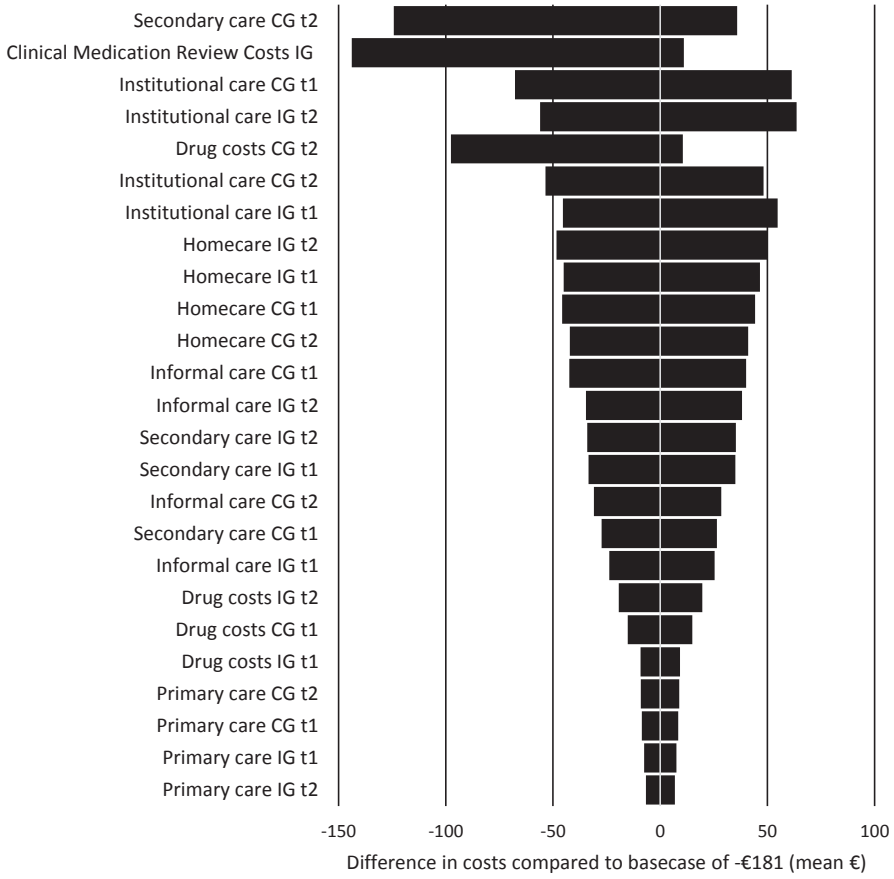

FIGURE 3: Tornado diagram which describes the effects of uncertainty for the different cost categories

Abbreviations: CG = control group, IG = intervention group, t1 = calculated over the period of 0-3 months after study start date, t2 = calculated over the period of 4-6 months after study start dat

DISCUSSION

This study shows that a CMR focusing on patient's preferences, goals and health-related complaints is dominant compared to usual care, when examining QALYs measured with EQ-VAS and effects measured as health-related complaints with impact on daily life over the study period of six months. When we focus on the incremental costs per QALY measured with EQ-5D, our results show a high chance of cost savings together with no differences in effects between both groups.

There is limited evidence for effects of CMR on clinical and economic outcomes [14,32,33]. The patient-centred approach applied during CMRs in this study improved relevant outcomes for older patients' lives based on the EQ-VAS and the number of health-related complaints with impact on patients' daily lives. Health utility values did not change. 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 [34,35]. 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]. 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 [36].

The average healthcare costs of the patients in this study are representative of the current Dutch situation for this age group [37]. A CMR could lead to small cost savings in healthcare compared to usual care. 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. Utilisation 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 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 with CMR. 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-centered CMRs.

Because of an 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 [38,39]. 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.

Strengths and limitations

There were several strengths of this study. First, this economic analysis is based on the data of 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, the healthcare consumption was measured by the medical consumption questionnaire by telephonic interviews every three months. Although this is a validated method of collecting these data, it could have introduced recall bias. However, this bias is unlikely to be different between both groups. Second, drug dispensing records were obtained via the pharmacy information system of the community pharmacy. Drugs 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 [40]. Finally, the follow-up period in this study was six months, so we do not know what the results are over a longer period.

CONCLUSION

A CMR focused on a patient's preferences, personal goals and health-related complaints for older persons aged 70 years and over using seven or more chronic drugs is an economically attractive intervention. There is a high chance of cost savings in healthcare costs along with similar or small beneficial effects on HR-QoL and health-related complaints with impact on patients' daily lives compared to usual care. Significant implementation of CMR in this population, could contribute to the containment of healthcare expenditure of the increasing older society.

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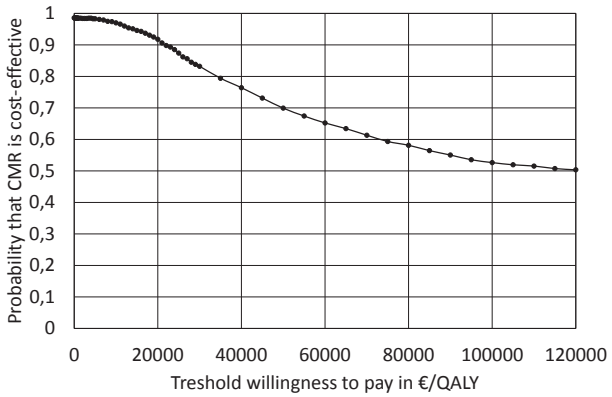
APPENDIX

A



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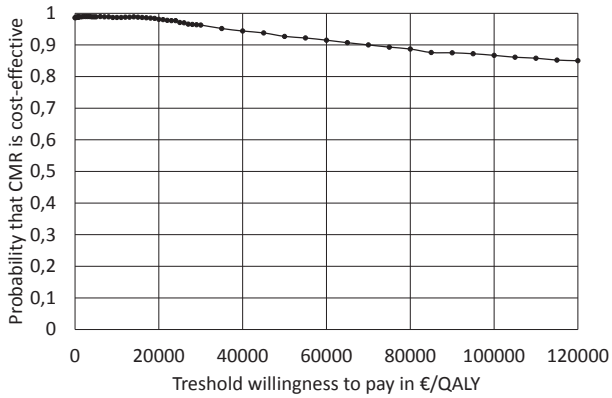

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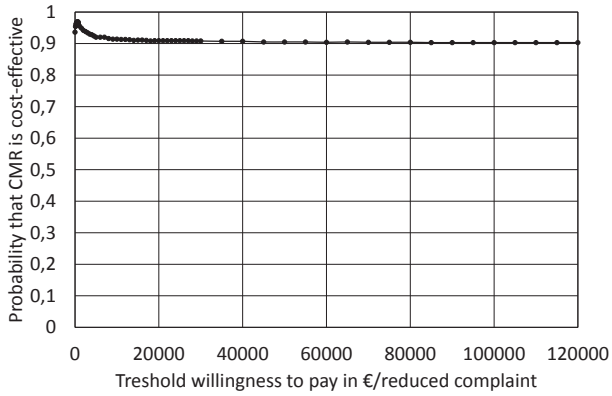

SUPPLEMENTARY - FIGURE S1A, B, C: Acceptability curves based on willingness to pay for a) costs/QALY measured with EQ-5D, b) costs/QALY measured with EQ-VAS and c) costs/effects determined as reduced complaints with impact. NB. QALY = quality-adjusted life year.

SUPPLEMENTARY TABLE 1: Mean costs per time point for each cost category between control and intervention group.

	Control group (n = 294)			Intervention group (n = 294)		
Cost category	**Baseline**	**T1: 3 months**	**T2: 6 months**	**Baseline**	**T1: 3 months**	**T2: 6 months**
Drugs	454 ± 873	434 ± 519	439 ± 365	383 ± 277	400 ± 316	433 ± 671
Primary care	206 ± 293	193 ± 293	221 ± 308	174 ± 245	186 ± 259	160 ± 232
Secondary care	330 ± 1087	325 ± 926	430 ± 1261	272 ± 723	323 ± 1181	377 ± 1197
Institutional care	24 ± 205	273 ± 2227	205 ± 1757	43 ± 472	114 ± 174	197 ± 2074
Home care	473 ± 1031	574 ± 1551	627 ± 1433	544 ± 1203	605 ± 1579	688 ± 1697
Informal care	152 ± 1046	315 ± 1421	159 ± 1025	119 ± 6034	164 ± 849	159 ± 1258

NB. Data are presented as mean costs ± standard deviation.
At each time point the costs are calculated over the three months before

PART 3

In depth analyses of the DREAMeR study

CHAPTER 7

The use of Goal Attainment Scaling during clinical medication review in older persons with polypharmacy

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ABSTRACT

Background and objective

Studies have shown that a clinical medication review (CMR) reduces drug-related problems (DRPs), but the effects on clinical outcomes are less clear. Perhaps, CMRs in older persons could me more effective when they focus on patients' personal goals and health-related complaints. The aim of this study was to investigate whether goal attainment scaling (GAS) is a useful tool for determining goals and monitoring their attainment during CMRs.

Methods

This study was an analysis based on data of the intervention group of the DREAMeR study; a randomised controlled trial investigating the effects of CMR in primary care. 315 persons aged ≥ 70 years using ≥ 7 drugs were randomised to the intervention: a CMR focused on personal goals using GAS. Outcome measures were: percentage of persons with health-related goals, attainment of goals measured with GAS scores after three and six months, type of health-related goals and implementation rates of recommendations for GAS-related DRPs and other DRPs.

Results

A total of 406 health-related goals were set for 283 of 315 included persons (90%). Of the 350 evaluated goals (86%), 37% were attained after three months and 43% after six months. The goals 'reduce pain' (n = 66, 16%), 'reduce number of pills' (n = 57, 14%) and 'improve mobility' (n = 37, 9.1%) were most prevalent. The implementation rate of recommendations for GAS-related DRPs was 81% compared to 62% for not GAS-related DRPs ($p < 0.05$).

Conclusion

Goal setting is important for prioritising the most important problems during clinical medication review and goal attainment scaling seems to be a useful tool for monitoring the attainment of these goals.

INTRODUCTION

A clinical medication review (CMR) is a structured critical examination of a patient's drug treatment. During a CMR both pharmacist, physician and patient are involved [1-3]. CMR can identify and resolve drug-related problems (DRPs) in older persons with polypharmacy [4-7]. The effectiveness of CMR on clinical outcomes is still sparse [5,8-10]. This could be explained by the fact that CMR is a complex and multifactorial intervention provided across a range of different settings [5,10,11]. The heterogeneity of the DRPs and interventions during CMRs makes it difficult to choose a generic outcome that measures the effects of CMR.

In previous studies, the focus of CMR was often on prescribing omissions based on guidelines and inappropriate prescribing [10,12-14]. Several tools, such as 'Screening Tool of Older Persons' Prescriptions' (STOPP) and Screening Tool to Alert doctors to Right Treatment' (START) criteria were developed to use during a CMR to facilitate the detection of these problems [15,16]. However, older persons with polypharmacy are often frail, suffer from multimorbidity, have complex health problems and subsequently may have various health-related complaints [17]. Therefore CMR in older persons could be more effective when they focus on patients' health-related complaints and goals. Several studies have shown that DRPs identified during a patient interview are the most important for the older persons [18-20]. Besides that, different studies in the geriatric field recommend a shift to goal oriented patient care and outcomes, which should be performed in a collaborative setting, where both patient and healthcare providers are involved [21,22]. A CMR could be an excellent multidisciplinary intervention to address goal setting during the patient interview.

One way to measure the outcome of goal setting, and other heterogeneous individual complex interventions, is the use of goal attainment scaling (GAS) [23]. In contrast to generic measures in which the same scale items are used for all patients, GAS is an individualised goal-setting and measurement approach that is useful for patients with multiple, individualised health problems [24,25]. GAS is a clinometric score that uses the baseline score of an individual as a reference [26,27]. Goal setting can help prioritise the most important problems for patients and the scale can help to quantify the extent of attainment of the proposed goals. GAS can be individualised for each patient to document progress but may also be indexed to measure effectiveness of an intervention on a population base. This could be useful for CMR where the interventions are very diverse; e.g. ranging from adding statins as preventive therapy to discontinuation of antihypertensive drugs because of side effects such as ankle oedema or dizziness. These variations in interventions during CMRs complicate comparison of currently used outcomes.

GAS was first described by Kiresuk and Scherman in 1968. They used GAS as a method for evaluation of mental health treatment [23]. Almost 50 years later, GAS has been applied in various fields including nursing, rehabilitation, pain management and geriatric care [25,28-32]. A previous study showed that older persons diagnosed with complex chronic health conditions are able to set personal health-related goals [31]. The authors suggest that GAS assessment could facilitate patient-centred care by focusing care on what patients want and judging performance by how patients' goals are met [21,26,31,33].

Although GAS has been recommended to measure the results of medication therapy management services, such as CMR, there are no studies which have used this outcome measure in this setting yet [32]. Therefore the aim of this study was to investigate whether GAS is a useful clinical tool for determining goals during a CMR and in monitoring their attainment in older persons with polypharmacy.

METHODS

Study design and setting

The DREAMeR study is a randomised controlled trial investigating the effects of a CMR focused on personal goals, on health-related quality of life and health-related complaints in older persons with polypharmacy. The extensive study protocol of the DREAMeR study has been published elsewhere [34]. Sample size calculations were performed on the primary outcomes in the RCT. The present study is an analysis based on data of the 315 patients randomised to the intervention group of the DREAMeR study. Participants were included between April 2016 and February 2017. Outcomes were evaluated at three and six months. The study was conducted in 35 Dutch community pharmacy franchisees of "Service Apotheek", located in both rural and urban areas spread throughout the Netherlands. In total, 43 community pharmacists working in 35 community pharmacies and 113 general practices participated in this study.

Participants

Patients aged ≥ 70 years and using seven or more chronic drugs were eligible for the study. Chronic drug treatment was defined as at least three prescriptions in the 12 months before the start of the study or a prescription for 90 days in the four months before the start of the study. Patients were excluded when they had an expected life expectancy shorter than six months, a hospital admission within one month before the inclusion date, a received CMR in the past 12 months and patients where the general practitioner (GP) was not the primary caregiver (patients receiving repeat prescriptions solely from a specialist).

Community pharmacists and training

Participating community pharmacists were accredited to perform CMR and had performed at least 25 CMRs annually over the past three years. Moreover all pharmacists received an additional training about the use of GAS, including how to communicate GAS to patients during a CMR. The implementation of GAS during the study was monitored by monthly web conferences with groups of 8-10 pharmacists. In these web conferences participating pharmacists presented case studies about a performed CMR and explained how they applied GAS in these cases. Also a helpdesk was available to help the pharmacists with cases and proposing GAS.

Intervention

The intervention was a CMR focused on personal goals and followed an implicit method as described in the Dutch multidisciplinary guideline 'Polypharmacy in the Elderly' [3]. The CMR started with a patient interview by the pharmacist at the patients home or in the pharmacy. All drugs in use (including effectiveness, side effects, usage, compliance and over the counter medication) and health-related complaints were discussed. At the end of the interview, one or more personal health-related goals were formulated by the pharmacist and the patient, based on the most important discussed issues. These goals were diverse and could focus on improving activities of daily living, reducing health-related complaints or reducing the number of pills for example.

After the patient interview, the pharmacist summarised all the DRPs. These DRPs could be related to the goals that were set, but also other DRPs could be identified (e.g. non-adherence to prescribing guidelines), because full medication records and clinical records (disease history and laboratory values) were available at the start of the CMR. The pharmacist formulated recommendations to solve the DRPs and to attain the goals. Subsequently the health-related goals, DRPs and recommendations were discussed with the GP. A pharmaceutical care plan was composed including which actions should be carried out when and by whom. This care plan was then discussed with the patient by the pharmacist or the GP and the actions were implemented gradually. Two follow-up moments were scheduled (within approximately three months), in which the pharmacist evaluated the agreed actions and proposed goals with the patient and, if necessary, adjusted the care plan.

Goal attainment scaling

The goal attainment scaling used in this study was based on a 6-point scale (-3 to +2) as used in previous studies and recommended in Dutch guidelines [29,35]. To support the pharmacists, a database with 50 common goal types with GAS scales (from -3 to +2) was composed (see examples in *Supplementary Figure S1*). This database was further expanded

during the study based on performed CMR. The goals were formulated SMART: specific, measurable, acceptable, realistic and time-bound. All the proposed goals with associated GAS scales were checked by the coordinating researcher (SV) before the assessment took place. After three and six months, different research assistants interviewed the patients about the attainment of their goals and subsequently assigned a GAS score (-3 to +2). They asked open questions, such as: "at the start of the medication review you scored your pain with a VAS-score of 8, how would you rank your pain today?" They also added a free text description of the patient's current health status in order to facilitate validation of the assigned scores.

Outcome measures

Primary outcomes were: percentage of patients with health-related goals, attainment of goals measured with GAS scores after three and six months. Attainment of health-related goals was defined as a GAS score of 0, +1 or +2. Improvement of health-related goals was defined as: a GAS score of -1, 0, +1 or +2. Secondary outcome measures were: number and type of health-related goals, number and type of GAS-related DRPs and other DRPs, recommendations to solve DRPs and implementation rates of these recommendations. DRPs were classified according to an adapted version of Hepler and Strand which is described in the STRIP-method of the Dutch multidisciplinary guideline 'Polypharmacy in the elderly' [3,36]. The implementation rate was defined as the percentage of the recommendations that were fully or partly (e.g. dose change when cessation of drug was proposed) accepted by pharmacist, GP and patient.

Data collection and analysis

Health-related goals with associated GAS and scores on GAS were recorded in an Excel-database. The pharmacists used medication review software (Service Apotheek Medication Review Tool (SAMRT), NControl, Amersfoort) to register GAS-related DRPs and other DRPs and interventions during the CMR [4]. Drug dispensing data were collected from the pharmacy information systems. In addition demographic characteristics: sex, age, ethnicity, living situation and 'Integrated Systematic Care for Older People' (ISCOPE) score which determines the domains of complex health problems [37] were collected. Health-related goals were grouped into type of goals by two researchers (SV and TV). We considered the type of health-related goal as the primary objective mentioned by the older patient. For example, when a patient could not walk to the supermarket because of pain, this goal was categorized under mobility and not under pain. Differences were discussed until consensus was reached.

