Optimising medication reviews in primary care

Floor Willeboordse

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Colofon

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General introduction

General introduction

The word pharmakia (φαρμακεία), of which we derived the words pharmacy, pharmacist, and pharmaceutical, means in ancient Greek both the use of medication and poisoning

Medication review may be a useful intervention in reducing inappropriate medication use, thereby reducing geriatric problems and improving quality of life. The objective of this thesis is first to investigate the effectiveness and implementation fidelity of an optimized medication review intervention in older people with geriatric problems in general practice and second to gain more insight into the types and effects of patient participation in medication reviews.

In this chapter the problem of inappropriate medication use, and the group of vulnerable older people and geriatric problems are described. The challenges and knowledge gaps within the field of medication reviews on the effectiveness, the best target group, patient participation and implementation issues are outlined. Finally, the aims and outline of each chapter of this thesis are explained.

Background

Increasing number of older people

The world population is aging, due to increased life expectancy and declined birth rate. Almost all countries are experiencing growth in the number and proportion of older persons in their populations. The number of people aged 80 years or over is increasing too; the global population aged 80 years or over is projected to grow from 125 million in 2015 to 202 million in 2030 and to 434 million in 2050.[1] In The Netherlands the prospects are that the number of older persons above 65 years will increase from 2.7 million in 2012 to 4.7 million in 2041, corresponding to an increase in proportion of the total population from 16% to 26%. In 2040, one third of all older adults above 65 years will be aged 80 years and older.[2] The rising number of older persons leads to an enormous

pressure on healthcare systems and costs because of chronic diseases and medication use.

Multimorbidity and medication use

Multimorbidity, defined as two or more chronic diseases is more common at higher age and is associated with reduced functional status, and increased use of health care and high mortality. Estimates of the prevalence of multimorbidity vary widely due to different definitions, settings and sources, and range from 13-72%.[3-5] The management of multiple chronic diseases poses many challenges, amongst others due to conflicting treatment guidelines and the use of multiple medications.[6] The use of multiple medications is often referred to as polypharmacy, the simultaneous use of several medications which is often defined as the concomitant use of four or five or more chronic medications.

The prevalence of polypharmacy is around 30% in people over 65 years and older in both Europe and the US.[7-9] Polypharmacy prevalence numbers rise significantly with age. In the Netherlands in 2015, 13% of the general population uses five or more medications, this percentage rises to 25% for people between 65 and 75, 33% for people between 70-75 years and 45% for people over 75 years.[9] Despite increasing attention for polypharmacy in older people, it is still increasing. This is partially explained by aging, but also due to the increase of medication use and the development and implementation of guidelines.[7,9] Polypharmacy in itself does not always pose a problem, a more accurate term to use when discussing the problems and challenges involving the use of multiple medications is "inappropriate polypharmacy". Polypharmacy is associated with adherence problems, an increased risk for and potentially inappropriate prescribing and medication use, including underprescribing, adverse drug reactions, unplanned hospital admissions, and mortality.[10-12]

Inappropriate prescribing and inappropriate medication use

Inappropriate medication may be related to prescriber-related factors (inappropriate prescription) and patients related factors (inappropriate medication use). Prescriber related factors include e.g. medically non-indicated medication or inappropriate dosage. Patient-related factors include e.g.

(perceived) ineffectiveness of drugs, adverse effects, lack of knowledge, user problems, and non-adherence problems. In addition, the organization of the healthcare system also contributes to inappropriate medication. This includes lack of knowledge or training on pharmacotherapy for older people among prescribers and dispensers. There may be barriers in communication and exchange of medical and medication files between different prescribers and pharmacists. In primary care, guidelines and limited consultation time often only allows to cover one or two complaints instead of the overall health and medication status and there is not always agreement on the primary responsible physician for the overview on the medication of the older person when multiple prescribers are involved.

International data suggests that one in five medication prescriptions for community-dwelling older adults is inappropriate.[13] Inappropriate medications for older people are defined by the American Beers Criteria Expert Panel as "medications or medication classes that should generally be avoided in persons 65 years or older because they are either ineffective or they pose unnecessarily high risk for older persons and a safer alternative is available".[14] Inappropriate prescribing is a major public health problem and a common cause of adverse drug events, drug-drug and drug-disease interactions in older people resulting in morbidity, high health care costs and mortality.[13,15] Inappropriate prescribing is associated with the female sex, advanced age and the number of medications prescribed.[16] A broadly studied topic are medication-related hospital admissions. In the Netherlands, the HARM study in 2008 showed that about 6% of the unplanned hospital admissions were medication related and almost half was potentially preventable. A recent report on medication safety in The Netherlands showed that the absolute number of medication related potentially preventable hospital admission is still increasing.[17] Determinants of preventable hospital admissions were impaired cognition, 4 or more comorbidities, dependent living situation, impaired renal function, non-adherence to medication and polypharmacy.[18]

One of the reasons for inappropriate medication use in older people is that pharmacokinetics and pharmacodynamics of many medications are altered with age. Relevant pharmacokinetic age-related changes are a reduction in first-pass metabolism, increased bioavailability, changes in the drug distribution of the body due to changes in body composition, protein

binding, and drug clearance of the liver and kidney. Some important age-related changes in pharmacodynamic responses are sedation and extrapyramidal symptoms for antipsychotics, bronchodilation for beta-agonists, antihypertensive effects for beta-blocking agents and verapamil, anticoagulant effects for vitamin K antagonists and a peak diuretic response for furosemide use. Variability in responses to medications are larger with advanced age, e.g. with antipsychotics.[19]

Inappropriate prescribing can be divided in underprescribing, misprescribing and overprescribing.

Explicit and implicit criteria are used to assess the (in)appropriateness of medication. Explicit criteria are medication list based tools such as the Beers criteria or START (Screening Tool to Alert doctors to Right Treatment) and STOPP (Screening Tool of Older Person's Prescriptions) criteria, based on expert opinions and evidence form the literature.[20,21] Explicit criteria are lists to screen for inappropriate prescribing, medications to be avoided by older people and some lists also assess underprescribing, potentially prescribing omissions. Explicit methods require little clinical insight and can sometimes be applied to existing datasets. Implicit methods involve a clinician's judgment of appropriateness for the individual patient based on the medical history and patients' information.