Statistical analysis

Descriptive statistics were used for basic characteristics. Frequencies and percentages were reported for categorical variables. Chi-square tests were used to compare differences in

prevalence and implementation rates between GAS-related DRPs and other DRPs. The data were analysed using IBM SPSS Statistics 24.0 (IBM Corporation, Armonk, NY, USA). A p-value < 0.05 was considered statistically significant.

Ethics

The DREAMeR study was 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. All data were anonymised using a randomly assigned subject number.

RESULTS

Descriptive statistics

Of the 2290 patients that were invited for the study, 707 (31%) consented to participate, 78 persons withdrew before the start of the study, which resulted in 629 patients that were randomised. Of these, 315 patients in the intervention group received a CMR in 35 community pharmacies (mean 9 CMRs per pharmacy (SD = 4.4)). Eight patients were lost to follow-up after three months and 13 patients after six months. In total 294 patients completed the study (93%). Patient characteristics are shown in **Table 1**.

Number and type of health-related goals

In total 406 goals were set (mean 1.4 per patient (SD = 0.52)). There were 283 (90%) patients who had at least one health-related goal. From these patients, there were 163 patients with one goal (58%), 117 patients with two goals (41%) and three patients with three goals (1.1%). The 'top-10 type of health-related goals' according to prevalence are shown in **Table 2**. The goal to 'reduce pain' (n = 66, 16%), 'reduce the number of pills' (n = 57, 14%) and 'improve mobility' (n = 37, 9.1%) were the three most prevalent goals. Underlying problems for mobility issues were mainly because of pain or dyspnoea. Underlying problems for the goal about doing activities were mainly problems with incontinence or dyspnoea. The distribution of all types of health-related goals can be found in *Supplementary Table S1*.

TABLE 1: Baseline characteristics of participants in the intervention group of the DREAMeR study

Characteristic		n = 315
Sociodemographic		
Age, median (IQR), years		80 (76-84)
Sex, female		56%
Ethnicity, European		97%
ISCOPE, complex health problems (score 3,4)		25%
Living situation, alone		44%
Drug related		
Number of drugs in use, median (IQR)		9.0 (7.5-10.5)
Multidose Drug Dispensing system in use		27%
Most prescribed drug classes (ATC)		
A02B	Drugs for peptic ulcer and GORD	83%
B01A	Antithrombotics	79%
C10A	Lipid modifying agents	71%
C07A	Beta blockers	60%
C08C	Selective calcium channel blockers	32%
A10B	Oral blood glucose lowering drugs	31%
C09A	ACE inhibitors	30%
C09C	Angiotensin II antagonists	29%
A11C	Vitamin A and D	25%
C03C	High-ceiling diuretics	23%

Abbreviations: SD = standard deviation; ATC = Anatomical Therapeutical Chemical; GORD = gastro-oesophageal reflux disease; CMR = clinical medication review; ISCOPE = Integrated Systematic Care for Older People (determines the domains of complex health problems). NB. every demographic has no more than 5% missing values

Scores on goal attainment scales

350 of 406 proposed health-related goals (86%) in 256 patients were evaluated after three months, 347 goals (86%) in 247 patients after six months and there were 327 goals who had both a three and six month measurement. The results of the scores on the GAS of the evaluated goals after three and six months are shown in **Figure 1**. Of all the evaluated goals, 37% were attained after three months and 43% after six months (defined as GAS score 0, +1, +2). Patients showed improvement (defined as GAS score -1, 0, +1 and +2) on 48% of the goals after three months and on 52% of the goals after six months. Of the 37% attained goals at three months, 86% sustained and 14% declined at six months. Besides that, there were 42 goals who were only attained after six months, and not yet after three months.

TABLE 2: Top 10 of most prevalent types of health-related goals with percentage of attainment at 3 and 6 months

			% Goals attained (score 0, 1, 2)	% Goals attained (score 0, 1, 2)
Type of health-related goal		**n**	**T = 3 months**	**T = 6 months**
1	Reduce pain	66	31%	36%
2	Reduce number of drugs	57	23%	21%
3	Improve mobility (walking stairs/ certain distance)	37	24%	40%*
4	Reduce fatigue	28	14%	25%
5	Reduce practical problems with administration/intake drugs	26	67%	74%
6	Improve activities of daily living/ participate in activities	25	63%	75%
7	Reduce problems with diarrhoea or obstipation	23	63%	75%
8	Reduce dry mouth	22	9.1%	27%
9	Other	17	35%	35%
10	Reduce dizziness	14	43%	57%

NB. * p-value < 0.05; indicating a significant change in percentage attained goals between t3 and t6

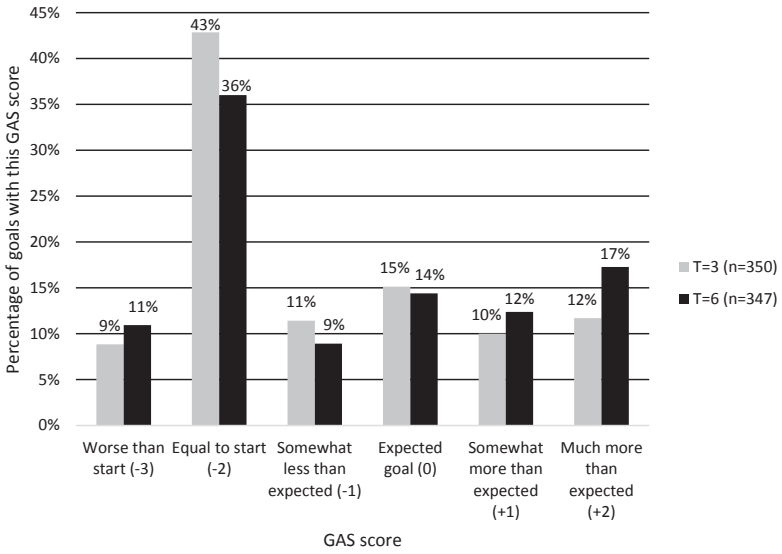

FIGURE 1: Frequencies of outcomes in GAS scores for all evaluated goal attainment scales after 3 and 6 months

When looking at the 'top-10 type of goals' according to attainment, the most frequently attained goals after six months were related to: reduction of practical problems (74% attained), improvement of activities, which were mainly due to complaints with incontinence or dyspnoea (75% attained) and reduction of problems with obstipation or diarrhoea (75% attained).

Relation of health-related goals and DRPs

The mean number of DRPs per patient was 5.8 (SD = 2.1). From the 1751 identified DRPs, 490 DRPs (28%) were related to a health-related goal and 1261 were other DRPs (72%). The different types of DRPs and the implementation rates of the recommendations associated with those DRPs, stratified into GAS-related DRPs and other DRPs, are shown in **Table 3**. The DRP type: adverse effect was relatively more frequent (22% vs. 13%; $p < 0.05$) among GAS-related DRPs compared to other DRPs and suboptimal therapy was relatively less frequent among GAS-related DRPs than other DRPs (25% vs. 33%; $p < 0.05$).

TABLE 3: Classification and solving of DRPs

	Identified (n, %)				Resolved (%)	
DRP type	**GAS-related**		**Other**		**GAS-related**	**Other**
Suboptimal therapy	123	25%	414	32%*	82%	50%*
Overtreatment	98	20%	237	19%	71%	54%*
(potential) adverse effect	110	22%	162	13%*	76%	70%
Drug not effective	55	11%	112	8.9%	89%	70%*
Drug interaction	1	0.20%	20	1.6%*	100%	80%
Contra-indication	5	1.0%	27	2.1%	60%	63%
Dose too high	7	1.4%	42	3.3%*	71%	74%
Dose too low	19	3.9%	45	3.6%	95%	76%
Non-compliance	13	2.7%	25	2.0%	100%	100%
Inconvenience of use	29	5.9%	70	5.6%	90%	77%
Wrong dosage form	2	0.41%	43	3.4%*	100%	86%
Other**	3	0.61%	22	1.7%	100%	91%
No DRP***	20	4.1%	42	3.3%	100%	50%*
Total	**490**		**1261**		**81%**	**62%**

Abbreviations: GAS = goal attainment scale; DRP = drug-related problem

*= p-value <0.05 ** "Other" consisted mainly of problems about necessary laboratory control (sodium, potassium and renal function) and updates of the pharmaceutical patient files. *** No DRP consisted of other problems that were not directly related to the drugs in use, but to other topics such as economic efficacy, cognition, loneliness and adding aids such as incontinence materials . NB. For 15 participants (4.8%) these data were missing.

Recommendations, interventions and implementation rates

The implemented recommendations are shown in **Table 4**. The overall implementation rate was 67%. 197 drugs were ceased in 130 patients (43% of patients) and 209 drugs were added in 149 patients (50% of patients). The difference in implementation rate for recommendations associated with GAS-related DRPs was 81% compared to 62% for recommendations associated with other DRPs ($p < 0.05$).

TABLE 4: Type of recommendations and associated implementation rates

	Related to GAS		Other		Implementation rate (%)	
Type of recommendation	**n**	**%**	**n**	**%**	**Related to GAS**	**Other**
Drug related						
Addition of drug	109	22%	345	27%*	80%	48%*
Cessation of drug	127	26%*	243	19%	75%	54%*
Replacement of drug	58	12%	119	9.4%	71%	36%*
Dosage change'	95	19%*	192	15%	80%	70%
Other						
Performance of (laboratory) monitoring	33	6.7%	182	14%*	100%	84%
Providing information/advice	50	10%	99	7.9%	100%	92%
Adjustment of dosage form	8	1.6%	50	4.0%*	88%	76%
Synchronisation of all drugs**	6	1.2%	18	1.4%	100%	89%
Other	4	0.8%	13	1.0%	100%	62%
Total	490		1261		81%	62%*

Abbreviations: GAS = goal attainment scale; * p-value < 0.05; **In 8/24 cases this consisted of the addition of a multidose drug dispensing system

DISCUSSION

This study shows that healthcare providers are able to formulate goals with older persons with polypharmacy during CMRs, because ninety percent of the participants managed to set at least one goal. Goal setting helps to identify the most important problems during a CMR, because it leads to a high percentage of resolved DRPs. Additionally, GAS is useful as outcome measure to evaluate the attainment of health-related goals in CMR. The results of this study demonstrate an attainment of health-related goals of 42% after six months and improvement of 52% after six months.

As far as we know, this is the first study investigating GAS as tool and outcome measure in CMR [32]. This is surprising, because GAS has been studied in other interventions in geriatric care and seemed to be useful in this population [24,31,38,39]. Besides that, a CMR identifies various problems and leads to many heterogeneous interventions, from adding preventive therapy to providing instruction on the use of complex medication such as inhalers [4,20,40]. Moreover, GAS has been used to evaluate diverse interventions, such as complex mental health programs, and has been suggested to be useful for the evaluation of services delivered to complex patients with multiple conditions [23,32]. The multidisciplinary character of a CMR and possibility for shared decision making about the optimal therapy for an individual patient, makes CMR a suitable intervention to apply GAS [41]. One study showed that pharmacists are capable to set goals with patients, however these goals were mainly focused on lifestyle and condition management in cardiovascular risk management and diabetes [22]. The attainment of 42% of goals in this study cannot be compared directly with other studies, because all studies were performed in different settings, such as geriatric day hospitals or nursing homes and these studies presented GAS results only as t-scores [24,26,31,39,42]. Moorhouse et al. showed a comparable mean number of goals per geriatric patient (1.6) and showed that 86% of patients improved on total GAS at discharge [26]. However these goals and interventions were different and broader than the goals in this study, because they were performed in a geriatric day hospital by multiple specialists. The goals that were set during the CMRs in this study, could only be attained by drug-related interventions.

The most frequent types of health-related goals in this study were pain reduction, reduction of number of drugs and improvement of mobility. GAS has already been demonstrated as a useful tool in pain management in different settings [30,43]. Pharmacist-led interventions have been shown to lead to improvements in pain management [44]. The results of this study showed that 35% of patients attained their goal to reduce pain. This is lower than another study investigating goal attainment in pain management in which 76% of participants met their goals of pain management. However, the sample size in this study was low and the intervention consisted of several additional interventions, such as exercise and distraction [43]. Improvement of mobility is a goal that has also been described in other GAS studies in this population, especially in geriatric day hospitals [24,39]. This study has shown that 40% of patients attained their mobility goals after six months. The wish to reduce number of drugs has not been described in GAS studies before. This study shows that 20% of the wishes for reduction the number of drugs were attained. This relatively low percentage could be explained by the fact that during the CMR also many drugs were added, for example preventive drugs such as vitamin D or symptomatic treatment such as analgesics. Several studies have shown that healthcare providers are often reluctant to discontinue medication [45,46]. It seems that additional attention is needed for “deprescribing”, or discontinuing medication, especially when this is a specific wish of older patients [47-49].

During CMRs, the use of different outcome measures (process and clinical outcomes) remains necessary to evaluate the heterogeneous interventions and effects [50]. DRPs are established process outcome measures during CMRs [5,10]. We saw that 28% of all DRPs were related to GAS. Mainly, the DRP type "adverse effect" was more prevalent among GAS-related DRPs. The high implementation rate of GAS-related DRPs suggests that GAS helps with prioritising the most important problems for patients and probably GPs and patients are more motivated to accept the recommendations in the pharmaceutical care plan.

Strengths and limitations

There were several strengths in this study. The first one is the innovative design using GAS during CMRs in a large sample of older persons, which was not investigated before. Second, this study was part of pragmatic trial, performed in daily clinical practice, which makes the generalisability of the results more likely. Third, the attainment of GAS was independently evaluated and scored by research assistants. This suggests that use of GAS is possible in research setting and this leads to less bias in the assessment of GAS scores compared to assessment by the health-care providers themselves [51].

There were also some limitations in this study. The most important methodological limitation is that we did not use GAS in the control group. Therefore, it cannot be excluded that the attainment of goals was caused by the natural course the patient's condition. However, using GAS in the control group of the DREAMeR study was not possible, because proposing goals during the CMR was an important aspect of the intervention, in which GAS was used to evaluate the attainment of the goals that were set. Therefore, only the outcomes of GAS in the intervention group are reported. We recommend that GAS should always be used next to other outcomes, which could be tested in a control group such as HR-QoL. Second, the concept of GAS was new for pharmacists and GPs in this study. There could have been a learning curve effect in the proposing of goals and the SMART formulation of goals together with the patients. However, despite the unfamiliarity with the concept of GAS pharmacists were able to set at least one health-related goal in 90% of the patients. The number of goals may become even higher when pharmacists become more experienced. Finally, although we used independent research assistants, they were not blinded to the baseline situation of the patients.

CONCLUSION

Older persons and pharmacists are able to set health-related goals during CMRs. Drug-related problems associated with health-related goals are more likely to be solved compared to other DRPs. Therefore, goal setting is important for prioritising the most important problems during the patient interview in the CMR. Goal attainment scaling showed to be a useful tool to evaluate the attainment of health-related goals after CMR, but in explanatory studies, GAS should be combined with other patient-reported outcomes.

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APPENDIX

SUPPLEMENTARY FIGURE S1: Examples of three different types of goal attainment scales

Level of attainment	Pain	Mobility	Number of pills
-3 Worse than start	Pain VAS-score > 6	Pt cannot walk to supermarket anymore (200m)	9 or more drugs in use (one or more drugs added)
-2 Equal to start	Pain VAS-score 6	Pt has to stop at least 3 times to rest (because of dyspnea) when walking to supermarket	8 drugs in use at start of CMR, no drug changes
-1 Somewhat less than expected	Pain VAS-score 5	Pt has to stop at 1-2 times to rest (because of dyspnea) when walking to supermarket	No drug ceased, 1 dosage reduction
0 Expected goal	Pain VAS-score 4	Walking to supermarket without resting is possible (200m)	7 drugs in use; 1 drug ceased successfully without recurrence of symptoms
+1 Somewhat more than expected	Pain VAS-score 3	Walking further than supermarket without stopping (200-400m)	7 drugs in use; 1 drug ceased and 1 dosage reduction
+2 Much more than expected	No pain anymore or VAS-score < 3	Walking >400m without stopping	< 7 drugs in use; more drugs are ceased successfully
Example of intervention	Start with painkillers; e.g. paracetamol in accurate dose. Evaluation of pain and side effects after 2-4 weeks and addition of another pain killer when necessary.	Instruction of inhaling techniques; addition of short acting beta2- agonist (salbutamol); evaluation of dyspnea after 2-6 weeks	Cessation of drugs which were not effective or with no apparent indication after critically examination. Evaluation of recurrence of symptoms after 4-8 weeks

SUPPLEMENTARY TABLE S1: All types of proposed health-related goals with frequencies

Type of health-related goal	n
Reduce pain	66
Reduce number of drugs	57
Improve mobility (walking stairs/distance)	37
Reduce fatigue	28
Reduce practical problems with administration or intake of medication	26
Improve activities of daily living / participate in activities	25
Reduce problems with diarrhoea or constipation	23
Reduce dry mouth	22
Other	17
Reduce dizziness	14
Attain optimal preventive therapies	14
Reduce itching	13
Reduce dyspnoea	11
Maintain current ADL (activities of daily living) functioning	10
Reduce psychological/social problems (anxiety, loneliness)	7
Improve sleep	7
Reduce gastric problems	7
Improve / reach target laboratory values	5
Reduce fall incidents	4
Improve cognition/stop decrease in cognitive abilities	4
Reduce (nocturnal) muscle pain/cramp	4
Reduce incontinence	3
Reduce dry eyes	2
Total	**406**

CHAPTER 8

Which older patients will benefit most from a clinical medication review on quality of life and health-related complaints?

Explorative subgroup analysis of the DREAMeR study

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Submitted

ABSTRACT

Background and objective

Eligible patients for a clinical medication review (CMR) are often defined by age and number of drugs. In order to select patients who are most likely to benefit from a CMR, there is need for additional selection criteria. The objective of this study is to explore subgroups that may experience more benefit on health-related quality of life (HR-QoL) and health-related complaints from a CMR.

Methods

This study was a planned subgroup analysis of the DREAMeR study; a randomised controlled trial among patients aged ≥ 70 years with polypharmacy (≥ 7 drugs), investigating the effects of a CMR. Primary outcomes were a relevant increase in HR-QoL (measured with EQ-5D-5L and EQ-VAS) and reduction of at least one health-related complaint with impact from baseline to six months. Explorative subgroup analyses were conducted among important baseline demographics using logistic regression analyses.

Results

501 patients (252 in the intervention group and 249 in the control group) were selected for this analysis. Patients using ≥ 10 drugs had more benefit from a CMR on improvement in HR-QoL measured with EQ-VAS (OR = 2.2; 95% CI 1.04 to 4.7; p = 0.04) and reduction of health-related complaints (OR = 2.2; 95% CI 1.01 to 4.6; p = 0.046). The subgroups patients living alone (compared to living together) and patients with complex health problems (compared to no complex health problems) also had a higher odds for improvement in EQ-VAS by CMR, but these interaction effects were not significant compared to control group. The subgroups: sex, age, multidose drug dispensing system and drug delivery at home, did not show differences in effects.

Conclusion

This study showed patients using 10 or more drugs had more benefit from a CMR on improvement in HR-QoL measured with EQ-VAS and reduction of health-related complaints.

INTRODUCTION

Selection criteria for eligible patients for a clinical medication review (CMR) are often based on age and number of drugs in use. Due to the increase in number of older (frail) people in the coming years [1,2], it is almost impossible to offer all older patients with polypharmacy a CMR. Besides that, effects of CMR on clinical outcomes are limited [3,4]. This could possibly be due to the heterogeneous patient groups that are investigated.

Several additional criteria for CMR were investigated in studies, such as impaired renal function, impaired cognitive function, increased risk of falls, non-compliance, living in a care home or recent unplanned hospital admissions. These criteria were mainly based on the 'Hospital Admission Related to Medication' (HARM) study, which showed that these factors predicted potentially preventable drug-related hospital admissions in older persons [5-8]. Other strategies that have been studied as selection criteria for a CMR, ranged from variation in age and number of drugs or co-morbidities, living situation, receiving drugs via multidose drug dispensing (MDD-users), taking more doses of medication per day, risk in mismanaging medication due to language difficulties, dexterity problems or impaired sight, confused mental state, vision or hearing impairment [3,4,9-13].

One factor that has often been used in studies investigating complex interventions in older people in primary care, but has not been used as selection criteria for CMR, is the presence of complex health problems. Different tools can be used to define complex health problems, but they all have in common that they identify problems on different domains (e.g. physical, psychological and social) [14]. It is known that having problems on multiple domains negatively affects health-related quality of life (HR-QoL) [15,16]. Potentially HR-QoL of these patients could be improved by a CMR.

In the 'Drug use Reconsidered in the Elderly using goal Attainment scales during Medication Review' (DREAMeR) study; a randomised controlled trial investigating the effects of a CMR, patients were included who were expected to benefit from a CMR. Selection criteria for patients in this study were set at an age of 70 years and over and number of drugs in use of at least seven [17]. The DREAMeR study showed that a CMR improved HR-QoL measured with EQ-VAS and reduced the number of health-related complaints with impact on patient's daily life compared to usual care [18]. The objective of this study is to explore which subgroups of patients experience most benefit from a CMR regarding HR-QoL and health-related complaints.

METHODS

Study design and population

The present study is a subgroup analysis of the DREAMeR study. The DREAMeR study was a pragmatic randomised controlled trial to investigate the effects of a CMR, focused on personal goals. The study was performed in 35 community pharmacies in the Netherlands was 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. All data were anonymised using a randomly assigned subject number. Details regarding the methods [17] and main results of the DREAMeR study have been reported elsewhere [18] and are briefly described below.

Participants

A total of 629 patients aged 70 years and over using seven or more chronic drugs were randomly allocated to the intervention (n = 315) or control group (n = 314). Patients were excluded when they had a life expectancy ≤ 6 months, a hospital admission within one month before the inclusion date, already received a CMR in the past 12 months, or received repeat prescriptions solely from a hospital specialist. In this sub-study, all patients were included who had both a baseline and a six-month measurement for all primary outcomes.

Procedure

Patients in the intervention group received a CMR focused on personal goals. The CMR was performed according to the Dutch multidisciplinary guideline 'Polypharmacy in the elderly' and patient, general practitioner (GP) and pharmacist were involved [5,17]. Patients in the control group received usual care and were placed on a waiting list to receive a postponed intervention after the study period.

Definition of subgroups

Seven subgroups were defined based on patient characteristics that were collected in the RCT. Subgroups were based on: 1) sociodemographics 2) drug-related factors and 3) complex health problems.

Sociodemographic characteristics

Sex and age are standard demographics that were collected in this RCT. Patients were stratified according to the median age of patients in the RCT, resulting in a subgroup of patients aged ≥ 80 years compared to patients aged < 80 years. Living situation could be extracted from the healthcare information system, but was determined with a questionnaire at baseline. This subgroup was divided into patients living alone or living together with a partner.

Drug-related characteristics

Drug dispensing data from the pharmacy information system were used to calculate number of drugs used. Patients were stratified according to the median number of drugs in use in the RCT population, resulting in a subgroup of patients using ≥ 10 drugs compared to patients using < 10 drugs. Other drug-related subgroups were use of an MDD and drug delivery at home. These characterstics were determined at baseline and these patient groups were expected to be more vulnerable.

Complex health problems

The last subgroup was based on the presence of complex health problems, measured with the 'Integrated Systematic Care for Older People' (ISCOPE) screening questionnaire. This questionnaire contains questions on four domains of health: a functional, somatic (health and illness), mental and social domain. Individuals with problems on three or four domains are classified as having complex health problems [16].

Outcome measures

The primary outcomes in the DREAMeR study were HR-QoL, measured with EQ-5D-5L and EQ-VAS, and the number of health-related complaints with impact, out of 12 common health-related complaints in older people (e.g. pain, dizziness, and stomach problems). EQ-5D-5L results were transformed to health-utility values [19]. A health-related complaint was defined as a complaint with moderate to severe impact on patient's daily life as: a severity scored with a VAS-score ≥ 5 and influence on daily life of moderate, severe or extreme (≥ 3 points on a 5-point Likert scale). For this study, HR-QoL was dichotomised into patients with or without a relevant improvement from baseline to six months of ≥ 0.05 points in health utility values (range -0.329 to 1) measured with EQ-5D-5L and a change of ≥ 5 points in EQ-VAS scores (range 0-100), from baseline to six months. The outcome health-related complaints was dichotomised into patients with or without a decrease of at least one health-related complaint with impact on patient's daily life.

Statistical analysis

Analyses were performed according to the intention-to-treat principle, including all randomised patients with a baseline and six-month outcome measurement. Patient characteristics were described as proportions. The method of multiple imputations was used to generate five imputed data sets with predictive mean matching, because ≤ 5% of patient characteristics were missing at random.

Logistic regression analyses were used to evaluate main treatment effects on primary outcomes. The same regression model was carried out for patients within individual

subgroups to estimate the magnitude of the intervention effect in each subgroup. Data were stratified based on the seven defined subgroups. Univariate logistic regression analyses were used to determine differences in effects for each subgroup for the three different binary outcomes, expressed as odds ratios (OR) with 95% confidence intervals (CI). Forest plots were made to show differences in effects for each subgroup. After this, the interaction effect between the treatment and subgroup terms was tested in the logistic regression model. A significant interaction was considered as a differential treatment effect. Statistical analyses were performed using IBM SPSS Statistics 24.0 (IBM Corporation, Armonk, NY, USA). A p-value < 0.05 was considered statistically significant.

Statistical power

As a standard two-arm RCT, the sample size calculation was powered on the primary outcome using all randomised participants. Therefore, sample size calculations for subgroup analyses were not conducted.

RESULTS

From the 629 randomised patients in the DREAMeR study, 501 patients (249 in control group and 252 in intervention group) were selected for this study. **Table 1** shows baseline descriptive data for both groups. **Table 2** presents the distribution of the three binary outcomes for the intervention and control group. For HR-QoL measured with EQ-5D, 27% of patients improved with ≥ 0.05 points in the intervention group compared to 23% in control group (p = 0.27). For HR-QoL measured with EQ-VAS, 42% of patients improved with ≥ 5 points in the intervention group compared to 34% in control group (p = 0.055). Finally, in the intervention group 40% of patients had at least one reduced health-related complaint with impact on daily life, compared to 32% in the control group (p = 0.063).

At the six month follow-up, in the total intervention group compared to the total control group, the OR for improvement of ≥ 0.05 points in HR-QoL with EQ-5D was 1.3 (95% CI 0.84 to 1.9). There were no differences in ORs for the subgroups and no significant interactions between the treatment and subgroups in all regression models (p = 0.23 to 0.91), indicating no statistical evidence of treatment differences for these subgroups (**Figure 1a**).

After six months, the OR for improvement of ≥ 5 points in EQ-VAS scores was 1.4 (95% CI 0.99 to 2.1) for the total intervention group compared to the total control group. The subgroups: patients using ≥ 10 drugs, patients living alone and patients with complex health problems were associated with a higher odds of improvement in EQ-VAS by a CMR

compared to their contrasting subgroup (**Figure 1b**). There was only a significant interaction between the treatment and characteristic: 'drugs in use' (OR = 2.2; 95% CI 1.04 to 4.7; p = 0.040). Patients using 10 or more drugs had more benefit from a CMR regarding EQ-VAS.

TABLE 1: Descriptive summary of characteristics by subgroup for control and intervention group

Characteristic	Control group (n = 249)	Intervention group (n = 252)
Sociodemographic		
Sex		
Female	124 (50%)	141 (56%)
Male	125 (50%)	111 (44%)
Age group		
70-79 years	147 (59%)	131 (52%)
≥ 80 years	102 (41%)	121 (48%)
Living situation		
Alone	92 (37%)	108 (43%)
As a couple	157 (63%)	144 (57%)
Drug-related		
Drugs in use		
≤ 9	129 (52%)	144 (57%)
≥ 10	120 (48%)	108 (43%)
Use of MDD system		
No	199 (80%)	189 (75%)
Yes	50 (20%)	63 (25%)
Drug dispensing		
Pick-up in pharmacy	154 (62%)	156 (62%)
Delivery at home	95 (38%)	96 (38%)
Complex health problems		
Complex health problems with ISCOPE score		
No (score 0, 1, 2)	189 (76%)	189 (75%)
Yes (score 3, 4)	60 (24%)	63 (25%)
Problems per domain of ISCOPE screening questionnaire		
Functional domain	50 (20%)	55 (22%)
Somatic domain	169 (68%)	174 (69%)
Mental domain	85 (34%)	101 (40%)
Social domain	65 (26%)	86 (34%)

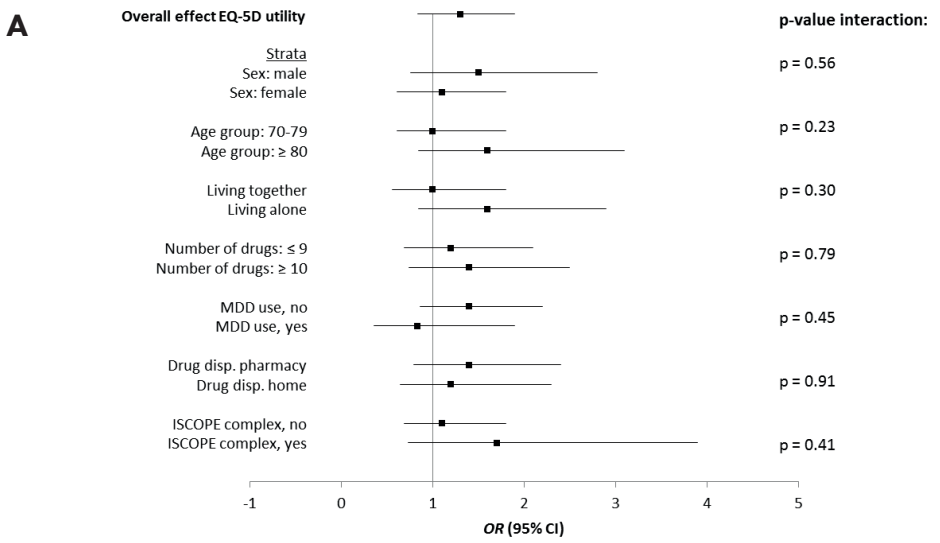
Abbreviations: MDD = multidose drug dispensing; ISCOPE = Integrated Systematic Care for Older People: determines patients with complex health problems

TABLE 2: Distribution primary outcomes between control and intervention group

Outcome	Control group (n = 249)	Intervention group (n = 252)
Health-related quality of life		
EQ-5D health utility values		
< 0.05 points improvement	192 (77%)	183 (73%)
≥ 0.05 points improvement	57 (23%)	69 (27%)
EQ-VAS		
< 5 points improvement	164 (66%)	145 (58%)
≥ 5 points improvement	85 (34%)	107 (42%)
Health-related complaints with impact		
No reduced complaints	170 (68%)	152 (60%)
At least one reduced complaint	79 (32%)	100 (40%)

Abbreviations: EQ = EuroQol; VAS = visual analogue scale

The OR for at least one reduced health-related complaint with impact after six months was 1.4 (95% CI 0.98 to 2.0) for the total intervention group compared to the total control group. There was only a significant interaction between the treatment and characteristic: 'drugs in use' (OR = 2.2; 95% CI 1.01 to 4.6; p = 0.046). Patients using 10 or more drugs had more benefit from a CMR regarding reduction of health-related complaints. There were no significant differences in effects for other subgroups (**Figure 1c).**



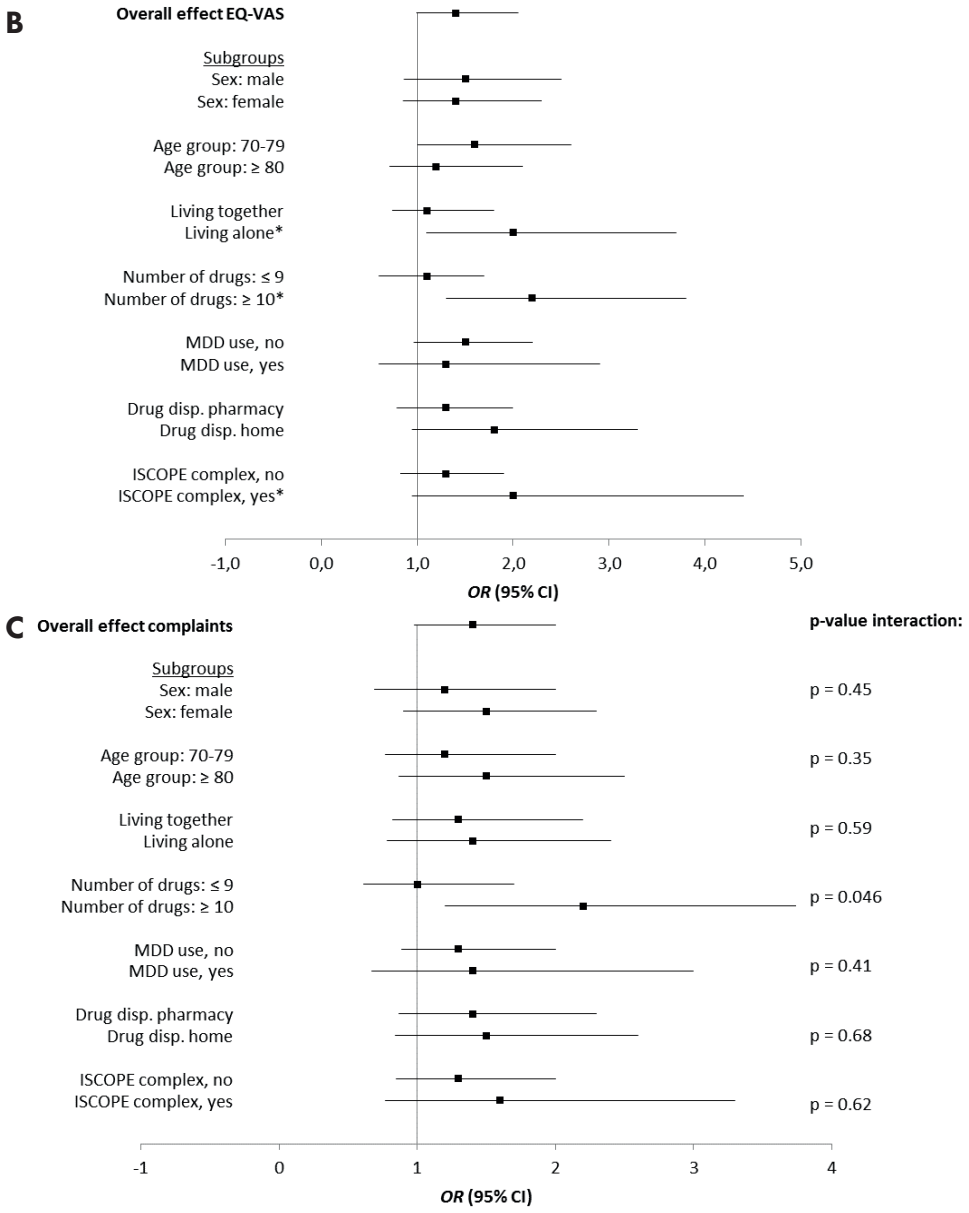


FIGURE 1A,B,C: Forest plots for differences in intervention effects between subgroups on three different outcomes.

Abbreviations: OR = odds ratio; CI = confidence interval; MDD = multidose drug dispensing system; drug disp = drug dispensing; ISCOPE = = Integrated Systematic Care for Older People and determines patients with complex health problems. NB. * means significant difference between subgroups. The right column shows the p-value for the interaction term between intervention and characteristic.

DISCUSSION

This explorative subgroup analyses showed that patients using 10 or more drugs had more benefit from a CMR regarding HR-QoL measured with EQ-VAS and reduction of health-related complaints with impact on patients' daily lives. Patients living alone and patients with complex health problems also had higher odds for improvement in EQ-VAS by CMR compared to their subgroups, but these intervention effects were not significant compared to control group. No differences were found for other subgroups and for effects on HR-QoL measured with EQ-5D.