In addition, to inappropriate prescribing, a variety of other problems with the use of inappropriate medication may interfere with the effectiveness and safety of effective pharmacotherapy. Examples of these problems are difficulties with adherence or compliance with the medication as prescribed by the patient, patient knowledge, monitoring or administration problems.

Drug related problems

Interventions to reduce inappropriate prescribing and medication use often aim to reduce potential drug related problems (DRPs). DRPs differ from inappropriate prescribing in their possibility to potentially affect health outcomes. According to the Pharmaceutical Care Network Europe (PCNE) a Drug Related Problem is an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes.[22] Inappropriate medication use by the patient such as adherence problems or user problems,

but also dosing or monitoring problems can all be drug related problems. DRPs are also called Medication Related Problems or Pharmaceutical Care Issues
There are different classification systems for DRPs, there is no uniformity on this subject. Classification can be relevant to document the DRPs in daily clinical practice, but also for research. Examples of these systems are the PCNE classification system, the system described by Hepler and Strand and DOCUMENT.[23-25] There are differences between these systems in terms of validity, hierarchical problem classification, number of categories and distinguishing between problems and causes. However, all systems use more or less the following main categories: drug selection problem, undertreatment, adverse reaction, dosage problems, adherence problems. The systems differ with respect to the inclusion of DRPs as monitoring problems, practical problems, education problems and treatment costs.

Inappropriate medication and geriatric problems

Bernard Isaacs was the first to use the term geriatric giants. He suggested that the clinical presentation of problems by older patients was dominated by the giants of geriatrics: immobility, instability, incontinence and intellectual impairment. They have in common multiple causation, chronic course, deprivation of independence and no simple cure.[26] The atypical (non-specific or silent) disease presentation is common in the older patient and a marker for frailty and predictive of poor hospital outcomes.[27] The term giant refers to the major burden of these functional impairments of daily living but also to the high prevalence among older people.

Inappropriate medication may increase the risk of the occurrence and persistence of geriatric giants. The symptoms of geriatric giants are among the most common adverse drug reactions. The relation between inappropriate medication and geriatric giants is for some problems better studied than for others and the causal pathway, the extent and order of the precise associations are complex. Most studies focused on the association between polypharmacy and geriatric giants.

For immobility it has been suggested that a higher number of medications used mediates the excess adverse drug events risk observed with

increasing mobility limitation.[28] The use of benzodiazepines and anticholinergics is associated with functional status decline, of which mobility is an important component. Its relation with suboptimal prescribing in general gave mixed results.[29] Inappropriate pain management and muscle pain or fatigue due to e.g. the use of statins may also limit mobility.

For instability, falls and medication use are studied most frequently. A large meta-analysis with mainly observational studies concluded that the use of sedatives, hypnotics, anti-depressants and benzodiazepines demonstrated a significant association with falls in older people.[30] These types of drugs are often considered inappropriate for elderly.[31,32] Studies on the withdrawal of fall-risk increasing drugs, including cardiovascular and psychotropic drugs, seem to be effective interventions for lowering the incidence of falls.[33] In the STOPP criteria, there is also a separate section of medications related to elevated fall risk[21] and there are lists with fall-risk increasing drugs for older people.[33] The relation between dizziness and inappropriate medication is somewhat less clear, however polypharmacy was found to be predictive of and associated with dizziness.[34,35]

Urinary incontinence is also associated with polypharmacy. In a longitudinal study polypharmacy was associated with an increased risk of lower urinary tract symptoms (LUTS) in women above 70 years.[36] Several medications, such as alpha-blockers and estrogens, are associated with urinary incontinence and have an impact on the lower urinary tract.[37] Moreover, when treating LUTS in older patients, with polypharmacy and comorbidities, the increased potential for drug-drug interactions should be considered.[38]

Several potentially inappropriate medications may impair cognition. In a prospective study sedative hypnotic agents, especially long-acting benzodiazepines, frequently caused cognitive impairment in an older population.[39] The Beers and STOPP criteria mention for amongst others certain anticholinergics, benzodiazepines, opiates, and antipsychotics to avoid these medications in demented or cognitively impaired older people.[20,21] Older people are particularly vulnerable to the more subtle cognitive effects (e.g., attention and memory deficits) of drugs with anticholinergic properties and more sensitive to adverse effects of antipsychotics.[40,41] The relative odd for adverse drug reactions associated with cognitive impairment increases with the number of prescribed drugs, exceeding to 9.0 for patients taking four or more

prescribed drugs.[39] In addition, impaired cognition is mentioned as one of the risk factors for medication related hospital admissions in a large prospective Dutch study.[18]

Many older people have two or more of these geriatric giants at the same time. In the nineties, Tinetti et al. already looked into the shared risk factors for incontinence, falls and functional dependence in an attempt to unify the approach to geriatric giants. Polypharmacy was associated with each of the geriatric syndromes and functional decline.[42] All geriatric giants are multifactorial, however medication use is probably one of the most modifiable or most easiest modifiable risk factor.[43] In this thesis, we refer to the geriatric giants as geriatric problems. In recent years other 'giants' are added to the original four I's of Isaacs, such as impaired vision and hearing loss, these are not discussed in this thesis as they have less relations with inappropriate medication.

Medication reviews

Definition and objectives

Medication reviews are one of the interventions that aim to reduce inappropriate prescribing and medication use. A medication review is defined by the UK Task Force on Medicines Partnership as a "structured, critical examination of the patient's medication with the objective of reaching an agreement with the patient about treatment, optimising the impact of medications, minimizing the number of drug related problems (DRPs) and reducing waste".[44] This definition is also used for this thesis. In 2008 three types of medication reviews are described by the National Prescribing Centre and the NHS in the UK.[45]:

- Type I; The prescription review addresses technical issues relating to the prescription or medication, the patient does not need to be present, nor access to patient's full notes.
- Type II; The concordance and compliance review addresses issues relating to the patient's medication taking behaviour, patients are usually present.