Different approaches of selecting patients for a CMR could be used. The most commonly used approach is to select patients based on characteristics, such as age and number of drugs, because these parameters are readily available in healthcare information systems [3,4]. In this study, we also tested whether patients living alone, patients using an MDD and patients who had their drugs delivered at home, were characteristics that could identify patients who would benefit more from a CMR. These patients were expected to be more vulnerable. These characteristics are not commonly used in most studies investigating CMR, whereas they could be extracted from a healthcare information system. However, this study showed that only patients living alone and patients using ≥ 10 drugs were associated with higher ORs compared to their subgroup.

Another approach of selecting patients for a CMR, could be to use questionnaires or parameters that identify older persons with complex health problems. There is increased attention in primary care for this patient group [14,16,20,21]. In this study, the ISCOPE screening questionnaire was used to determine complex health problems [16]. Patients with complex health problems experienced more benefits of the intervention on EQ-VAS compared to patients with no complex health problems. However, the interaction term of this characteristic and intervention was not significant. This could possibly be due to lack of power (only one fourth of patients had complex health problems) and requires further investigation.

Strengths and limitations

There were several strengths in this study. First, this study was performed in daily clinical practice which could increase the generalisability of the results. Second, we performed a planned subgroup analysis in a large population with few missing data, which gave us the opportunity to perform this analysis and identify differences in subgroups.

Exploratory subgroup analyses also have their limitations. First, as a standard RCT, the DREAMeR study was powered on the primary outcomes only, using all randomised patients.

The results of all other analyses, are reported elsewhere [18] and the subgroup analyses reported here, are therefore exploratory in the sense that they are considered as hypothesis generating rather than confirmed findings. Second, the initial selection criteria of age and number of drugs in the DREAMeR study were already higher than the selection criteria used in most studies investigating CMR [3], which could lead to smaller effects in subgroups. Finally, the findings of this study are relevant for studies investigating CMRs focused on improvement in HR-QoL and health-related complaints. It is possible that other subgroups may experience greater benefits regarding other outcomes such as drug-related hospital admissions or adherence to treatment guidelines.

CONCLUSION

This study showed patients using 10 or more drugs had most benefit from a CMR regarding HR-QoL measured with EQ-VAS and reduction of health-related complaints. Patients living alone and patients having complex health problems may also be associated with a higher likelihood of benefits from CMRs.

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Caring for our seniors is perhaps the greatest responsibility we have. Those who walked before us have given so much and made possible the life we all enjoy

- JOHN HOEVEN

CHAPTER 9

General discussion

GENERAL DISCUSSION

Due to an ageing society, the number of older independently living persons with polypharmacy and multimorbidity will keep increasing in the next decade. These persons are expected to live independently at home as long as possible. However, they are at an increased risk for inappropriate medication use and drug-related hospital admissions. Preventive strategies are needed to manage the health and independence of older persons. These preventive strategies should concurrently contribute to the containment of healthcare expenditure. Clinical medication reviews (CMRs) are increasingly performed, and numerous studies have shown that CMRs resolve drug-related problems (DRPs). Because of the heterogeneous patient groups, settings, interventions, and research designs, it is difficult to demonstrate the effect of CMRs on clinically relevant outcomes, such as hospital admissions or health-related quality of life (HR-QoL). Therefore, there is a need for (new) patient-reported outcomes to determine the effects of CMRs. Moreover, the expected increase in eligible patients for CMRs in the upcoming years makes it necessary to optimise the CMR process. Supportive materials, such as checklists with explicit criteria, and more differentiation of patient groups may be needed to support the efficiency and quality of medication reviews. The effects of CMRs will probably be determined by different aspects. Defining selection criteria for eligible patients for a CMR, improving the effectiveness of the intervention with explicit criteria incorporated into computer software (computer rules) or a patient-centred approach (using personal goals), together with choosing appropriate outcomes of CMRs, can all contribute to evidence showing the benefit of CMRs for older patients. All these aspects are investigated in the studies presented in this thesis, and the main findings are summarised below.

Main findings of this thesis

- Chapter 2: Only the minority of the DRPs identified during a CMR were associated with a 'Screening Tool of Older People's Prescriptions' (STOPP) or 'Screening Tool to Alert to Right Treatment' (START) criterion. The START criteria occurred more frequently, whereas the STOPP criteria were implemented more frequently.
- Chapter 3: A clinical decision support system (CDSS) with 46 clinical rules generated a large number of alerts for potential DRPs, but these potential DRPs were less frequently resolved compared to DRPs identified by a structural assessment of pharmacotherapy including a patient interview.
- Chapter 4: Study protocol of the 'Drug use Reconsidered in the Elderly using goal Attainment scales during Medication Review' (DREAMeR) study; a randomised controlled trial investigating the effects of a patient-centred CMR focused on patient's

preferences, personal goals, and health-related complaints on health-related quality of life (HR-QoL) and health-related complaints in older persons (≥ 70 years) with polypharmacy (use of ≥ 7 chronic drugs).

- Chapter 5: A CMR improved HR-QoL measured with EQ-VAS with 3.4 points on a scale from 0 to 100 and reduced the number of health-related complaints with an impact on daily life by 12%, whilst the number of drugs used decreased, compared to usual care. The EQ-5D health utility values did not change.
- Chapter 6: A CMR is an economically attractive intervention for older patients with polypharmacy. Compared to usual care, there was a high probability of healthcare cost savings combined with a small beneficial effect on HR-QoL measured with EQ-VAS and health-related complaints.
- Chapter 7: Pharmacists were able to set health-related goals together during a CMR in 90% of patients. After six months, 52% of the personal goals were improved and 43% were attained. The DRPs associated with goal attainment scaling (GAS) were more likely to be solved compared to other DRPs.
- Chapter 8: Patients using ≥ 10 drugs, patients living alone, and patients with complex health problems were the most likely to benefit from a CMR regarding HR-QoL measured with EQ-VAS.

Reflection on three main topics

Finally, in this chapter 9, the results of this thesis are put into a broader perspective on the basis of three questions, which are all related to each other:

1. How should one select the appropriate patients for a CMR?
2. What is the best way to perform a CMR (using computer rules or a patient-centred approach with personal goals)?
3. How can one measure the effects of a CMR?

This chapter finishes with recommendations for clinical practice and future research.

How should one select the appropriate patients for a CMR?

There is still debate about the most appropriate criteria to select patients for a CMR. The term 'appropriate' could be confusing. Appropriate indicates patients who benefit the most from a CMR. However, different outcomes can be used to determine effects of a CMR, which are further highlighted in question 3 of this chapter. This first question discusses possible approaches to selecting patients who are more likely to benefit from a CMR in light of the findings of this thesis combined with other literature.

Patients are currently often selected for a CMR based on their age (≥ 65 years) and chronic medication use (≥ 5 chronic drugs). Although patients can be easily selected from healthcare information systems with these criteria, there is some doubt on the specificity of these criteria. The current Dutch multidisciplinary guideline 'Polypharmacy in the elderly' recommends at least one additional risk factor next to age and number of drugs [1]. Suggested risk factors are impaired renal function, impaired cognition, increased risk of falls, non-compliance, living in a care home or unplanned hospital admissions. These risk factors are considered appropriate because they are associated with preventable drug-related hospital admissions in older persons [2]. However, pragmatic issues may prohibit the selection of patients based on these additional risk factors. Impaired cognition, increased risk of falls, and recent hospital admissions, are not always registered and thus cannot systematically be used for selection of patients. To establish a considerable reduction of the population of patients eligible for a CMR, the Dutch healthcare inspectorate has recommended that every older person aged ≥ 75 using ≥ 7 drugs with at least one risk factor should be offered a CMR [3]. However, neither the recommendations from the multidisciplinary guideline or from the healthcare inspectorate are completely evidence based. Recommendations for selecting patients who will benefit of a CMR to improve their quality of life or preventing DRPs and drug-related hospital admissions are discussed below.

Increase cut-off values for age and number of drugs

Research has shown that the number of drugs in use is associated with the number of DRPs [4]. Due to age-related changes in pharmacokinetics and pharmacodynamics, older people are at an increased risk of DRPs compared to younger people [5,6]. Therefore, increasing the cut-off value for age and the number of drugs could be one way to select patients who are most likely to benefit from a CMR. In the first part of this thesis (chapter 2 and 3), the selection criteria for patients were still set at patients aged 65 years or older using five or more drugs. In these studies, the mean number of DRPs ranged between 3.2 and 3.6 per patient. In the second part, the selection criteria in the DREAMeR study were narrowed to patients aged 70 years or older using seven or more drugs. Chapter 5 showed that the mean number of DRPs per patient increased to 5.8. This increase in DRPs may be explained by the stricter selection

criteria but also by the fact that documentation of DRPs may be more strictly emphasised in the randomised controlled trial (RCT) than in daily clinical practice, presented in the studies in the first part. The criteria for eligible patients for CMR regarding age and number of drugs were narrowed in the DREAMeR study, because the hypothesis was that this would increase the likelihood that patients had multiple problems and thus sufficient room for improvement. As this is one of the first studies that, in addition to solving DRPs, showed effects on HR-QoL, narrower selection criteria may be an efficient strategy to select patients who are more likely to benefit from a CMR. Within this population, additional patient characteristics were collected to investigate if the selection of patients could further be improved. Chapter 8 concluded that a CMR may especially improve health-related complaints and HR-QOL in patients aged ≥ 70 years using ≥ 10 drugs. This suggests that these patients could be prioritised when pharmacists offer a CMR. Application of the selection criteria of ≥ 70 years and ≥ 7 drugs in an average Dutch community pharmacy would identify around 300 to 400 patients for a CMR compared to 600 patients when the current criteria of ≥ 65 years and ≥ 5 drugs is applied [7]. Based on our trial data, further narrowing the selection criteria to patients ≥ 70 years and ≥ 10 drugs would reduce the number of eligible patients by approximately 50%, which is around 150 to 200 patients per pharmacy. A similar strategy is currently recommended by the UK's National Institute for Clinical Excellence (NICE) in their multimorbidity guideline. The National Institute for Clinical Excellence (NICE) recommends to first take responsibility for patients who are prescribed 15 or more regular medicines, because they are likely to be at a higher risk of adverse events and drug interactions [8].

Identify patients who are likely to benefit from CMR

For older persons with few health-related complaints and a high baseline quality of life, a CMR may not be very useful. Patients who are more likely to benefit from a CMR probably have health-related complaints or problems in multiple domains. A potential approach to reach those patients could be to inquire into patients' vulnerability, health-related complaints or preferences related to their medication by using similar questionnaires as used in the DREAMeR study. Based on completed questionnaires, pharmacists could select patients for a CMR based on present problems that must be evaluated. Sending questionnaires could be a time consuming process in practice, but it could also identify patients that really need a comprehensive CMR and thus save time in the long term.

Chapter 8 showed that patients living alone and patients with complex health problems (determined with an Integrated Systematic Care for Older People [ISCOPE] score of 3 or 4) are more likely to show improvements in quality of life compared to their subgroup. These patients are more vulnerable than other patients. Patients living alone could be extracted from healthcare information systems, whereas indicators for complex health problems are currently not available. Questionnaires, such as the ISCOPE screening questionnaire, could

be sent after pre-selection based on age and number of drugs. Nevertheless, compared to number of drugs in use, these indicators were not better in selecting patients with more improvement regarding HR-QoL. However, while only one fourth of the DREAMeR population had complex health problems, the subgroup analysis might not have sufficient power to investigate the additional value of the ISCOPE score for patient selection. In addition, patients who receive their drugs in a multidose drug dispensing system (MDD) or through a drug delivery service at home were expected to be more vulnerable, but no differences in effects were found for these subgroups.

A slightly comparable approach as described in the paragraphs before was used in the OptiMed study. In this study, patients were also selected for a CMR based on the presence of 'geriatric giants' (i.e. mobility problems, dizziness, urinary incontinence, problems with cognition or fear of falling) in the general practice [9]. These geriatric giants are comparable with a number of the health-related complaints and most common personal goals that were identified in the DREAMeR study.

Increase involvement of patients and informal carers

In clinical practice, but also in clinical studies, patients are generally invited for a CMR by healthcare providers. It may be interesting to investigate ways to increase proactive involvement of patients and informal carers. Although half of the older patients with polypharmacy are of the opinion that a periodical evaluation of their medicines is an appropriate idea [10], in clinical practice, they seldom request this service. Public awareness campaigns, e.g. in general practices and community pharmacies, may stimulate patients to ask for a CMR themselves. Informal carers may especially have an accurate view of the health problems of the persons for whom they care and could be motivated to seek a CMR for those patients.

Establish referral by other healthcare providers

As a CMR is a multidisciplinary intervention, effective collaboration in primary care could also contribute to the selection of patients who are most likely to benefit from a CMR. Patients could be referred for a CMR by other healthcare providers, such as general practitioners (GPs), practice nurses specialising in geriatric care or homecare employees. The professional judgement of these healthcare providers can probably identify patients who are likely to benefit from a CMR. An interesting example to improve collaboration in CMR with home care is the 'Home Observation of Medication-related problems by homecare Employees' (HOME) instrument. A mobile version of the HOME instrument and a monitoring and consulting system for primary care was developed to help homecare employees to report observed problems related to medication use during home visits and to communicate these with GPs and pharmacists [11]. Effective cooperation in the triangle of GP practice, pharmacy and home care could strengthen the management of older persons' medication use.

Increase focus on high-risk patients

Although the studies in this thesis illustrate that CMRs improve wellbeing for patients in primary care, many of these patients fortunately will never be admitted to a hospital. As one of the goals of CMRs is to prevent serious drug-related morbidity and hospital admissions, it may be necessary to specifically target CMRs to patients at high risk for these events. Some risk factors for drug-related hospitalisations became apparent in the HARM study and have been translated into recommendations in the HARM-Wrestling report [2,12]. The recommendations of these authors have led to new initiatives such as CMRs, but they have also encouraged the improvement of medication and laboratory data transfer in daily practice and the introduction of clinical rules in healthcare information systems, e.g. regarding the prevention of gastrointestinal bleedings from non-steroidal anti-inflammatory drugs (NSAIDs) [12].

A strategy could be to select patients for CMRs based on the occurrence of more specific (combinations of) clinical rules in a CDSS which identify patients who are potentially at risk for drug-related hospital admissions. In chapter 3, we investigated whether more DRPs were detected and solved when clinical rules were incorporated into a CDSS. This study showed that slightly more DRPs were identified, but this did not result in more DRPs that were actually solved. This suggests that the occurrence of one clinical rule does not identify patients who will benefit most from CMR. However, the relation between the occurrence of more than one clinical rule in the same patient and the occurrence of DRPs that were solved was not studied, as well as the relationship between the occurrence of clinical rules and improvement on clinical outcomes. In daily practice, the most relevant clinical rules may, however, already be acted upon during regular drug dispensing in the community pharmacy. For example, at the first prescription of an NSAID, a proton-pump inhibitor will be added in case the patient should receive gastro protection according to current guidelines. Besides that, before clinical rules can be used to select patients who are at risk for DRPs, the algorithms of these clinical rules must be further improved (e.g. by considering the drug dispensing history, co-morbidities and laboratory data).

Finally, a strong risk factor for a drug-related hospital admission may be a previous acute (drug-related) hospital admission [13]. A recent drug-related hospital admission could thus be a sufficient trigger to start a CMR. Studies have investigated the effects of CMR in patients who were recently discharged from the hospital [14]. Other events such as falls or admissions to nursing homes could also be reasons to start a CMR to critically evaluate a patient's medicines. In some cases, transmural collaboration may be needed to perform CMR [15]. This will pose new challenges, such as questions about who is responsible for the start of the CMR, who is responsible for the medical file of the patient, how will the exchange of information occur at discharge and who will perform the follow-up and monitoring [16].

Focus on currently underrepresented patients

A limitation of studies investigating CMR and daily clinical practice is that certain patient populations are difficult to reach. In the DREAMeR study, the percentage of non-Western persons was significantly low. Unfortunately, we did not have data about socio-economic status or health-literacy. Patients with low (health) literacy, (non-Western) immigrants, low socio-economic status or those who typically avoid healthcare may likely benefit from CMRs, but they are often underrepresented in studies. More insight into the specific issues regarding medication in these populations is needed to improve their participation in CMRs. In addition, language problems could be a challenge and will require support of family members or translators. Future studies should consider strategies to specifically reach these types of patients, e.g. by providing materials to non-Western immigrants in their native language or cooperating with other communal institutions such as churches or mosques to make contact [17].

Final considerations regarding patient selection for CMR

Combining all potential approaches for patient selection, including the results from our own studies, narrowing eligibility criteria for CMR to patients aged ≥ 70 years using ≥ 10 drugs seems a sound initial strategy for pharmacists to start with when reviewing the process. It will probably identify patients with more DRPs for whom CMR is more likely to improve HR-QoL. However, the predictive value of the criteria age and number of drugs remains relatively low. Excluding younger patients with lower numbers of drugs will also exclude many patients who could still benefit from a CMR. Therefore, a focus on patients aged ≥ 70 years using ≥ 10 drugs should not lead to the exclusion of other patients. Further research into the selection of patients, including the options mentioned above, is still needed. Selecting the most appropriate patients for a CMR is also related to the actual conduct of the intervention and the outcomes and effects that will be investigated. This is further described in the next paragraphs.

What is the best way to perform a CMR?

The CMRs performed in this thesis broadly followed the ideal CMR described in the Dutch multidisciplinary guideline 'Polypharmacy in the Elderly', which consists of five different steps: 1) patient interview, 2) analysis, 3) discussion between pharmacist and GP, 4) implementation of actions and 5) follow-up and monitoring (**Figure 1**) [1]. These five different steps in the CMR process are discussed in light of the results of the studies presented in this thesis combined with other literature. Overall, we have investigated two different approaches to optimise the CMR intervention.

In step 1 of the process – 'patient interview' – we have investigated whether the effectiveness of a CMR on clinical and patient-reported outcomes could be improved by a more patient-centred CMR (focused on 'personal goals'). Goalsetting could also contribute to step 4 of the process – 'implementation of actions' – through shared decision making in the implementation of actions. In step 2 of the cycle – 'analysis and identification of DRPs' – we have investigated whether the efficiency of identifying DRPs could be improved by using explicit criteria operationalised as 'computer rules'.

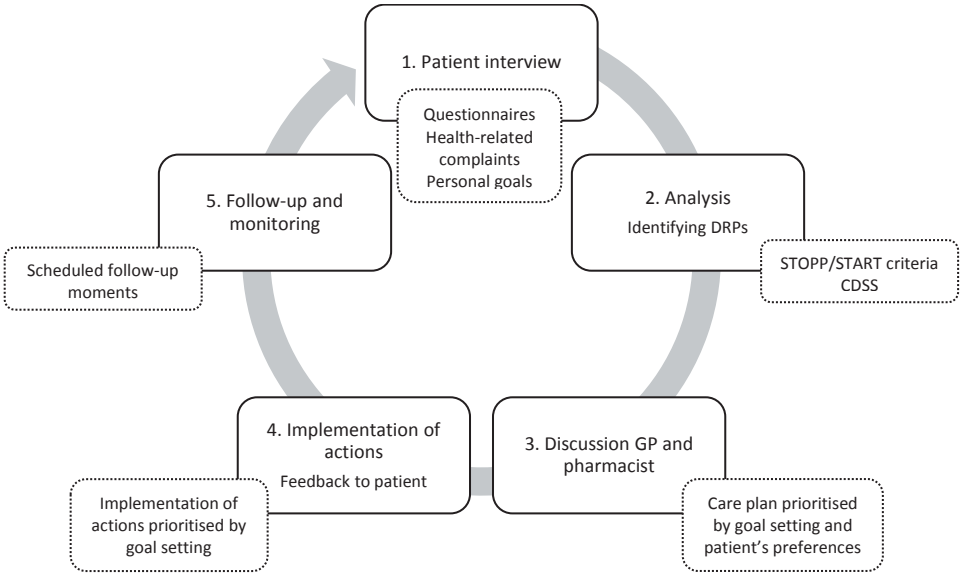

FIGURE 1: Schematic process of the five steps of a CMR as described in the multidisciplinary guideline, including investigated aspects in this thesis

Step 1: Patient interview

Patient participation in CMR may improve identification of DRPs, such as side effects, lack of effect, practical issues and inadequate patient understanding. The DRPs identified in a patient interview by a community pharmacist received the highest priority and led more often to implemented drug changes [18]. The results of this thesis underline the relevance of DRPs identified through a patient interview. The results in chapter 2 demonstrate that only the minority of the DRPs were associated with explicit criteria and that the majority of DRPs were derived from a structural assessment by the pharmacist after a patient interview. The main reasons to add drugs, such as the addition of painkillers, were because of complaints of

patients that emerged from the interview. The findings presented in chapter 3 are in line with chapter 2. Only a minority of DRPs were identified with clinical rules from the CDSS, and moreover, these DRPs were less frequently solved.

Another option for the patient interview that has been investigated is the use of a questionnaire instead of a patient interview. A questionnaire showed reasonable agreement with a patient interview, but patients still reported more drugs and DRPs in the interview than in the questionnaire [19]. The Opti-Med study found no effect of a CMR on HR-QoL and geriatric problems [9]. This may be explained by the absence of a face-to-face interview between healthcare providers and patient, but the fact that only 57% of the patients in this study had polypharmacy may also have contributed. Overall, we concluded that patient interviews remain needed to show the effects on the outcomes of relevance for patients but that sending questionnaires in advance may be used to improve the efficiency of the interview.

Therefore, the DREAMeR study (chapter 4) was designed to pay specific attention to patients' preferences, personal goals and health-related complaints in the patient interviews. In addition to 'scientific evidence' and the 'experience of health care professionals', our patient-centred CMRs structurally added the 'patient's values and preferences' to complete the three main components of evidence-based medicine. Many previous studies did not structurally involve this aspect. The results presented in chapter 5 show that this CMR improved HR-QoL measured with EQ-VAS and reduced the number of health-related complaints with an impact on patients' daily lives. Chapter 7 described that a CMR led to 43% goal attainment, 52% improvement on personal goals and only 11% deterioration compared to baseline. The DREAMeR study is one of the first studies that shows an effect of CMR on outcomes that are of relevance for older patients' wellbeing. We believe that the focus of the patient interview has contributed to these effects. Two innovative components of this patient interview must be highlighted.

First, personal goalsetting in the DREAMeR study was part of the intervention. Although goalsetting was relatively new for the community pharmacists, 90% of pharmacists were able to have patients set at least one goal (chapter 7). Goalsetting and formulating GAS during a patient interview requires training and support. In the DREAMeR study, a training day, including communication skills, was organised, and pharmacists were supported by an expert team, monthly web conferences and a database with the most common 'SMART' - specific measurable acceptable realistic time bound - formulated GAS. There may have been a learning curve for pharmacists who participated in the DREAMeR study to apply GAS, so the number of goals that can be formulated during CMRs may become even higher when pharmacists are more experienced. Chapter 7 illustrated that the implementation rate of recommendations associated with GAS-related DRPs was higher than for other DRPs. This

indicates that goalsetting helps with prioritising the most important problems for patients. Most of the goals were focused on issues that hamper patients during their daily activities, e.g. pain, distance walking and fatigue.

Second, questionnaires (ISCOPE and health-related complaints) completed before the start of the CMR presented valuable input for the goal setting in patient interviews in the DREAMeR study. An (adapted) questionnaire focusing on health-related complaints, indicators for complex health problems and examples of personal goals of patients, may help patients and their caregivers to prepare themselves for the interview. This questionnaire can be used by the pharmacist during the patient interview to obtain more in-depth information.

Step 2: Analysis – identification of DRPs

After the patient interview, the next step is the identification of DRPs based on all collected information. These DRPs can be identified in a CMR with implicit and explicit criteria. An implicit method is a structural assessment of all medical, medication and patient data [1,20]. This requires time, adequate professional judgment and sufficient training and education. This implicit method is recommended in the Dutch multidisciplinary guideline 'Polypharmacy in the Elderly' [1]. Below, we discuss three possible ways to support the identification of DRPs as a complement to the implicit method.

First, checklists with explicit criteria can support the identification and analysis of DRPs during CMRs. Most of these explicit criteria identify potential inappropriate medications (PIMs) in older persons [21]. Some checklists, such as the START criteria, also consider prescribing omissions (POMs) [22,23]. In chapter 2, the applicability of the European-based STOPP/START criteria was investigated. These criteria have also been added to the multidisciplinary guideline [1]. This study showed that only one fifth of the DRPs that were identified with an implicit method were associated with a STOPP or START criterion. In addition, the implementation rate of the DRPs that were associated with a STOPP or START criterion was lower than the implementation rate of the other DRPs. This suggests that explicit criteria may not always be considered relevant or that some of these criteria are so obvious (e.g. starting a statin after myocardial infarction) that non-adherence to the criteria is often deliberate (e.g. the patient has a limited life expectancy or developed myalgia on four different statins). Explicit criteria may be particularly helpful for pharmacists and GPs with little experience in CMR to identify PIMs and POMs, but healthcare providers should always be aware that these checklists cannot detect all DRPs and that they always require clinical judgment. Explicit criteria can be used for automated searches in healthcare information systems to monitor the quality of pharmacotherapy on a population base. In addition, the use of a CDSS during prescribing or dispensing can prevent the initiation of PIMs (e.g. replacement of a long-acting benzodiazepine for a short-acting benzodiazepine to prevent

falls) or prevent omissions of prophylactic drugs (e.g. addition of gastric protection with an NSAID). Finally, checklists with explicit criteria should be updated regularly, as guidelines and pharmacotherapy often change.

Second, the main advantage of explicit criteria is that they can be easily integrated as clinical rules into a CDSS. Such a CDSS can automatically identify potential DRPs with computer software. A CDSS has been investigated in different settings, but only a few studies have investigated the applicability during medication review in primary care [24-27]. One study found that explicit criteria yielded more DRPs than an implicit method by a pharmacist [24]. Chapter 3 of this thesis also shows that the number of identified DRPs increased after the introduction of clinical rules in a CDSS. However, the number of resolved DRPs remained the same. The implementation rate of CDSS-related DRPs was lower than other DRPs, which indicates that the clinical relevance of these DRPs was lower. This could possibly be explained by the fact that the studied clinical rules were not specific enough. Lack of specificity and alert fatigue due to too many displayed alerts are commonly described as disadvantages of CDSS [28,29]. Further development of a CDSS, including specific algorithms and adequate linking of medical data and laboratory values, is needed to further improve the analysis of DRPs during CMRs.

A third option to support identification of DRPs is the use of expert teams [9,30]. Experts could identify more (potential) DRPs than pharmacists in practice [30]. It must, however, be said that these studies using expert teams were completed when many pharmacists were still learning how to perform a CMR. Today, many more pharmacists are accredited and increasingly experienced in performing CMRs in the Netherlands. Besides that, the pharmacists identified a higher proportion of clinically relevant DRPs compared with expert reviewers [30]. Moreover, a CMR must be seen as an opportunity for the pharmacist to work on a trustful relationship with the patient. This will stimulate the implementation of actions and potential future consultations of the patient. Therefore, community pharmacists should not outsource their CMRs to external professionals on a regular basis. An interesting option could be to have some pharmacists or GP experts in the field of pharmacotherapy in older persons who could help pharmacists with difficult cases or complex care plans.

Step 3: Discussion between pharmacist and GP

After the analysis of the DRPs, in step 3, the community pharmacist discusses all potential DRPs and associated recommendations with the GP of the patient to prepare a pharmaceutical care plan, preferably in a face-to-face meeting [31,32]. Closer collaboration between the GP and pharmacist is associated with higher implementation rates of recommendations [33]. To guarantee close collaboration between GPs and pharmacists in the DREAMeR study, accredited pharmacists with experience in CMR and (self-reported) sufficient collaboration

with GPs were invited. The extent of integration and collaboration with the GPs in our study was not measured separately, so it was not possible to investigate whether specific aspects of collaboration could have influenced the results.

One important aspect that can be optimised in the collaboration between the GP and pharmacist is sharing clinical data. There is large variation in information exchange between the GP and pharmacist in primary care practices. Integrated care information systems can facilitate the exchange of information between different healthcare providers (and sometimes also with patients). An example of a study in the Netherlands where the exchange of information was well established is the integration of a non-dispensing pharmacist (NDP) into a general practice [34]. In this setting, the pharmacist actually worked in the general practice and had full access to the medical file. Moreover, these pharmacists added their analysis, actions and information on the follow-up to the same patient records in which the GP also worked. Full integration with the GP could add value to patient-centred clinical pharmacy services [35]. However, there were no differences in drug-related hospitalisations of the pharmaceutical care found between an NDP and a 'care plus' pharmacist with accredited training in CMR and sufficient collaboration with the GP [36]. As this thesis focuses on CMRs performed by the community pharmacists, another solution could be that community pharmacists perform patient interviews in the GP practice, has regular face-to-face meetings with the GP and gain access to the GP information system. In summary, multidisciplinary collaboration and exchange of information is important, and there is no golden standard of the best performance. The best solutions will depend on local settings and agreements.

Step 4: Implementation of actions

After a pharmaceutical care plan has been proposed, in step 4, actions should be implemented stepwise. Studies have shown broad ranges of implementation rates for recommendations to solve DRPs [33]. Implementation needs shared decisions and agreements about the recommendations between pharmacist, GP and patient. This is also reflected in the results of this thesis. The implementation rate of recommendations associated with DRPs in the CMRs performed in the DREAMeR study (chapter 7) was higher than after the CMRs described in chapter 2 and 3. This suggests that a patient-centred CMR focused on a patient's preferences and personal goals can contribute to higher implementation rates of actions, because shared decision making is more integrated. For a stepwise approach in implementing actions, prioritising of DRPs and interventions can be helpful. Chapter 7 showed that goalsetting helps with prioritissing the most important problems and may motivate the patient for potential interventions. Most of the goals were related to health-related complaints and preferences of the patient and are therefore more relevant.

Step 5: Follow-up and monitoring

The last step of the CMR process is the follow-up and monitoring of the performed interventions. Follow-up may be the most neglected aspect of CMR in clinical practice. The limited evidence for the effects of CMR on clinical outcomes may even be caused by inadequate follow-up. The effects of any drug change on health-related complaints, adverse effects or target (laboratory) values should be monitored. The conSIGUE trial performed in Spain, where CMRs consisted of six follow-up moments, showed a beneficial effect of medication review on HR-QoL [37]. Although extensive follow-up requires a large time investment, which is probably difficult to implement in practice, sufficient follow-up may be essential to establish effects of CMRs on clinical outcomes such as HR-QoL. The setting of the NDP, which was described before, also provided room for extensive follow-up and evaluation moments in pharmaceutical care services, resulting in a high proportion (83%) of solved DRPs [38]. In the protocol of the DREAMeR study (chapter 4), pharmacists were asked to introduce at least two follow-up moments in every CMR.

To improve the efficiency of follow-up in CMR and to reduce costs of pharmacists and GPs, the follow-up could be mostly delegated to a (geriatric) practice nurse, e.g. (laboratory) monitoring, or a pharmacy technician, e.g. inhalation technique or other practical aspects. Finally, mobile e-health and applications should be developed to support follow-up. Patients could receive a notification on a smartphone every two to four weeks to monitor health-related complaints or drug changes. Such applications may currently be difficult to implement in this older, vulnerable population; nevertheless, older persons are becoming increasingly accustomed to mobile applications on smartphones and tablets [39,40].

Final considerations regarding the best way to perform a CMR

It remains difficult to pinpoint a definite moment in time when a CMR is completed. In our study, we chose a period of approximately three months to complete the CMR and six months to investigate outcomes. Even longer follow-up periods may be needed to show effects on specific outcomes, such as hospital admissions. This is elaborated further in the next paragraph about the appropriate outcomes for a CMR. The completion of the five steps finishes the CMR process, but the cyclical nature of this process implies that a new CMR could be restarted at any moment if necessary. Debate will arise when the previous CMR is finished and a new CMR should be started. In geriatric care facilities, it has been recommended to perform a medication review every six months [31], because this is a vulnerable population in which changes can occur quickly. The Dutch multidisciplinary guideline 'Polypharmacy in the Elderly' recommends a repeated CMR every year [1]. However, no studies have been published yet about the benefits of repeating CMRs in primary care and the extent of CMRs, so this provides opportunities for future research.

The final consideration regarding CMRs that must be addressed is the upcoming debate about 'deprescribing': the process of intentionally stopping a medication or reducing its dose to improve the person's health or reduce the risk of adverse side effects [41,42]. Deprescribing receives increased attention in studies in geriatric care [43-46]. A CMR could be an excellent opportunity to address deprescribing, because it gives the opportunity to balance all potential benefits and harms of current drug use in a multidisciplinary setting. The CMRs as performed in the DREAMeR study were suitable examples to address deprescribing, because they involved aspects of goalsetting and shared decision making to balance the optimal pharmacotherapy. The results in chapter 5 showed that the number of drugs used was slightly reduced in the intervention group over six months compared to the control group. These results demonstrate that it is possible to cease drugs in this population. Finally, the personal goals and preferences of patients that are described in chapter 7 (e.g. related to the wish to reduce the number of drugs) and present health-related complaints (chapter 5) could be excellent starting points for deprescribing. The results in chapter 7 showed that the goal to reduce the number of drugs was the second most common goal of older persons. This indicates that patients would also like to cease drugs when possible. As healthcare providers need support to perform the cessation of drugs, and patients need extra information to make the decision to cease (preventive) drugs, there is need for the development and implementation of adequate guidelines [47-49].

How can one measure the effects of a CMR?

Finally, this last question discusses what the most appropriate outcomes are to use in studies investigating the effects of CMRs. The term 'appropriate' indicates outcomes that fit the intervention and are able to demonstrate changes. The potential effects of a CMR are related to the type of patients that were selected and the form of execution of the intervention, both of which are described in the previous paragraphs. First, clinical outcomes are discussed, which can be divided into humanistic or patient-reported outcomes and other clinical outcomes, such as hospital admissions and mortality rates. This paragraph is completed with the discussion of economic outcomes and final considerations.

Use of patient-reported outcomes in a patient-centred CMR

The overall aim of care for older persons is to improve their daily functioning, health and wellbeing [50]. A recent report from the Ministry of Health, Welfare and Sport underlined the importance of this aim for care for older persons with the initiative of a program titled 'Living Longer at Home', which has been signed by multiple organisations to improve care for older persons to help them live longer independently at home with a high quality of life [51]. The DREAMeR study was also designed to try to improve outcomes that are related to health and wellbeing. The hypothesis was that a patient-centred CMR could potentially influence a

patient's quality of life. To measure HR-QoL, different questionnaires could be used [52-54], but the EQ-5D is preferred in most health technology assessment guidelines, because it has well-validated tariffs of valuation sets for different countries [55,56]. The effects of a CMR on HR-QoL are limited. Not only is the EQ-5D difficult to improve, but the effects on other HR-QoL measures such as SF-12 or SF-36 are also lacking [57]. The results of the DREAMeR study in chapter 5 showed that there was no difference between the intervention and control group in HR-QoL measured with EQ-5D, whereas an effect was found on HR-QoL measured with EQ-VAS. An explanation for this phenomenon could be that the EQ-5D is effective at detecting changing health status of patients who are moderately ill (health utility values around 0.5), but for persons with relatively high or low utility values, the EQ-5D could be not sensitive enough to detect changes [58,59]. Even if there would be some improvement or deterioration in these patients, it would not result in influencing the patient's response on the five possible answers. Surprisingly in this older population with multiple drugs, the baseline health utility values of the patients in our study were relatively high, as shown in chapter 5. This offers little room for improvement. The baseline EQ-VAS values were slightly lower, and this outcome measure contains a continuous scale, which has already been shown to be slightly more responsive than EQ-5D and demonstrates a means of summarising overall health that is closer to the patient's perspective [60,61]. Perhaps in future studies investigating effects of CMR on HR-QoL, patients with low baseline HR-QoL values could be selected, because they have more room for improvement in this outcome.