- Type III. A Clinical Medication Review (CMR) addresses issues relating to the patient's use of medication in the context of their clinical condition and requires patients to be present.[45]

The different medication review services currently being implemented in different countries have mostly similar objectives, but with different intensity, definitions, and tools. A lot of countries have their own clinical guideline and name. Examples of these services are medication therapy management (MTM) in the USA[46], medicines use review (MUR) or clinical medication reviews in the UK [45,47], home medication review (HMR) in Australia [48], Comprehensive Medication Reviews in Finland [49], Lund Integrated Medicines Management (LIMM) model in Sweden [50], and medication reviews (MBO) in The Netherlands [51]. There are differences between countries or regions in intensity and tools used, which mainly depend on the organization of the health care system; however the purpose of medication reviews are often similar. In most countries, medication reviews are conducted and/or initiated by pharmacists. A survey among European countries revealed that the majority of the European countries only perform type I and II reviews.[52]

Medication reviews in the Netherlands

In 2012, a multidisciplinary guideline was published in the Netherlands for the 'treatment' of polypharmacy in older people.[51] Clinical Medication Reviews using the stepwise approach of the Systematic Tool to Reduce Inappropriate Prescribing (STRIP) are outlined in this guideline. This is a combination of using the implicit START and STOPP criteria (Dutch translation) and explicit criteria following a stepwise approach:

Step 0: Preparation and patient selection
Step 1: Pharmacotherapeutic history
Step 2: Pharmacotherapeutic analysis
Step 3: Consultation between GP and pharmacist and drafting of the pharmacotherapeutic treatment plan
Step 4: Feedback to the patient and determine the pharmacotherapeutic treatment plan

The target group for this guideline is defined as older people above 65 years using five or more chronic prescribed medications with one or more of the following risk factors:

- Diminished renal function
- Impaired cognition
- Elevated fall risk
- Signals of compliance or adherence problems
- Not living independently

In addition to this guideline, in July 2015 the Health Care Inspectorate of The Netherlands (IGZ) did come up with new standards for medication reviews and directives for implementation. These included:

1. Agreements on cooperation between prescribers and pharmacists should be documented.
2. Prescribers and pharmacists should conduct medication reviews that follow the inclusion criteria as described in the multidisciplinary guide 'Polypharmacy for elderly. At least all patients of 75 years and older, using 7 or more medications and have renal failure [(eGFR < 50 ml/ min/ 1,73 m^2] should receive a medication review.
3. Healthcare providers should conduct medication reviews in a systematically and measurable manner.
4. Healthcare providers should conduct a minimum number of medication reviews based on a pre-defined growth-model for 2015-2017. In 2017, a pharmacist should conduct medication reviews for at least 100 patients and a GP for at least 25 patients.

In the Netherlands, GPs and pharmacists are the most designated healthcare providers to conduct medication reviews for community-dwelling older people for several reasons. First, non-institutionalised Dutch inhabitants are obligatory listed at a general practice and most patients are registered with one community pharmacy. Second, in general the GP has the most complete overview of the medications used and morbidities compared to other healthcare providers. Third, repeat prescriptions from most prescribers are arranged by the patients' own GP and pharmacist. Finally, most GPs and pharmacists are participating and organized within regularly pharmacotherapeutic consultation groups.

Challenges and knowledge gaps

Effectiveness of medication reviews

The effectiveness of medication reviews and other pharmacotherapeutic interventions to improve inappropriate medication is a widely studied topic. This is reflected by the large number of Cochrane reviews, systematic literature reviews and meta-analyses published in the last decade.[53-67] Different settings (primary care, hospitalised or institutionalised patients), for specific or broader subgroups such as community-dwelling elderly, cardiovascular patients, or specific types of medication review were studied. Clinical outcomes measures included quality of life, hospital admission or mortality or population specific morbidity outcomes. Other more indirect outcome measures are prescribing appropriateness measures, DRPs, number of drugs used, adherence, patient knowledge, patient satisfaction, and costs.

The evidence for medication reviews to reduce inappropriate medication use is moderate. There are many different outcome measures for inappropriate medication, such as the Medication Appropriateness Index (MAI), number of drug-related problems, STOPP/START criteria, Beers criteria and many more. Moreover, there is also a large variety in type of interventions, clinical medication reviews or more general interventions to reduce inappropriate medication use or prescribing. This made pooling of results often very difficult. Several recent and less recent systematic literature reviews report that a range of interventions demonstrated improvements in appropriate polypharmacy or reducing potentially inappropriate prescribing, and drug related problems. However, there was a wide range of effect sizes reported and the quality of evidence was rated as low (GRADE).[53,54,57,58]

Evidence on the effectiveness in terms of health outcomes such as improved quality of life, reduced hospital admission rates or mortality is still minimal, inconclusive or lacking. Here again, pooling was not possible due to the large heterogeneity in type of interventions, populations and outcome measures.[48,54,60,64] The evidence on costs of healthcare use and medications and cost-effectiveness of medication reviews is also mixed and of low quality.[68] It seems that there is a lack of robust evidence demonstrating clinical effectiveness and cost-effectiveness of medication reviews compared with

usual care. This thesis focuses on the effectiveness and cost-effectiveness of medication reviews on quality of life and on geriatric problems.

Target group for medication reviews

There is no consensus on the best target group for medication reviews. Most guidelines and research focused on polypharmacy patients, with or without additional risk factors. The health care setting, primary care, hospital care, hospital discharged or institutionalized care, also vary. The question is which patients benefit the most, or possibly which target group is most feasible to conduct a review for, or even which target group for medication reviews is most cost-efficient for society. A Dutch case study advocates to pay attention to patients that fall outside the current selection criteria for medication review, but also may have a valid indication for a medication review, such as patients without polypharmacy but with undertreatment or geriatric problems such as falling and dizziness. The authors also state that the current selection criteria for medication reviews in The Netherlands are based on limited available evidence and expert opinions.[69]

In this thesis, a relatively new target group is studied. We focus on older patients presenting with a new geriatric problem to their general practitioner, instead of e.g. the number of medications used.

Patient participation

As described in several guidelines and within the definition of a clinical medication review, patient participation is an essential element of a clinical medication review.