In addition to quality of life, we also investigated new patient-reported outcome measures (PROMs) that could be related to a patient's health and wellbeing. To examine these measures, a questionnaire regarding 12 health-related complaints was developed (chapter 4). These health-related complaints could be associated with patients' drugs use and health and could be influenced with interventions in a CMR. Pain has been investigated in CMR studies before [62,63], but no other studies investigated a broad range of health-related complaints that could have an impact on the patient's life, such as dizziness or gastrointestinal problems. As the perception of a complaint is different between individuals, we also wanted to investigate the clinical relevance of a complaint. Therefore, a visual analogue scale (VAS) was used to measure severity (range 0 to 10), and a Likert scale was used to measure the impact on daily life (range from 'no influence' to 'extreme influence') [64]. The questionnaire was tested in a pilot study, but a formal validity study was not performed. There was large variation in the prevalence and severity of these complaints, as presented in chapter 5. It could be debated what exact cut-off points should be used to indicate whether a health-related complaint is of impact on a patient's daily life. We decided to choose a cut-off value for severity of ≥ 5 on a VAS from 0–10 together with a moderate-to-severe impact on daily life on a 5-point Likert scale. These cut-off points were expected to indicate moderate-to-severe complaints [65].

The third outcome measure that was used in the intervention group of the DREAMeR study was GAS, which is particularly useful when goalsetting is part of the intervention. The use of GAS in clinical studies investigating CMR was new, although GAS has been recommended for use in pharmacy practice before [66]. Chapter 7 describes the results of GAS in the intervention group of the DREAMeR population. As goalsetting was part of the intervention, it was impossible to use GAS in the control group; thus, it cannot be excluded that the attainment of goals was caused by the natural course of the patient's condition. Therefore, in explanatory studies, GAS should be combined with other PROMs that can also be measured in the control group. However, using GAS in studies investigating heterogeneous interventions in this older population seemed to be useful, because 90% of healthcare providers were able to set at least one goal with a patient. The main advantage of GAS is that in contrast to generic measures in which the same scale items are used for all patients, GAS is an individualised clinometric score that uses the baseline score of an individual as a reference and can thereafter be compared at the group level [67,68]. It is important that GAS should utilise a SMART formulation, because when unrealistic goals are set, this may possibly have a negative effect on the patient's quality of life.

The above mentioned outcomes are examples of PROMs. Studies have recommended that PROMs are important in evaluating complex health interventions [57,69]. A similar approach that has been investigated as a PROM in medication review studies is the 'Patient-Reported Outcome Measure, Inquiry into Side Effects' (PROMISE) instrument [70]. This instrument was mainly focused on potential adverse effects of drugs. The PROMISE instrument could provide meaningful information on drug-associated symptoms in CMRs, but the RCT showed that the number of drug-associated symptoms was not reduced by a CMR compared with usual care. As PROMISE was both part of the intervention and outcome measure, it is still unknown if this PROM was useful in detecting change in older persons [70]. Further development and research is needed before this PROM can be used in studies investigating the effects of CMRs.

Use of other clinical outcomes in studies with high-risk patients

Health interventions, including (new) drugs, generally aim to improve clinical outcomes for patients. In CMR research, the most important clinical outcomes could be the reduction of drug-related hospital admissions and improvement of HR-QoL, which have been discussed previously. As morbidity and mortality in this older population are influenced by a wide range of factors, it difficult to show the effects of CMR on these outcomes.

In this thesis, we decided not to investigate effects of CMR on hospital-admissions, as we expected that to measure an effect on hospital admissions, two specific study designs are most appropriate: 1) studies in high-risk patients who have recently been discharged for a drug-

related hospital admission (e.g. patients with severe heart failure) or 2) population-based studies with very large sample sizes and extensive follow-up, because of the low baseline prevalence of hospital admissions in the general population. The first study design was not an option, as this thesis was focused on primary care and not the hospital setting. The second study design was not feasible because of budget constraints. Instead of measuring drug-related hospital admissions, many studies focus on process outcomes such as PIMs, POMs and reduction of DRPs, because these are related to drug-related hospital admissions. Despite all efforts in the past 10 years to reduce drug-related hospital admissions, a recent study showed that the number of drug-related hospital admissions has still not been reduced and has even increased [71]. This was mainly attributed to the absolute increase in older persons. However, it also indicates that it remains difficult to reduce hospital admissions with all the current interventions. However, the most recent data in this study referred to 2013 when CMRs in the Netherlands were still limited.

Use of economic outcomes in studies focusing on reducing healthcare expenditure

Due to an ageing society, it is important to manage the expected increase in healthcare expenditure in the upcoming years. Therefore, it is also imperative that studies investigate the cost effectiveness of an intervention. A CMR could influence healthcare consumption and costs, especially drug costs, but it is also a time consuming intervention which can contribute to additional costs. For this reason, in this thesis, an economic evaluation was also performed in chapter 6. Before this study, only the conSIGUE study conducted in Spain had shown that a CMR was cost effective [37]. This study could not directly be translated to the Netherlands, because the healthcare and community pharmacy care standards in the Netherlands are different compared to other countries. Chapter 6 showed that a CMR is an economically attractive intervention, because there was a high chance of cost savings in healthcare costs along with several beneficial effects on HR-QoL and health-related complaints compared to usual care. This study suggests that broad implementation of CMR in the older population with polypharmacy would be beneficial and could provide input for policymakers to make decisions about reimbursement and investment.

To measure healthcare expenditure, different approaches can be chosen. In the DREAMeR study, healthcare costs were measured from a societal perspective with the Dutch Medical Consumption Questionnaire, including informal care during telephonic assessments [72]. This is a validated and useful questionnaire that has been recommended to use in health technology assessment [72,73], although it could have also introduced recall bias. Other options to collect the data could be to directly extract data from hospitals and GP practices, but this would be time consuming and difficult. As we measured a broad range of healthcare utilisation, it would be impossible to collect data from all these different healthcare providers. Another option that could be used in future research is to extract healthcare data from health

insurance databases. However, in both options, informal care would be missing. Data on informal care is only needed in economic evaluations performed from a societal perspective. Nevertheless, even without including informal care costs in the analysis, the results of chapter 6 would still show high potential for cost savings.

Next to measuring healthcare costs, studies focusing on the economic aspect of an intervention could also investigate how the efficiency of an intervention could be improved. For CMRs, more research is needed to examine how community pharmacists are utilising the available time for CMRs [74]. Although CMRs are already implemented in most practices, certain tasks could be supported by the pharmacy technician or practice nurse, such as the preparation and follow-up, as mentioned earlier in this chapter. Additional time could be created for pharmaceutical care services such as CMRs by improving the efficiency of other daily tasks of the pharmacists, e.g. logistics, dispensing and quality control [74]. In addition, CMRs must be adequately reimbursed. In the Netherlands, CMRs are reimbursed, but current fee rates are lower compared to the estimated intervention costs presented in chapter 6. This could discourage health care providers to proactively engage in and provide this service to patients. As multidisciplinary collaboration is important in CMRs, all healthcare providers should have a jointly financial incentive to provide CMRs.

Finally, when more attention will be paid to deprescribing in the coming years, CMR could further reduce drug costs. Pharmacist-led interventions have been shown to be effective in reducing inappropriate drug use [75,76]. The results of the DREAMeR study (chapter 5) also showed that a CMR could slightly reduce the number of drugs compared to usual care. However, for pharmacists, deprescribing also has drawbacks. On the one hand, this intervention can further contribute to their work as healthcare providers and will require pharmaceutical expertise. On the other hand, this will lead to lower income for pharmacists, as their main income still consists of a fee for dispensing, so policymakers should think about incentives to stimulate deprescribing.

Final considerations regarding outcomes in CMRs

Studies investigating CMRs cannot be performed without presenting results on process and other intermediate outcomes, such as DRPs, type of interventions, drug changes and implementation rates. Although CMRs have been frequently shown to reduce DRPs, it is important that all studies still present these results to obtain insight into the quality and performance of CMRs. Different classification systems for DRPs can be used [1,77-79], but most of them consist of overarching terms, including overtreatment, suboptimal therapy, adverse effect, interaction, wrong dosage, problems with usage of drugs, and compliance (over and underuse).

A new development being currently published is a core outcome set for CMR that is recommended to be used in all clinical trials investigating CMR in multimorbid older patients with polypharmacy [69,80,81]. A core outcome set may be needed, because the heterogeneity in selected patients, interventions, outcomes and study design make it difficult to compare the results in systematic reviews (as the above paragraphs also indicated). The recommended core outcome set consists of seven outcomes: 1) drug-related hospital admissions, 2) drug overuse, 3) drug underuse, 4) potentially inappropriate medications, 5) clinically significant drug-drug interactions, 6) health-related quality of life and 7) pain relief [81]. The outcomes chosen in this set differ in their clinical importance, ranging from process outcomes, such as drug interaction and over- and underuse, to clinical outcomes such as hospital admissions and QOL. During the design of the DREAMeR study, this core outcome set was not yet available, but almost all the proposed outcomes were included. In addition to over- and underuse and interactions, other DRPs were measured. Pain was measured as one of the health-related complaints, and hospital admissions were measured in the medical consumption questionnaire. The number of PIMs was not calculated, but PIMs will be indirectly measured as DRPs, including overtreatment and (possible) side effects.

Although the proposal of a core outcome can improve the quality and comparability of studies in CMRs, the specificity of the proposed outcomes may be discussed. The outcomes that should be used in studies should derive logically from the study design, including the target patient group and the nature of the intervention. Process outcomes (such as all DRPs and interventions) should always be measured, because these outcomes provide insight into the actual execution of the intervention. In addition, clinical outcomes, including humanistic outcomes, should be measured, but the exact choice may differ. In an intervention aimed at frequent fallers, falls are an obvious outcome, whereas pain scores should be measured when pain management is an important focus of the intervention. As pharmacy practice research will increase its focus on patient-centred care in the upcoming years, it is important that studies investigating CMRs also use PROMs. The PROMs used in this thesis, e.g. health-related complaints and GAS, could potentially be used in future studies.

Final implications for future research and development of CMR

In this final section, the previously discussed three questions are summarised into implications for future research and practice. An ideal view of the future of pharmaceutical patient care for older persons is described after we summarise the lessons from this thesis and earlier studies.

What can we learn from this thesis and other studies?

Studies in CMRs have historically generally focused on identification and reduction of DRPs and improved adherence to prescribing guidelines. The multidisciplinary guideline

'Polypharmacy in the Elderly' provided recommendations for an ideal CMR consisting of five steps, including an implicit method for analysis (as seen in **Figure 1**). Explicit criteria have been developed and are increasingly operationalised as clinical rules into CDSS to detect PIMs, POMs and unnecessary drug use. These clinical rules could be useful to identify DRPs and perform interventions, but they often still lack specificity. Only a few studies have measured clinical outcomes such as drug-related hospital admissions, pain scores and falls.

This thesis introduced a more patient-centred approach with specific attention for patient preferences, personal goals and health-related complaints ('CMR one step beyond') and provided some evidence that a CMR could improve older patients' HR-QoL and that CMRs seem to be an economically attractive intervention. This study provides starting points for further optimisation of personalised care. Considering that 20 years after 'to err is human' and 10 years after the HARM study, there are still too many patients experiencing preventable drug-related hospital admissions. Additional efforts are required to improve pharmaceutical care for older persons with polypharmacy and multimorbidity.

On what could future research focus?

First, future studies could focus on improvement of information technology to support CMR. Future development of CDSS is needed to identify more clinically relevant potential DRPs, and additional technology is needed to support the CMR process (e.g. electronic questionnaires, information exchange with physicians and facilitation of follow-up through mobile health). Second, studies could focus on further improvement of selection criteria for a CMR. Algorithms including several patient characteristics could be developed that detect patients at the highest risk for drug-related hospital admissions or that identify patients who have room for improvement regarding HR-QoL. Third, further development of questionnaires aimed at identifying health-related complaints is needed in addition to more insight in the applicability of GAS in CMRs. Goal attainment scaling requires additional qualitative research to investigate barriers and facilitators for applying GAS in daily clinical practice, including the formulation of SMART goals. Patient-centred care in pharmacy practice should be further developed. Studies investigating deprescribing in CMRs in which deprescribing could be related to personal goals or health-related complaints are required. Economic evaluation of more efficient CMR methods and of specific target groups could be performed to investigate whether the cost-benefit ratio of CMR could be further optimised. Finally, future studies investigating CMR should include process outcomes (DRPs, interventions and implementation rates) together with PROMs and other clinical outcomes. The PROMs and clinical outcomes to be used depend on the chosen study design, patient group and intervention.

How could CMRs be further developed in the future?

In the future, there will ideally be continuous structural pharmaceutical care for older persons. Healthcare providers, such as GPs and practice nurses but also homecare nurses, physiotherapists, elderly physicians, social workers and informal carers, will work together in referring older patients to the right discipline. This referral process will be supported by information technology. A comprehensive CMR could be a starting point for this continuous care. Patients should first be selected based on their age and drugs, but they could also receive an additional questionnaire to identify whether they really need a comprehensive CMR. These CMRs will be prepared by pharmacy technicians and will be supported by a seamless exchange of medical information, e.g. by access for the pharmacists to the medical information system of the GP. Patients complete digital questionnaires about their health-related complaints, wishes and preferences related to their drugs and health before the start of a CMR to prepare themselves for the interview and to provide meaningful input for the pharmacist. The patient interview, performed by the pharmacist, focuses on patient's preferences, personal goals and health-related complaints. The identification of DRPs could be further supported by more specific clinical rules in the CDSS, which are based on the linkage of drug-related and clinical information. Shared decision making during CMRs is common, and goalsetting will help with prioritising the DRPs and interventions in the pharmaceutical care plan. Deprescribing is addressed when the benefits of the drugs no longer outweigh the disadvantages, especially when the patient has the preference to diminish the number of medicines or when the patient has health-related complaints that are associated with drug use. Deprescribing guidelines will support healthcare providers and patients. Follow-up is organised and includes (geriatric) practice nurses, pharmacy technicians and the use of mobile applications. The CMR becomes a continuous process. Pharmacists perform a yearly quick desktop search on the older person's medications and have access to his or her medical file. If needed, this could be followed by a less comprehensive type of medication review or a full CMR. Regular short consultations between pharmacists, GPs and other healthcare providers help to continuously update the pharmaceutical care plan. Acute life events, such as discharge from the hospital or admission to a geriatric care home, initiate a comprehensive CMR. Smaller events, such as initiation of an MDD or recent fall, could also initiate a CMR. All healthcare providers receive accredited joint training in CMRs, and when needed, pharmacist and GP experts in the geriatric field can be consulted with difficult cases. These experts may be based in so-called geriatric day hospitals (GDH), which were already developed in the United Kingdom in the late 1950s to help bridge the gap between inpatient and community care for older adults [82,83]. Complicated patients may also be referred to a GDH, where goals can be set together with multiple healthcare providers.

For this vison to become a reality, the active involvement of every player in the healthcare system is needed, including boards and governing bodies, government agencies, public-private partnerships, health care organisations, researchers, professional associations, regulators, educators, the healthcare workforce, and patients and their families.

Finally, this continuous pharmaceutical care including CMRs will result in a large number of older persons that are still living independently at home with a relatively high HR-QoL, despite their multimorbidity. Although these interventions would require initial investments, in the long run, healthcare costs may even be reduced by lowering drug costs and preventing unnecessary drug-related hospital admissions or uptake into nursing homes.

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APPENDICES A

SUMMARY

The impact of the ageing society on the sustainability of the current healthcare system is one of the major challenges of the next decades. The rapid increase in the number of older people, especially the oldest old, leads to an increase in the demand for care for these groups. Multimorbidity and the associated use of five more chronic drugs (polypharmacy) is common among persons of 65 years and older. Although preventive medication may increase life expectancy and may contribute to improved health, medication use also has his drawbacks. Five percent of acute hospital admissions are drug-related and almost half of them could be avoided. Because of the positive and negative consequences of polypharmacy, medication use in older people needs secure management. A clinical medication review (CMR) is a structured critical examination of a patient's medicines and can identify and resolve drug-related problems (DRPs). A CMR involves the patient, pharmacist and general practitioner (GP) and has been recommended to minimise the risk for adverse events and drug-related hospital admissions. The objective of this thesis is to generate evidence that may contribute to further optimisation of CMRs for older patients with polypharmacy in primary care. Three aspects of CMR have been investigated during the studies performed in this thesis: the selection criteria for eligible patients of CMR, the performance of the intervention (using computer rules and a patient-centred approach using personal goals) and (new) outcome measures to investigate the effects of CMRs.

This thesis consists of three parts. In **part 1** we investigated whether CMR can be optimised in terms of efficiency, e.g. by the use of checklists with explicit and automated criteria. An example of extensively used European based explicit criteria are the Screening Tool of Older People's Prescriptions (STOPP) and Screening Tool to Alert to Right Treatment (START) criteria. In **chapter 2,** these STOPP/START were retrospectively applied to already identified DRPs during 457 CMRs. The mean number of DRPs was 3.6 per patient and 81% of these DRPs were not associated with STOPP/START criteria. The percentage of START criteria present in identified DRPs was higher than the percentage of STOPP criteria (13% vs. 5.7%). The implementation rate for recommendations associated with STOPP criteria was higher compared to recommendations associated with START criteria (56% vs. 39%). Both implementation rates of STOPP and START recommendations were lower compared to recommendations that were not associated with STOPP/START criteria. As the majority of DRPs was not associated with STOPP/START criteria, these findings suggest that healthcare providers cannot solely depend on the STOPP/START criteria to identify DRPs in primary care. A structural analysis including a patient interview is needed to identify all DRPs during CMR.