Patient participation is a difficult concept with no clear definition. The model and definition of Thompson[70] is used in this thesis. Participation is seen as being co-determined by patients and professionals and occurring only through the reciprocal relationships of dialogue and shared decision making. Thompson et al. 2007 defined levels of patient involvement from the patient perspective. According to Thompson the main distinguishing feature between patient involvement and patient participation is the degree of decision making.[70] Not everyone wants to be involved on the same level, some patients prefer the physician to make health care decisions (professional-determined involvement) and others want to take a fully active role (patient-determined

involvement) or somewhere in between. Moreover, the same patient may wish to be involved at different levels in different circumstances.

For a medication review, the identification of certain DRPs, such as adherence and user or medication knowledge problems can only be identified by the patient. In addition, the actual medication use as indicated by the patient can differ from what is known in the pharmacy and/or with the physician. These discrepancies are known to be larger in outpatients taking a higher mean number of drugs and in people in whom multiple prescribing physicians next to the GP are involved.[71] The input from the patient about their preferences and medication use, including information of any use of over the counter medication is therefore essential. Involving patients in medication reviews increases the number of identified DRPs, and it seems that these DRPs are assigned a higher priority and have a better implementation rate.[72]

However, patient participation is very time-consuming. The care is also complex because the patient involvement concerns multimorbidity patients and several different medication guidelines for specific conditions for each patient. For physicians it is very difficult to deal with sometimes seemingly contradictory evidence of the harms and benefits of following disease specific guidelines, and even more to explain this to patients. A qualitative study cited concerns among primary caregivers about patients' and families' inaccurate understanding of harms and benefits of their medication use.[73]. This means for the patient that there is no easy choice between for example two treatment options, but a scala of factors and interactions has to be taken into account.

In this thesis we aimed to provide more insight into the types and effects of patient participation in medication reviews. In addition, patient participation in medication reviews by means of completing a questionnaire has been investigated.

Implementation issues

In The Netherlands, the Dutch guideline for polypharmacy for older people was published in 2012, however since then, its implementation in primary care has had some difficulties. [74] An evaluation report by Dutch Organization for Health Research and Development (ZonMw)[75] concluded that important barriers for performing medication reviews in daily practice were patient selection, the working procedure of the medication analysis, assuring continuity of the

process, medication initiated by medical specialists and the considerable time-investment. The limited options for recording in the current electronic patient records of both GPs and pharmacists hinders the patient selection, assuring the continuity of the process and recording and exchange of data and agreements between GPs and pharmacists. Responsibilities were not always clear to all key players.

Also in other countries, the organization and implementation of CMRs are difficult and time consuming.[76] Due to the limited access to medical information for pharmacists, performing full clinical medication reviews including the patient's information is in many countries still limited.[52]

In this thesis we investigated a medication review method that we hypothesized to be more feasible and to overcome some of these implementation issues. This method may be less time consuming, by streamlining the patient-selection, involving practice nurses and make use of external expert teams.

Pilot studies

In preparation of the studies described in this thesis, two pilot care innovation projects on medication reviews in polypharmacy patients in 2009 and 2011 were performed in respectively 14 and 4 general practices of the Academic Network for General Practitioners of the VU University Medical Center in Amsterdam. The first pilot revealed that the time-investment for GPs, pharmacotherapeutic knowledge and organization of the process were barriers for implementation in routine care. In the second pilot project, a patient questionnaire on DRPs was used to reduce the number of contacts with the patient. Streamlining of the medication review process, the use of a patient questionnaire and the use of a dedicated team was deemed suitable for routine care.

Research questions and outline of this thesis

Based on the identified gaps in the literature and experiences from daily practice we formulated the following questions for this thesis:

1. What is known in the literature about ways of patients participation in the medication review process and its effects on the outcomes of a medication review?
2. Can patient participation in medication reviews be achieved via a questionnaire instead of an interview?
3. What is the (cost)-effectiveness of an optimized clinical medication review on quality of life and geriatric problems in comparison with usual care, in older patients with geriatric problems presented in general practice?
4. What is the implementation fidelity of optimized clinical medication reviews in the setting of general practice?

Patient participation was addressed by a systematic literature study and an empirical study comparing personal interviews with a questionnaire. To study the effectiveness and cost-effectiveness of clinical medication reviews we conducted a cluster randomised controlled trial with 518 patients from 22 general practices (the Opti-Med study). On overview of the methods used per research question is presented in table 1.1.

Table 1.1 Overview of the methods used per research question

Research questions	Study and methods	Chapter
1. Patient participation in the medication review process known in literature	Systematic literature review	2
2. Patient participation via a questionnaire instead of an interview	Empirical study comparing personal interviews with a questionnaire	3
3. (Cost)-effectiveness of optimized clinical medication reviews	Cluster randomised controlled trial (Opti-Med)	4;5;6
4. Implementation fidelity of optimized clinical medication reviews	Process evaluation alongside cluster randomized controlled trial using quantitative and qualitative data	7

Chapter 2 is a systematic literature review on patient participation in medication reviews. As preparation for the RCT a questionnaire was developed and evaluated. **Chapter 3** presents the results of an agreement study between the questionnaire and an interview on patient information on medication use and drug-related problems in older patients. **Chapter 4** describes the protocol of the Opti-Med study. **Chapter 5** presents the results on the effectiveness of the Opti-Med intervention on quality of life and geriatric problems. **Chapter 6** presents the results on the cost-effectiveness of the Opti-Med intervention. **Chapter 7** shows the results of the process-evaluation of Opti-Med, describing the implementation fidelity of such an intervention.
Chapter 8 discusses the main findings of this thesis and recommendations for future research and daily primary care practice

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2

Patient participation in medication reviews is desirable but not evidence-based: a systematic literature review

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Abstract

Aim

The aim of this systematic literature review is to investigate which types of patient participation in medication reviews have been practiced and what is known about the effects of patient participation within the medication review process.

Methods

A systematic literature review was performed in multiple databases using an extensive selection and quality assessment procedure.

Results

In total, 37 articles were included, most were assessed with a weak or moderate quality. In all studies patient participation in medication reviews was limited to the level of information giving by the patient to the professional, mainly on actual drug use. Nine studies showed limited results of effects of patient participation on the identification of drug related problems.