Explicit criteria can be easily incorporated into clinical decision support systems (CDSS). In **chapter 3** we investigated the effect of adding a CDSS to medication review software on identifying and solving DRPs in daily pharmacy practice. There were 46 different explicit criteria incorporated into medication review software. We performed a pre-post analysis and the number and type of identified and resolved DRPs during CMR were compared in a cohort of 121 pharmacies in the year before and after the introduction of this CDSS. The mean number of identified DRPs per patient was higher after the introduction of CDSS (3.2 vs. 3.6), but the resolution rate of the DRPs was lower after the introduction of CDSS (50% vs. 44%), which overall resulted in 1.6 resolved DRPs per patient in both groups. After the introduction of a CDSS, 41% of DRPs were detected by the CDSS. The resolution rate of DRPs generated by CDSS was lower than for DRPs identified without the help of CDSS (29% vs. 55%). We concluded that a CDSS generated a large number of potential DRPs during CMR, but that these DRPs identified by CDSS were less frequently resolved compared to DRPs identified by a structural assessment of pharmacotherapy including a patient interview. Further development of CDSS with more specific alerts, linking dispensing and clinical information, could make the CMR process more efficient.

Part 2 of this thesis presents the design, results and evaluation of the 'Drug use Reconsidered in the Elderly using goal Attainment scales during Medication Review' (DREAMeR) study. The extensive study protocol of the DREAMeR study is presented in **chapter 4**. The DREAMeR study is a pragmatic randomised controlled trial (RCT) investigating the effects of a CMR focused on personal goals on health-related quality of life (HR-QoL) and health-related complaints in older persons (≥ 70 years) with polypharmacy (use of ≥ 7 chronic drugs).

Chapter 5 presents the results of this RCT. The DREAMeR study included 629 persons of whom 315 persons were randomly assigned to receive the intervention and 314 persons to receive usual care. In total, 43 community pharmacists (working in 35 community pharmacies) and 113 GPs participated in this study. This study showed that a patient-centred CMR focused on patient's preferences, personal goals and complaints, improved HR-QoL measured with EQ-VAS with 3.4 points on scale from 0-100 and reduced the number of health-related complaints with an impact on daily life with 12%, whilst the number of drugs used slightly decreased with 3.6%, compared to usual care after six months. There was no change between the intervention and control group for HR-QoL measured with EQ-5D-5L and total number of complaints. The mean number of DRPs per patient was 5.8 and in 90% of patients, there was at least one health-related goal proposed. We concluded that including patient's preferences during the patient interviews in CMR is important to establish effects of this intervention that are important to older patient's life and wellbeing.

In **chapter 6** the results of an economic evaluation of the DREAMeR study are presented. The cost-perspective was added to the clinical effects derived from the previous study. A cost-utility and cost-effectiveness analysis was performed from a societal perspective. The total mean healthcare costs per patient after six months were €3809 in the intervention group compared to €4189 in the control group, resulting in incremental healthcare costs of €380. The mean time to perform a CMR was 107 minutes for the community pharmacist, 7 minutes for a pharmacy technician and 12 minutes for the GP, which resulted in an average intervention cost of €199 for a CMR. We concluded that a patient-centred CMR is an economically attractive intervention for older patients with polypharmacy. Compared to usual care, there was a high probability (> 90%) of healthcare cost savings combined with beneficial effects on HR-QoL measured with EQ-VAS and health-related complaints.

Part 3 describes two in-depth analyses of the DREAMeR study. In **chapter 7**, the results of the intervention group were further analysed. We investigated a new tool and outcome measure during CMR: goal attainment scaling (GAS). The results of this study showed that goalsetting during CMR was possible because 90% of older patients were able to set at least one goal together with the pharmacist. After six months, patients showed improvement on 52% of the goals and 43% of the goals were actually attained. The goals 'reduce pain', 'reduce number of pills' and 'improve mobility' were the three most prevalent goals. The implementation rate of recommendations for GAS-related DRPs was 81% compared to 62% for not GAS-related DRPs We concluded that GAS showed to be a useful tool to evaluate the attainment of health-related goals after CMR. DRPs associated with GAS were more likely to be solved compared to other DRPs, which implicates that goal setting is important for prioritising the most important problems during the patient interview in the CMRs.

Chapter 8 shows the results of a subgroup analysis of the DREAMeR study in 501 patients (252 in the intervention group and 249 in the control group). Seven subgroups were defined, based on: sex, age, living situation, number of drugs in use, use of a multidose drug dispensing system, drug delivery service at home and the presence of complex health problems (determined with the ISCOPE screening questionnaire), and were analysed using logistic regression analyses. Patients using ≥ 10 drugs had more benefit from a CMR on improvement in HR-QoL measured with EQ-VAS (OR = 2.2; 95% CI 1.04 to 4.7) and on reduction of at least one health-related complaint (OR = 2.2; 95% CI 1.01 to 4.6). The subgroups: patients living alone and patients with complex health problems also had a higher odds for improvement in EQ-VAS by a CMR, but these interaction effects were not significant compared to the control group. The subgroups: sex, age, multidose drug dispensing system and drug delivery at home, did not show differences in effects. We concluded that patients using 10 or more drugs had the most benefit from a CMR on improvement in HR-QoL measured with EQ-VAS and on reduction of health-related complaints.

Finally in **chapter 9**, the findings of these studies are considered into a broader perspective by discussing three different questions: 1) How should one select the appropriate patients for a CMR? 2) What is the best way to perform a CMR (using computer rules or a patient-centred approach with personal goals) and 3) How can one measure the effects of a CMR?

There are different ways to select the most appropriate patients for a CMR. It depends on the aim of the CMR and the used outcome measures, what the most appropriate selection criteria are. One approach to tailor the currently recommended selection criteria, of patients aged 65 years and over with polypharmacy, could be to select patients of older age with a higher number of drugs in use. In the DREAMeR study we increased age and number of drugs to patients aged 70 years and older using seven or more chronic drugs and we found small effects of the intervention. The subgroup analysis showed that patients using 10 or more chronic drugs were associated with higher effects of a CMR. Other possible options to select patients for a CMR that needs to be further investigated could be to use questionnaires at the start of a CMR to select patients who really prefer or need a CMR, to select vulnerable patients with complex health problems, or to work together with other healthcare providers.

The most efficient and effective way to perform a CMR is possibly by using personal goals and more selective computer rules. A CDSS could identify potential DRPs at the start of a CMR, but should be made more selective to select more clinically relevant DRPs. A CMR cannot be replaced by computer rules, because a CDSS can only detect the minority of DRPs. We showed that a patient-centred CMR is important to improve outcomes that are relevant to older patients lives and wellbeing. Using personal goals during the patient interview could help prioritising the most important DRPs for a patient during a CMR. It contributes to shared-decision making about the pharmaceutical care plan and the optimal pharmacotherapy for each individual older patient.

The most appropriate clinical and economic outcome measures to use in studies investigating the effects of CMRs, depend on the aim and focus of the CMR. Clinical medication reviews that are aimed to improve older patients' lives and wellbeing should preferably include HR-QoL. Clinical mediation reviews aimed to reduce drug-related hospital admissions should preferably include high-risk patients. Reporting process outcomes, such as DRPs, interventions and implementation rates is important to show the quality and performance of the CMRs. Goal attainment scaling and health-related complaints are outcome measures that could be useful in evaluating interventions like CMRs, but these outcomes should be further investigated in future research.

In conclusion, this thesis presented a series of studies focused on CMR, which showed that a CMR in older persons with polypharmacy can contribute to the improvement of older

patient's pharmacotherapy and the improvement of outcomes that are relevant to older patients wellbeing, like HR-QoL, health-related complaints and the attainment of personal goals. The slight reduction in number of drugs combined with the high probability of healthcare cost savings, could also support the management of the expected increase in healthcare costs in the next decades.

SAMENVATTING

De impact van de vergrijzende samenleving op het huidige zorgsysteem is een van de grootste uitdagingen voor de komende decennia. De snelle groei van het aantal ouderen, voornamelijk de oudste ouderen, leidt tot een grotere zorgvraag die drukt op de maatschappij. Bijna tweederde van de 65-plussers heeft meerdere chronische aandoeningen en een-vijfde van deze personen gebruikt vijf of meer chronische geneesmiddelen. Er zijn steeds meer preventieve medicijnen die de levensverwachting van mensen kunnen verhogen en kunnen leiden tot een betere gezondheid. Chronisch medicatiegebruik heeft echter ook een keerzijde.

Van de acute ziekenhuisopnames is vijf procent geneesmiddel gerelateerd en bijna de helft van deze ziekenhuisopnames kan voorkomen worden. Vanwege de positieve en negatieve kanten van geneesmiddelgebruik, moet de balans tussen effectiviteit en veiligheid van deze geneesmiddelen regelmatig geëvalueerd worden. Een medicatiebeoordeling (MBO) is een interventie die daarbij kan helpen. Een MBO is een gestructureerde evaluatie van de medicijnen, aandoeningen en laboratorium waarden van een patiënt. Een MBO kan problemen rondom het gebruik van geneesmiddelen opsporen en oplossen. Denk hierbij aan bijwerkingen, problemen met innameschema's, geneesmiddelen die niet effectief meer zijn of preventieve medicatie die ontbreekt. Medicatiebeoordelingen worden aanbevolen door richtlijnen om het risico op bijwerkingen, die in ernstige gevallen zelfs kunnen leiden tot ziekenhuisopnames, te verlagen.

Het belangrijkste doel van dit proefschrift was om te onderzoeken of een MBO verder geoptimaliseerd kon worden voor oudere patiënten met polyfarmacie. In de zeven onderzoeken die beschreven zijn in dit proefschrift, hebben we ons drie verschillende aspecten gericht. Aspect één is de verfijning van de selectiecriteria voor de patiënten die het meeste baat kunnen hebben van een MBO. Aspect twee is de uitvoering van de MBO's. Door het gebruik van automatische beslisregels en zorg op maat m.b.v. persoonlijke doelen kan een MBO mogelijk efficiënter en effectiever gemaakt worden. Aspect drie is het gebruik van nieuwe uitkomstmaten om de effecten van een MBO te onderzoeken. De MBO's in de onderzoeken in dit proefschrift zijn uitgevoerd door openbaar apothekers en huisartsen in Nederland.

Dit proefschrift bestaat uit drie delen. **Deel 1** beschrijft twee studies die onderzoeken of een MBO efficiënter uitgevoerd kan worden, door het gebruik van checklists met expliciete criteria en automatische beslisregels. We hebben ervoor gekozen om als expliciete criteria, de Europese STOPP (Screening Tool of Older People's Prescriptions) en START (Screening Tool to Alert to Right Treatment) criteria, te gebruiken. Deze lijsten kunnen potentieel ongewenste geneesmiddelen en het ontbreken van preventieve medicatie bij ouderen

opsporen. In het onderzoek dat wordt beschreven in **hoofdstuk 2**, werden deze STOPP/START criteria achteraf toegepast op de problemen rondom het gebruik van geneesmiddelen. Deze problemen waren ontdekt tijdens 457 MBO's die al waren uitgevoerd in 13 apotheken in Nederland. Het gemiddeld aantal problemen met medicatie was 3.6 per patiënt. Van deze problemen werd 81% niet gevonden met een STOPP of START criterium. De START criteria konden vaker toegepast worden dan de STOPP criteria (13% vs. 5.7%). Bij elk probleem wordt een voorstel gedaan door apotheker en huisarts om dit op te lossen. Hierbij kan gedacht worden aan het stoppen of starten van een geneesmiddel of het geven van een inhalatie instructie bijvoorbeeld. Het aantal voorstellen wat echt wordt doorgevoerd wordt, is de implementatiegraad. De implementatiegraad van de aanbevelingen die geassocieerd waren met een STOPP criterium was hoger vergeleken met de aanbevelingen die geassocieerd waren met een START criterium (56% vs. 39%). De implementatiegraad van zowel de STOPP als START aanbevelingen was lager vergeleken met de implementatiegraad van de overige problemen die waren gevonden na het patiëntgesprek en de analyse door de apotheker. Deze bevindingen suggereren dat het gebruik van STOPP/START criteria alleen tijdens een MBO, niet voldoende is om alle relevante medicatie problemen van ouderen te vinden. Het patiëntgesprek en een zorgvuldige analyse van de medicatie en de aandoeningen van de patiënt door apotheker en huisarts, zijn belangrijk voor het vinden van de meeste problemen die te maken hebben met het geneesmiddelgebruik.

Een belangrijk voordeel van checklists met expliciete criteria is dat ze vrij eenvoudig ingebouwd kunnen worden als zogenaamde medisch-farmaceutische beslisregels (MFB's) in computer software. In **hoofdstuk 3** beschrijven we de resultaten van een onderzoek waarbij het effect van MFB's wordt onderzocht op het opsporen en oplossen van problemen rondom medicatiegebruik. Er waren 46 MFB's ingebouwd in een computersysteem. We hebben in 121 apotheken gekeken bij MBO's die waren uitgevoerd voor en na de invoering van de MFB's, naar het aantal problemen met geneesmiddelen die werden ontdekt en opgelost. Het gemiddeld aantal gevonden problemen per patiënt was hoger na het gebruik van de MFB's (3.2 vs. 3.6). Na invoering van de MFB's, werden er wel minder problemen opgelost (50% vs. 44%), waardoor het gemiddeld aantal opgeloste problemen per patiënt in beide groepen gelijk was, namelijk 1.6 per patiënt. Van het totaal aantal problemen was 41% gevonden met een MFB. De overige 59% was gevonden in het patiëntgesprek of de analyse door de apotheker en huisarts zelf. De implementatiegraad van de aanbevelingen die hoorden bij een MFB was echter lager dan die van de andere problemen die waren gevonden in het patiënt gesprek of na de analyse van de apotheker (29% vs. 55%). Op basis van dit onderzoek hebben we geconcludeerd dat MFB's een groot aantal potentiële problemen kunnen opsporen bij een MBO. Deze problemen werden echter minder vaak opgelost vergeleken met andere

problemen. Wanneer informatie over de ziekten en de laboratorium waarden (zoals de nierfunctie) van de patiënt, gekoppeld zouden kunnen worden aan de informatie over het geneesmiddelgebruik, kan het MBO proces vermoedelijk efficiënter gemaakt worden.

Deel 2 van dit proefschrift beschrijft in drie hoofdstukken het ontwerp, de resultaten en de evaluatie van het DREAMeR *(Drug use Reconsidered in the Elderly using goal Attainment scales during Medication Review)* onderzoek. De aanleiding voor dit onderzoek en een uitgebreide beschrijving van de wijze waarop het onderzoek is uitgevoerd, staan beschreven in **hoofdstuk 4**. Het DREAMeR onderzoek is een gerandomiseerd gecontroleerd klinisch onderzoek. Dit betekent dat deelnemers door een bepaling van het lot in een controlegroep of interventiegroep ingedeeld worden. De effecten tussen deze twee groepen worden vergeleken. De deelnemers uit de interventiegroep ontvangen een MBO. De deelnemers uit de controlegroep kunnen na afloop van het onderzoek alsnog een MBO krijgen. In het onderzoek is er sprake van een patiëntgerichte aanpak van de MBO's, waarbij gefocust wordt op persoonlijke doelen. Er worden patiënten geselecteerd met een leeftijd van 70 jaar of ouder, die ten minste zeven geneesmiddelen gebruiken. De effecten van een MBO worden onderzocht op de gezondheidsgerelateerde kwaliteit van leven, de gezondheidsklachten (zoals pijn, duizeligheid en maag-darmklachten) en het aantal gebruikte geneesmiddelen.

Hoofdstuk 5 presenteert de resultaten van het DREAMeR onderzoek. Aan dit onderzoek deden 629 ouderen mee. Van deze groep kregen 315 patiënten een MBO en 314 patiënten vormden de controlegroep. In totaal werkten 43 openbaar apothekers (uit 35 apotheken) en 113 huisartsen mee aan dit onderzoek. De resultaten van dit onderzoek laten zien dat een MBO, die focust op de persoonlijke wensen, doelen en gezondheidsklachten van de patiënt, de kwaliteit van leven van ouderen kan verbeteren met 3.4 punten op een schaal van 0-100 (EQ-VAS) ten opzichte van de controlegroep na zes maanden. Daarnaast verlaagt een MBO het aantal gezondheidsklachten die het dagelijks leven van de patiënt beïnvloeden met 12%. Tot slot is er na zes maanden ook een lichte daling in het aantal geneesmiddelen te zien van 3.6% na een MBO ten opzichte van de controlegroep. Er was geen verschil in effect tussen beide groepen op kwaliteit van leven gemeten met de EQ-5D en het totaal aantal gezondheidsklachten (ongeacht ernst en invloed op het dagelijks leven). Het gemiddeld aantal problemen rondom het gebruik van geneesmiddelen, dat ontdekt werd tijdens de MBO's was 5.8 per patiënt. Bij 90% van de patiënten was tenminste één persoonlijk doel opgesteld. Op basis van deze resultaten concluderen we dat het belangrijk is om tijdens een MBO de persoonlijke wensen en doelen van de patiënt te bespreken. Deze patiënt gerichte interventie is effectief in het verbeteren van uitkomsten die belangrijk zijn voor het welzijn van ouderen.

In **hoofdstuk 6** presenteren we een economische evaluatie van het DREAMeR onderzoek. Hierbij hebben we, zo nauwkeurig mogelijk, alle gemaakte zorgkosten van de deelnemers aan

het onderzoek in kaart gebracht. Vervolgens hebben we deze kosten gerelateerd aan de effecten die gevonden zijn in het onderzoek. Er is een kosten-utiliteit en kosten-effectiviteit analyse uitgevoerd vanuit een maatschappelijk perspectief. Dat betekent dat alle zorgkosten worden meegenomen, waaronder ook die van mantelzorgers. De totale gemiddelde zorgkosten per patiënt na zes maanden waren €3809 bij de mensen die een MBO kregen en €4189 bij de controlegroep. Dit resulteerde in een gemiddeld verschil in zorgkosten per patiënt van €380. De gemiddelde tijdsinvestering voor een MBO was 107 minuten voor de openbaar apotheker, 7 minuten voor de apothekersassistente en 12 minuten voor de huisarts. Dit resulteerde in gemiddelde kosten van €199 voor een MBO. Dit bedrag is lager dan de bespaarde kosten. We concluderen daarom dat een patiëntgerichte MBO een economisch aantrekkelijke interventie is voor de maatschappij. Vergeleken met standaardzorg, is er een hoge kans (> 90 %) dat de interventie kosten besparend is. Daarnaast is er een klein effect aangetoond van de interventie op het verbeteren van de kwaliteit van leven (gemeten met EQ-VAS) en het verminderen van het aantal gezondheidsklachten die het dagelijks leven van de patiënt beïnvloeden.