Conclusions

The effects of patient participation are not frequently studied and poorly described in current literature. Nevertheless, involving patients can improve patients' knowledge, satisfaction and the identification of drug related problems. Patient involvement is now limited to information sharing. The profit of higher levels of patient communication and shared decision making is until now, not supported by evidence of its effectiveness.

Introduction

Patient participation is seen as the key to modern health care and has been widely implemented in medical decision-making and the management of chronic diseases.[1] The World Health Organization (WHO) programme Patients for Patient Safety also emphasizes the central role patients should play in efforts to improve the quality and safety of health care.[2] Positive effects of a structured two-way communication between patients and healthcare professionals can be increased patient knowledge, adherence, and satisfaction.[3] With respect to pharmaceutical care, patient participation is thought to improve concordance between the patient and the healthcare provider on the pharmacotherapy.[3] It is also suggested that involvement of patients in pharmaceutical interventions, such as medication reviews, is important for motivation to change and long-term effectiveness of pharmacotherapy.[4]

The UK National Prescribing Centre defines a medication review as '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, and minimising the number of drug related problems'.[5] Drug related problems (DRPs) frequently occur in elderly and can be drug interactions, inefficacy of treatment, adverse drug reactions, prescription errors but also noncompliance with treatment and user problems. The medication review definition includes patient participation in the medication review process and agreement between patient, physician and about the treatment.

The definition of patient participation is not self-evident. Patient participation, patient collaboration, patient involvement, partnership, patient empowerment or patient-centered care, are used interchangeably.[1] Street and Millay defined patient participation in medical consultations as "the extent to which patients influence the content and the structure of the interaction as well as the health care provider's beliefs and behaviour by, for example, asking questions, descriptions of health experiences, expressing concerns, giving opinions, making suggestions and stating preferences".[6]

Thompson et al. 2007 defined levels of patient involvement from the patient perspective.[7] Parallel to a literature-based ranking of professional-determined levels of involvement, Thompson, on the basis of a comprehensive qualitative data, defined several levels of patient-desired involvement (table 2.1). This follows the three decision making models, paternalistic, informed and professional-as-agent of Charles et al.[8] Participation is seen as being co-determined by patients and professionals and occurring only through the reciprocal relationships of dialogue and shared decision making. In a dialogue the patient gives information and there is consultation by the professional, in shared decision making the professional acts as agent. The model and definition of Thompson is used in this research.[7]

Furthermore, giving information during a dialogue between patient and caregiver has a different purpose than shared or informed decision making. In the context of medication reviews, patient input is needed as preparation for the medication review, to incorporate the patient's perspective. The purpose of information giving by the caregiver is mainly educational. On the other hand there is the decision making process, where the purpose is to make a joint decision.

Active patient participation in medication reviews is increasingly recognized as a prerequisite for a successful medication review and consequently in optimal pharmacotherapy and acknowledged in international and recent Dutch guidelines.[5,9-11]

In the field of treatment counselling, especially for oncology and e.g., there is indeed evidence that the involvement of patients and shared-decision making led to more satisfied patients, better adherence to therapy and better health outcomes.[12-14] However, little is known about the effects of patient participation in medication reviews on patient outcomes. Before studying possible effects of patient participation, the different types of patient participation researched must be identified.

The aim of this systematic literature review is to investigate which types of patient participation in medication reviews have been practiced and what is known about the effects of patient participation within the medication review process. The following research questions were formulated:

1. Which types of patient participation in medication reviews have been researched?

2. What are the effects of patient participation in medication reviews on drug related problems (DRPs) and other patient outcomes?

Table 2.1 Levels of patient involvement in healthcare consultations

Patient-desired level	Patient-determined	Co-determined *(participation)*	Professional-determined
4	Autonomous decision-making		Informed decision making
3		Shared decision making	Professional-as-agent
2	Information-giving	Dialogue	Consultation
1	Information-seeking/receptive		Information-giving
0	Non-involved		Exclusion

Adapted from Thompson et al.[7]

Methods

A systematic literature review was conducted following the PRISMA statement.[15] A literature search was performed in the databases PubMed, EMBASE, CINAHL, and Cochrane Library in July 2013. A search strategy was developed by the first author (FW) and an experienced information specialist (Supplementary Material I). The search strategy combined different synonyms and related terms of patient participation with synonyms of medication reviews. Inclusion- and exclusion criteria for articles are displayed in box 2.1. In addition, the references from all included articles were also examined for relevant articles.

Three types of medication reviews can be distinguished based on the data used: 1) clinical medication reviews are based on medication records, medical records and patient data, 2) concordance and compliance medication reviews are based on medication records and patient data, and 3) prescription reviews are based on medication records only, so without patient data.[16] In the present literature review only clinical medication reviews or concordance and compliance reviews[6], have been included. According to Thompson's model of

patient participation (table 2.1), patient participation starts at the level of information giving to the healthcare professional by the patient or his carer.[7]

Box 2.1 In- and exclusion criteria

Inclusion criteria

- Original research AND;
- Medication review with any type of patient participation AND;
- Adult or elderly population.

Exclusion criteria

- No original research, editorials, letter to the editors, comments, conference abstracts;
- Single case-studies;
- Study design articles, without any results;
- Medication review without any type of patient participation, care in which the patient does not give any information and is not involved at all;
- Insufficient description of the patient participation, unable to define the level by Thompson et al.[7]
- Child or adolescent population;
- Studies in the palliative care setting.
- Articles in other languages than English or Dutch

Selection procedure

The selection procedure of relevant articles included three steps, 1. Screening of title and abstract, 2. Full-text based selection, and 3. Quality assessment (figure 2.1). References of selected articles were also screened for relevant articles and extra articles could be added on the basis of expert opinion. Two authors (FW, PJME) screened all 1,257 titles and abstracts independently. In case of doubt, an article was included for full-text review. The first 50 titles and abstracts were screened and discussed to reach agreement on interpretations, definitions and in- and exclusion criteria. After screening all titles and abstracts, consensus was reached in a consensus meeting for all disagreements. In total, 133 articles were selected for full-text review. The measure of agreement between the reviewers, Cohen's Kappa (κ) was calculated.

The first author screened all 133 full-text articles on in- and exclusion criteria according to box 2.1. In case of any doubt, the full-text article was

discussed with at least one other author. In total, 37 articles were selected for quality assessment and included in this literature review, of which one was obtained from the references of the selected articles, and one article was added on the basis of expert opinion.

Quality assessment

Quality assessment was carried out independently by three authors (FW, PJME, JGH) for all 37 articles. One reviewer (FW) assessed all relevant full-text articles and two other reviewers (PJME, JGH) assessed both half of the articles, independently of each other.

The complexity and heterogeneity of the articles for the first research question required a specific qualitative assessment based on the description of information about patient participation and whether an evaluation was carried out. Mainly, the completeness of reporting was assessed, assuming a correlation with the quality of reporting and the quality of the study. For the second research question, again articles were very heterogenic, and studies were mainly of an observational or qualitative nature. Existing tools were used, with minimally adaptions, to assess the quality of the article. Three checklists are used, dependent on the literature review objective and whether the results were quantitative or qualitative (box 2.2).

Strong, moderate or weak final ratings were given based on predefined criteria. Quality assessment tools were piloted with ten articles by the reviewers and differences in assessment were discussed. Disagreements in final ratings were discussed with a fourth reviewer (FGS).

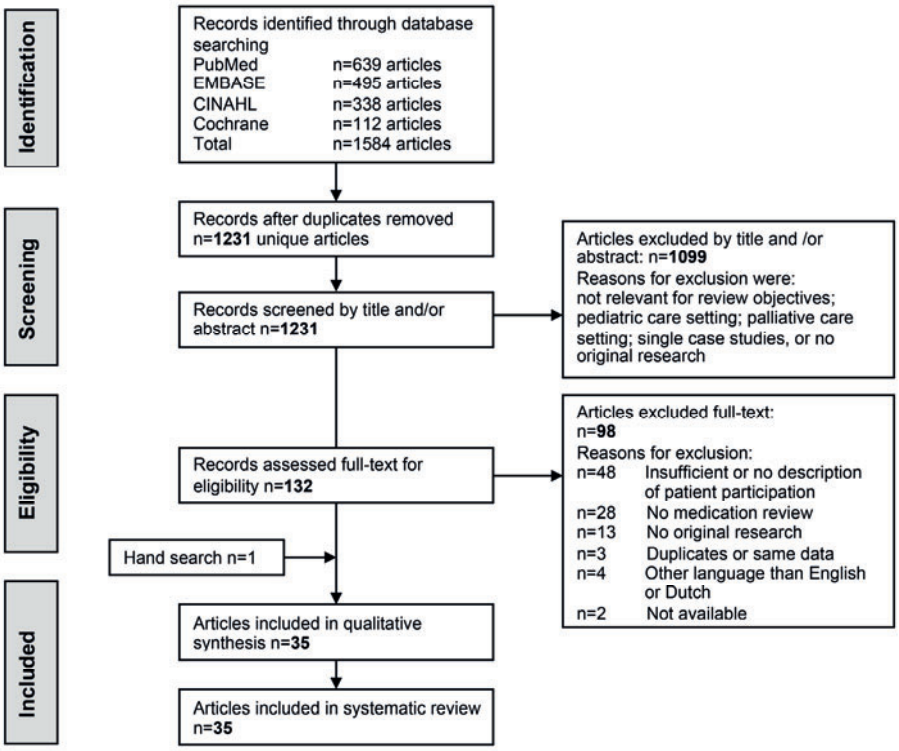

Figure 2.1 Flow diagram of selection process

Box 2.2 Checklist for quality assessment

1. Checklist for description and evaluation of patient participation.
   Qualitative assessment on adequacy of the description of patient participation and evaluation of patient participation. The following questions were included in the checklist, which consisted of two sub ratings; description and evaluation of patient participation.

1. Description of patient participation	
1.1	Is there sufficient info to derive a level of participation?
1.2	Is there info on type of communication?
1.3	Is there info on which healthcare professional is involved?
2. Evaluation of patient participation	
2.1	The study describes how often patient participation is carried out according to protocol
2.2	The study evaluated the healthcare professional-patient communication
2.3	The study evaluated the patient input in the medication review
2.4	Info on time consumption of the patient participation
2.5	Info on the costs of patient participation
2.6	Info on other evaluation topics of patient participation

Explanation and exact interpretation of all questions were discussed among the reviewers. Weak, moderate and strong ratings were assigned to the articles based on the sub ratings. In total, all 30 quantitative articles were assessed with this checklist.

2. Checklist for quantitative studies: Methodological quality of studies on the effects of patient participation.
   This checklist is based on the Effective Public Health Practice Project (EPHPP) Quality Assessment Tool.[17] This tool has been judged suitable to be used in systematic literature reviews of effectiveness, had fair inter-rater agreement in individual domain scoring and excellent agreement in final grade assigned to among raters and has been reported to have content and construct validity.[18] The questions on blinding were not applicable for this topic. Nine articles were assessed with this checklist.

3. Checklist for qualitative studies: Methodological quality of studies on the evaluation of patient participation. This checklist is based on the detailed questions of the CASP qualitative checklist. The CASP checklists have been evaluated, pilot tested in workshops, including feedback and review of materials, using successively broader audiences. Weak, moderate and strong ratings were assigned based on the number of 'yes answers'.[19] Seven qualitative articles were assessed with this checklist.

Data extraction and analyses

Data extraction was carried out for all included articles by the first author (FW) in evidence tables. For every article, general characteristics and the type of medication review were extracted. Secondly, the description of patient participation was extracted for four components, when available, as follows:

1. Level of participation according to Thompson et al.[7](see table 2.1);
2. Type of information given by the patient for the medication review;
3. Kind of consultation by the professional to the patient on the medication;
4. Evaluation of the patient participation.

Qualitative studies are described separately in overview tables with the description and evaluation of the patient participation. When present, data on the effects of patient participation was collected, specifically on DRPs and possible other outcomes. All data were analysed in a descriptive manner for the results section and summarized in overview tables.