Deel 3 beschrijft twee verdiepende analyses van het DREAMeR onderzoek. In **hoofdstuk 7** worden de resultaten van de patiënten die een MBO hebben gekregen nader bestudeerd. In het onderzoek werd een nieuwe uitkomstmaat getest die gebruikt kan worden bij MBO: goal attainment scaling (GAS). Dit is een schaal (van -3 tot +2) die het behalen van persoonlijke doelen kan meten. De resultaten van het DREAMER onderzoek laten zien dat meer dan 90% van de ouderen in staat waren om, samen met de apotheker, één of meerdere doelen op te stellen. Na zes maanden, scoorde 52% van deze patiënten verbetering op deze doelen en 43% van de doelen werd ook daadwerkelijk behaald. De drie meest voorkomende doelen waren: 'het verminderen van pijn', 'de wens tot het gebruik van minder pillen' en 'het verbeteren van mobiliteit'. De implementatiegraad van aanbevelingen die verband hielden met deze persoonlijke doelen was 81%. Van de overige gevonden problemen rondom medicatie (die waren bijvoorbeeld gebaseerd op richtlijnen) was 62% van de aanbevelingen doorgevoerd. Op basis van deze resultaten concluderen we dat GAS een bruikbaar meetinstrument lijkt om het behalen van persoonlijke doelen na een MBO te meten. Daarnaast is een patiëntgerichte aanpak, die gefocust is op persoonlijke doelen, belangrijk voor het prioriteren van de belangrijkste problemen van ouderen tijdens een MBO.

Hoofdstuk 8 presenteert de resultaten van een andere verdieping van het DREAMeR onderzoek bij 501 van de geïncludeerde patiënten (252 in de interventiegroep en 249 in de controlegroep). Deze patiënten waren gekozen omdat van hen alle data van de begin- en eindmetingen beschikbaar waren. Dit onderzoek bekijkt of er bepaalde patiënten zijn die meer baat hadden van een MBO dan anderen. We hebben hierbij gekeken naar een aantal kenmerken van de patiënten, namelijk: geslacht, leeftijd, leefsituatie, aantal geneesmiddelen in gebruik, gebruik van een zogenaamde baxterrol, het bezorgen van de medicatie bij de patiënt

thuis en de aanwezigheid van complexe gezondheidsproblemen (vastgesteld met de ISCOPE screenings vragenlijst). Patiënten die ≥ 10 geneesmiddelen gebruikten hadden meer effect van de interventie op verbetering in kwaliteit van leven gemeten met de EQ-VAS schaal. Deze groep had ook meer effect in het verminderen van het aantal gezondheidsklachten die van invloed zijn op het dagelijks leven van de patiënt. De subgroepen: alleenstaande patiënten en patiënten met complexe gezondheidsproblemen, hadden ook een hogere kans op verbetering van kwaliteit van leven (EQ-VAS), maar dit effect was niet significant vergeleken met de controlegroep. Geslacht, leeftijd, het gebruik van een baxterrol en bezorgen van medicatie thuis, hadden geen invloed op het effect van een MBO. Op basis van deze resultaten, concluderen we dat patiënten die 10 of meer geneesmiddelen gebruiken het meeste effect hebben van een MBO.

Tot slot worden de resultaten van de studies uit dit proefschrift in een breder perspectief geplaatst in **hoofdstuk 9**. Daarbij hebben we geprobeerd om drie vragen te beantwoorden: 1) Hoe kunnen de meest geschikte patiënten voor een MBO worden geselecteerd? 2) Wat is de beste manier om een MBO uit te voeren (door het gebruik van beslisregels of een patiëntgerichte aanpak met een focus op persoonlijke doelen)? en 3) Met welke meetinstrumenten kunnen de effecten van een MBO het beste gemeten worden?

Er zijn verschillende manieren om de meest geschikte patiënten voor een MBO te selecteren. Dit hangt af van het doel van de MBO en de gebruikte uitkomstmaten. Een manier om de huidige selectiecriteria, van 65 jaar en ouder en een gebruik van vijf of meer geneesmiddelen, te verfijnen, zou kunnen zijn om de leeftijd en het aantal geneesmiddelen te verhogen. In het DREAMeR onderzoek hebben we deze criteria verhoogd naar 70 jaar en ouder en het gebruik van zeven of meer geneesmiddelen. Daarbij vonden we effecten van een MBO die belangrijk zijn voor het verbeteren van de gezondheid en het welzijn van oudere patiënten. Andere mogelijke opties die nader onderzocht moeten worden, kunnen zijn: het gebruik van vragenlijsten bij de start van de MBO om patiënten te herkennen die zelf een MBO willen of veel problemen hebben, het identificeren van kwetsbare patiënten met complexe gezondheidsproblemen en het beter samenwerken met andere zorgverleners.

De meest efficiënte en effectieve manier om een MBO uit te voeren is waarschijnlijk door een persoonlijke aanpak te combineren met het gebruik van MFB's. Medisch farmaceutische beslisregels kunnen potentiële problemen herkennen bij de start van een MBO. De specificiteit van deze MFB's moet echter nog verbeterd worden, om meer klinisch relevante problemen op te sporen. Een MBO kan in ieder geval niet volledig vervangen worden door een computer met MFB's, omdat MFB's veel problemen niet kunnen opsporen. Hiervoor is een patiënt gesprek en een zorgvuldige analyse van alle medicijnen en aandoeningen van de patiënt essentieel. Een patiëntgerichte MBO is belangrijk om uitkomsten te verbeteren

die van belang zijn voor de gezondheid en het welzijn van de patiënt. Het inventariseren van persoonlijke voorkeuren en doelen tijdens het patiëntgesprek, helpt de apotheker en huisarts om de belangrijkste problemen te prioriteren. Het draagt bij aan gezamenlijke besluitvorming, waardoor zorg op maat geleverd kan worden. Hierbij wordt een persoonlijk behandelplan opgesteld om een optimale behandeling met geneesmiddelen te bereiken voor iedere individuele patiënt.

De meest geschikte uitkomstmaat voor onderzoek naar het effect van een MBO, hangt af van het doel van de MBO. Medicatiebeoordelingen die gericht zijn op het verbeteren van de gezondheid en het welzijn van ouderen, zouden bij voorkeur kwaliteit van leven als uitkomstmaat moeten gebruiken. Medicatiebeoordelingen die zijn gericht op het verminderen van ziekenhuisopnames, zouden bij voorkeur patiënten met een verhoogd risico op zo'n ziekenhuisopname moeten includeren. Denk hierbij aan mensen die net in het ziekenhuis opgenomen zijn geweest en een grote kans hebben om daar opnieuw terecht te komen. Daarnaast zou elke studie die MBO's onderzoeken, bij voorkeur ook altijd procesuitkomsten zoals het aantal en type problemen met geneesmiddelen en de uitgevoerde interventies moeten rapporteren. Dat is nodig om te beoordelen of de MBO's wel goed zijn uitgevoerd. Goal attainment scaling en een vragenlijst met gezondheidsklachten zijn uitkomstmaten die bruikbaar kunnen zijn bij het evalueren van interventies zoals MBO. Deze uitkomstmaten kunnen verder onderzocht worden in vervolgonderzoek.

Concluderend presenteert dit proefschrift een serie onderzoeken over MBO's, die heeft laten zien dat een MBO bij oudere patiënten met polyfarmacie kan bijdragen aan het optimaliseren van de behandeling met geneesmiddelen. Daarnaast kan een MBO leiden tot een verbetering van uitkomsten die belangrijk zijn voorde gezondheid en het welzijn van oudere mensen, zoals kwaliteit van leven, gezondheidsklachten en het behalen van persoonlijke doelen. Tevens kan het aantal gebruikte geneesmiddelen licht verminderd worden en zijn er mogelijk besparingen te boeken op zorgkosten. Daarmee kan MBO bij ouderen een bijdrage leveren aan het remmen van de verwachte stijging in zorgkosten in de komende jaren.

A goal without a plan
is only a dream

DANKWOORD

Goal attained!

Toen ik vijf jaar geleden aan dit promotietraject begon, had ik drie belangrijke persoonlijke doelen. Doel 1 was om medicatiegebruik bij ouderen te optimaliseren en daardoor hun kwaliteit van leven te verbeteren door middel van een medicatiebeoordeling. Na vijf jaar kan ik zeggen, doel (grotendeels) behaald. Ik denk dat een deel van dit doel behaald is, zoals de resultaten in dit proefschrift laten zien. Daarnaast is er ook nog steeds ruimte voor verdere doorontwikkeling van de farmaceutische zorg voor ouderen in de eerste lijn, zoals uitgelegd in de General Discussion. Doel 2 was om de positie van de openbaar apotheker als zorgverlener in de eerste lijn te versterken met behulp van praktijkonderzoek. Na vijf jaar kan ik bij dit doel ook zeggen: doel (deels) behaald. Ik hoop dat dit proefschrift hieraan een mooie bijdrage levert door te laten zien dat een MBO zorg op maat kan leveren, waardoor het welzijn van de patiënt verbeterd kan worden. Ik realiseer me dat dit soort veranderingen niet altijd snel gaan, maar dat er al belangrijke stappen zijn gezet. In de komende jaren kan deze rol van de apotheker nog verder door ontwikkeld worden en daarvoor wil ik me ook zeker blijven inzetten. Doel 3 was om het beste uit mezelf halen en mezelf te ontwikkelen als onderzoeker, door een proefschrift te schrijven, vele vaardigheden te ontwikkelen en te promoveren. Dit doel scoor ik als véél meer dan doel behaald. Wat heb ik de afgelopen jaar ontzettend veel geleerd, veel vaardigheden ontwikkeld, veel inspiratie opgedaan door te praten en samen te werken met bijzondere en gedreven mensen. Bovenstaande doelen zijn alleen behaald door de vele hulp en ondersteuning van andere mensen. Doordat jullie het mogelijk gemaakt hebben dat ik mijn passie en interesse met mijn werk heb kunnen combineren, zowel op apotheekgebied, als onderzoeksgebied als privé. Iedereen die mij geholpen heeft, verdient dan ook een apart woord van dank in dit hoofdstuk.

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Marcel, tijdens mijn onderzoekstage op de universiteit hebben wij elkaar al leren kennen. Jij hebt mijn interesse voor praktijkonderzoek gewekt. Jij was destijds in 2011 de begeleider voor mijn masterscriptie, die ik al geschreven heb over medicatiebeoordelingen. Toen wist ik, hier wil ik mee verder. Via jou ben ik in aanraking gekomen met Henk-Frans en is het balletje gaan rollen. Wat ben ik blij met jou als promotor. Altijd stond je voor me klaar. Ik vond het heel fijn dat je zelf ook zo geïnteresseerd was in dit onderwerp en me altijd wist te helpen

met alles. Ik denk dat je voor een promotor misschien wel veel meer voor me hebt gedaan dan gebruikelijk is en daar ben ik je ontzettend dankbaar voor! Ik hoop dat we elkaar in de toekomst blijven tegenkomen en ons sterk kunnen maken voor het vak van de apotheker als zorgverlener. Mooi vind ik het hoe je altijd zo rustig blijft, vol met ideeën en inspiratie zit en altijd mooie verhalen te vertellen hebt. Je hebt mijn teksten altijd erg uitgebreid beoordeeld, ingekort en verbeterd. Zoals dit dankwoord wellicht ook aangeeft, was ik altijd nogal lang van stof. Ik weet dat ik je daarmee wel eens wat veel uurtjes werk heb bezorgd, maar toch nam je altijd weer de tijd om mij goed te helpen. Dat je naast je hoogleraarschap ook gewoon in de dagelijkse praktijk in de apotheek staat om ideeën op te doen en met mensen te praten, vind ik echt heel mooi. Nogmaals, ik kon mij geen betere promotor wensen. Dank voor alles!

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Henk-Frans, mijn co-promotor, en ik jouw eerste promovenda. Zonder jou had ik deze kans nooit gekregen, daarvoor ben ik je echt heel dankbaar! Via Marcel en mijn onderzoekstage op de universiteit ben ik met jou en de rest van de SIR in contact gekomen. Ik wist daarvoor helemaal niet dat er zo'n mogelijkheid bestond om praktijkonderzoek te combineren met werken als apotheker in de praktijk. Mijn interesse was meteen gewekt toen ik jou leerde kennen en je werk ging lezen. Ik wist dat ik met medicatiebeoordeling verder wilde en jij bood me de kans om samen met jou een wetenschappelijk artikel te schrijven over de STOPP/START criteria tijdens mijn masterstudie. Ik weet nog dat je in jouw dankwoord noemde dat je hoopte dat ik ook verder zou gaan met praktijkonderzoek. Die kans kwam al sneller dan verwacht. Een paar maanden nadat ik was begonnen in de apotheek, belde je me met de vraag of ik het vervolgonderzoek op jouw proefschrift over medicatiebeoordelingen wilde doen. Ik ben je heel dankbaar dat deze kans mij destijds gegund was en ik heb de afgelopen jaren heel fijn met je samen gewerkt. Dit heeft uiteindelijk tot vele nieuwe ontwikkelingen geleid, waarbij onze workshop over GAS en 'deprescribing' op het ESCP congres (tot twee

jaar toe helemaal vol!) één van de hoogtepunten is. Ik hoop dat we deze samenwerking op het gebied van onderzoek, richtlijnen en doorontwikkeling van onze cursus door kunnen zetten in de toekomst. Mooi vind ik het hoe jij je werk in de praktijk met hart voor de patiënt met al je andere taken weet te combineren. Dank voor al je hulp en onze samenwerking in de afgelopen jaren!

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LIST OF PUBLICATIONS

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- Het gebruik van medisch-farmaceutische beslisregels bij het uitvoeren van een medicatiebeoordeling. *Prisma symposium, 20 May 2014, Amersfoort, The Netherlands*
- Een vergelijking van farmacotherapie gerelateerde problemen voor en na de invoering van medisch-farmaceutische beslisregels tijdens een medicatiebeoordeling. *Prisma symposium, 19 May 2015, Amersfoort, The Netherlands*
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- Which patients will have the highest risk for drug-related problems? A comparison between frail and non-frail patients. *44th ESCP Symposium on Clinical Pharmacy, 28-30 October 2015, Lisbon, Portugal.*
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- Goal Attainment Scales als mogelijk hulpmiddel en meetinstrument bij een medicatiebeoordeling? Een pilot studie. *Prisma symposium, 24 May 2016, Amersfoort, The Netherlands*
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- Toepassing van gezondheidsgerelateerde doelen bij een medicatiebeoordeling; een interim analyse van de DREAMeR studie. *NHG Wetenschapsdag, 2 June 2017, Zeist, The Netherlands*
- Use of health-related goals during medication review; process analysis of the DREAMeR study. *46th ESCP Symposium on Clinical Pharmacy, 9-11 October 2017, Heidelberg, Germany.*
- Effecten van medicatiebeoordeling uitgaande van persoonlijke behandeldoelen van ouderen met polyfarmacie; resultaten van de DREAMeR studie. *Prisma symposium, 15 May 2018, Amersfoort, The Netherlands.*
- Effecten van medicatiebeoordeling uitgaande van individuele behandeldoelen van ouderen met polyfarmacie; de DREAMeR studie. *NHG Wetenschapsdag, 8 June 2018, Amsterdam, The Netherlands*
- Effects of a clinical medication review focused on personal goals in older patients with polypharmacy; results of the DREAMeR study - a randomised controlled trial. *47th ESCP Symposium on Clinical Pharmacy, 24-26 October 2017, Belfast, Northern Ireland.*

- Effects of a clinical medication review focused on personal goals, quality of life and complaints in older persons with polypharmacy; a randomised controlled trial (DREAMeR study). *11th PCNE Working Conference 2019, 6-9 February 2019, Egmond aan Zee, the Netherlands.*

ABOUT THE AUTHOR

Marguerita Alexandra (Sanne) Bakker-Verdoorn was born on 6 March 1989 in Papendrecht, the Netherlands. She lives in Sliedrecht together with her husband Jeroen Bakker. She studied pharmacy in the city of Utrecht between 2007 and 2013. In 2011, during her study, she started working in the Thorbecke Apotheek Sliedrecht, to support the pharmacists with projects on pharmaceutical patient care. She wrote her master thesis about medication reviews in community pharmacies. After this, her interest for pharmaceutical care for older persons was awakened.

In 2013, she obtained her Master of Science in Pharmacy *cum laude* at Utrecht University. After receiving her pharmacy degree, she started working as a pharmacist in the Thorbecke Apotheek in Sliedrecht and started the post-academic advanced community pharmacist education programme. Within this programme, she followed the training as specialist community pharmacist in conjunction with a PhD track between 2014 and 2016. Since 2014, she combined her job at the community pharmacy with a researcher position at the SIR Institute for Pharmacy Practice and Policy in Leiden. She started her PhD research with the main objective: clinical medication review in older persons with polypharmacy, at the Division of Pharmacoepidemiology and Clinical Pharmacology of the Utrecht Institute for Pharmaceutical Sciences of Utrecht University.

Since 2018, she is a member of the Special Interest Group "Elderly" of the Royal Dutch Pharmacists Association (KNMP) and she became a member of the workgroup: module "deprescribing" , which is part of the updated version of the Dutch multidisciplinary guideline "Polypharmacy in the Elderly".

After completing this PhD, she aims to combine her work as a community pharmacist with pharmacy practice research and education focused on pharmaceutical care for older persons. In 2019, she will start as a managing community pharmacist in apotheek Hoogland in Sliedrecht and will continue to combine this job with her job at the SIR Institute for Pharmacy Practice and Policy.

Eight years ago, I visited an older man at his home. All drugs lay on the table. This man was vomiting and he was confused about all the drugs he should take. I immediately consulted his physician and we made a new drug treatment plan. I contacted this man several times and he got well again.

Sanne Verdoorn (1989) frequently came in contact with older persons using unnecessary drugs, experiencing side effects or difficulties in using their medication. This motivated her to start this thesis with the main objective to improve older persons' drug use, health and wellbeing by a clinical medication review.