Results

General characteristics of publications

The authors who reviewed all titles and abstracts, reached strong agreement (Cohen's κ=0.73). General characteristics of all 37 included publications are presented in table 2.2.[20-56] All studies described medication reviews, but none of the studies was an RCT on the effectiveness of patient participation. In total, 30 studies were of a quantitative nature with different study designs, six publications had qualitative designs. Half of the studies were carried out in Europe, mainly the UK, The Netherlands and Norway, the other half was mainly from the USA and Australia. Almost all studies were carried out in elderly with a variety of risk factors for medication problems, such as polypharmacy, multi-morbidity, recent hospital admission or specific diseases. More than a third of the quantitative studies were small scale or pilot studies with less than 100 participants. The majority of the medication reviews was carried out by pharmacists or pharmacists in cooperation with general practitioners (GPs).

Of the 30 articles assessed with the checklist for quantitative studies on description and evaluation of patient participations, 20 articles had a final

moderate rating, five a strong rating and five a weak rating. All but one of the qualitative studies were assessed with a strong rating. Of the nine articles that were assessed with the quality assessment for effects of patient participation, five articles had a moderate and four a weak rating.

Table 2.2 General characteristics of the included publications

Reference; country	Study design	Patient characteristics	Setting	MR carried out by
Leendertse 2013	Open controlled	674 elderly, using ≥5 drugs, at risk for hospital admission	Home dwelling in primary care	Pharmacists and GPs
Kilcup 2013	Retrospective	494 elderly, at risk for hospital readmission	Home dwelling recently discharged from hospital	Pharmacists
Olsson 2012	Randomised controlled	150 elderly, using ≥5 drugs	Home dwelling recently discharged from hospital	GPs
Akazawa 2012	Prospective intervention	508 elderly	Home dwelling	Pharmacists
Kwint 2012	Cross-sectional	155 elderly, using ≥5 drugs	Home-dwelling visiting community pharmacists	Pharmacists and GPs
Elliot 2012	Prospective randomised	80 elderly, using ≥2 drugs	Home-dwelling referred to Aged Care Assessment Teams	Pharmacists or GPs
Willoch 2012	Prospective randomised	77 elderly rehabilitation patients, using ≥3 drugs	Patients admitted to a rehabilitation ward	Clinical pharmacist
Stewart 2012	Observational case series	219 adults	Ambulatory care patients	Pharmacists
Swain 2012	Prospective case series	56 elderly neurological patients	Ambulatory neurologic patients	Pharmacists
Sheridan 2012	Qualitative	27 patients with ≥1 risk factors for drug problems	Independently-living patients	Pharmacists

- Table 2.2 continues -

-Table 2.2 continued -

Reference; country	Study design	Patient characteristics	Setting	MR carried out by
Lam 2011	Cross-sectional	43 adults and elderly, with ≥1 chronic disease, using ≥4 drugs	Patients in an on-going RCT in pharmacies	Pharmacists
Niquille 2010	Cross-sectional	85 elderly cardiovascular patients, using ≥1 cardiovascular drugs	Home-dwelling outpatients visiting community pharmacies	Pharmacists
Granas 2010	Retrospective evaluation	73 elderly, using ≥2 diabetic type II drugs	Diabetic type II patients visiting the pharmacy	Pharmacist
Hernandez 2010	Observational	35 middle-aged and elderly heart transplantation patients	Hospitalised heart transplantation patients	Pharmacist
Hugtenburg 2009	Controlled intervention	715 elderly, using ≥5 drugs	Patients discharged from hospital	Pharmacists
Karapinar-Carkit 2009	Prospective observational	262 pulmonology patients, using ≥1 drugs	Patients discharged from the pulmonology ward	Pharmacists
Pindolia 2009	Retrospective analysis	520 elderly, ≥2 chronic diseases, using ≥2 drugs	Primary care	Pharmacists
Latif 2008	Qualitative	Purposeful sample of 54 adult and elderly	Patients counseled at community pharmacies	Pharmacists
Moultry 2008	Cross-sectional	30 elderly, 60% is using ≥7 drugs	Patients identified for medication management services	Pharmacists
Bissell 2008	Qualitative	49 coronary heart disease patients	General practice patients recruited within an RCT	Pharmacists
MEDMAN 2007	Randomised controlled	1493 coronary heart disease patients	General practice patients	Pharmacists
Salter 2007	Qualitative	29 elderly	Hospitalized patients recruited within an RCT	Pharmacists

- Table 2.2 continues -

-Table 2.2 continued -

Reference; country	Study design	Patient characteristics	Setting	MR carried out by
Nguyen 2007	Prospective uncontrolled	24 elderly, ≥1 risk factor for medication misadventure	Patients discharged from hospital	Pharmacists
Viktil 2006	Prospective multicenter	96 hospitalized elderly, using mean 4.7 drugs	Hospitalized patients; internal medicine and rheumatology	Pharmacists
Sorensen 2004	Randomised controlled	400 patients with ≥1 risk factor for inappropriate medication use	Community dwelling patients (rural and urban)	Pharmacists and GPs
Griffiths 2004	Pre-post test + cross-sectional	24 elderly; diminished knowledge/ management of medication	Patients receiving regular community nursing care	Community nurses
Petty 2003	Qualitative	18 elderly, using mean 5.5 drugs	Ambulatory patients attending a medicine review clinic	Pharmacists
Naunton 2003	Randomised controlled	121 elderly, using ≥ 4 drugs	Discharged from hospital	Pharmacists
Gilbert 2002	Implementation trial	1000 patients at risk for DRPs	Community dwelling patients identified by GPs	Pharmacists and GPs
Zermansky 2001	Randomised controlled	1188 elderly using ≥1 drugs	Community dwelling patients visiting GPs	Pharmacists
Jameson 2001	Randomised controlled	168 patients, using ≥5 drugs	Ambulatory care patients	Pharmacists and GPs
Krska 2001	Randomised controlled	332 elderly, with≥2 chronic diseases, using ≥4 drugs	Ambulatory care patients	Pharmacists
Sellors 2001	Randomised controlled	132 elderly , using ≥4 drugs	Patients visiting GPs	Pharmacists
Grymonpre 2001	Prospective randomised controlled	135 elderly, using ≥2 drugs	Community dwelling ambulatory care patients	Pharmacists

- Table 2.2 continues -

-Table 2.2 continued -

Reference; country	Study design	Patient characteristics	Setting	MR carried out by
Chen 2000	Qualitative	25 patients referred for medication review	Patients from community pharmacies and GPs	Pharmacists
Nathan 2000	Qualitative	20 elderly or middle-aged, using long-term medication	Patients who had 3-9 months ago a medication review	Pharmacists
Schneider 1994	Prospective un-controlled and qualitative	39 elderly, using mean 6 drugs	Housebound patients, referred by GP	Pharmacists

***** Clinical medication review; availability of data: Patient interview, medical records and medication records.

* Concordance and compliance review; availability of data: Patient interview and medication records.
DRP=Drug Related Problem; GP=General practitioner; MUR=Medicines Use Review; MR=Medication Review; RCT=Randomised Controlled Trial

Type of patient participation

The type of patient participation in medication reviews has been summarized in table 2.3 for quantitative studies and, in table 2.4 for qualitative studies. Overall, the description of the involvement of patients in the medication review process in all publications was minimal. Only studies in which the patient gave information to the professional (level 2 in table 2.1) were found.

Of the 37 publications, 14 studies included home visits, 14 included patient interviews at the pharmacy or in the GP office, four studies involved patients during or at discharge of their hospital stay and five studies used mixed or other methods to involve the patient. Communication with the patient, especially as preparation before the medication review, was most often carried out by the pharmacist or jointly by the pharmacist and GP. Furthermore, one third of the studies mentioned the duration of the patient contact with the healthcare professional; the time investment ranged between 15-90 minutes per patient.

Information exchange between patient and healthcare professional

In all studies patients provided information about their actual drug use. Additional information included knowledge about the medicines they used, adverse drug events, allergies, adherence and compliance, perceived effectiveness, practical or management problems, lifestyle and social support related, hoarding problems and attitude towards certain medicines.

Healthcare professionals counseled patients often about proposed changes in medication, education on their medication, lifestyle or health problems and gave follow-up instructions for medication monitoring, laboratory tests or new visits.

Evaluation of patient participation

In some studies the involvement of patients during medication reviews was evaluated. Information on actual drug use often added new information to the records e.g. on prescribed drugs, over the counter (OTC) drugs, compliance, adherence or other drug user problems.[23,24,27,30,37,48] Several studies carried out a satisfaction survey among patients who participated in medication review programs. The majority of the patients was satisfied with the review services and indicated to have increased knowledge and was able to ask questions about their medications. Two British qualitative studies[38,48] observed that patients were not actively involved in the consultations with pharmacists for their medication review and did ask very few questions. Furthermore, in three qualitative studies[40,42,51], patients called on the higher authority of the GP or specialist above the pharmacists to discuss their medicines (table 2.4).

Effects of patient participation

The effects of patient participation in medication reviews on DRPs or other patient outcomes have been described in nine studies (table 2.5).[20,26,27,29-31,39,49,50] Of all DRPs identified, 27% to 73% were found as result of a patient interview. Many of these problems would not have been identified if only medication or medical records were used. In two Dutch studies[27,30], the DRPs identified in the interviews were also assigned a higher priority or the recommendations based on patient information were more often implemented than problems identified through medication records or in the medical history. Some other studies mentioned the type of DRPs, which was interpreted as

originating from the patient interview.[21,23,24,37] However, these results are not included in this literature review to answer the effects research questions, because it is not described how and if patient's involvement led to these effects. The studies that showed effects on DRPs were assessed with higher quality on description and evaluation of patient participation than studies that reported no effect data.

One study found no difference in quality of life after the medication review between patients who were enabled to participated and control patients. However, in this study very few patients actively participated in the medication review process and the sample size was too small to assess quality of life differences.[39]

There was no difference in effects or level of patient involvement between different care settings, e.g. hospital or community, or for specific patient groups versus less specific, general polypharmacy or multi-morbidity patients.

Table 2.3 Type of patient participation in medication reviews –quantitative studies–

Reference	Type of communication and by whom	Information given by patient to professional	Consultation by professional	Evaluation of patient participation	Quality assessment
Leendertse 2013	Interview by pharmacist, follow-up of plan by GP and follow-up in time by pharmacist	- Actual drug use - DRPs that involved the patient (not further defined)	Follow-up evaluation of the advised pharmacotherapy changes as agreed with the patient in the pharmaceutical care plane	-	Moderate
Kilcup 2013	Telephone interview with pharmacist	- Actual drug use - Unexplained discrepancies - Drug related problems	Opportunity to ask questions on: - understanding of medication - how medication intended to work - common safety concerns - how to take medication as intended	-	Moderate
Olsson 2012	Home visit by study nurse	- Actual drug use - Compliance	Written drug regimen was provided to enable patient participation	-	Weak
Akazawa 2012	Visit at pharmacy (brown bag method)	- Actual drug use - Reason for choosing OTCs - Adherence - Storage	- Appropriate feedback - Potential safety issues	>90% had ≥1 positive responses (ease concerns on interaction or ADE or duplications, get confirmation, better understanding, others) 45% had ≥1 negative responses (tiresome to bring, time, insufficient advice, others)	Moderate

- Table 2.3 continues -

-Table 2.3 continue –

Reference	Type of communication and by whom	Information given by patient to professional	Consultation by professional	Evaluation of patient participation	Quality assessment
Kwint 2012	Home-visit by community pharmacist	- Actual drug use	Not described	-	Strong
Elliot 2012	Home-visit by clinical pharmacist or GP	- Actual drug use	Not described	- Pharmacist home visit is more feasible than by GP - Satisfied patients with home-visit	Strong
Willoch 2012	Interview with standardized form during hospital stay and follow-up home visit by clinical pharmacist	- Actual drug use - Medication knowledge - Adverse drug effects - Efficacy - Post-discharge effects	Targeted counselling talk on medications and medication changes by pharmacist.	-	Moderate
Stewart 2012	Interview at care centre by (student-)pharmacist	- Actual drug use	Not described	-	Weak
Swain 2012	Interview at clinic by pharmacist	- Actual drug use	Education and counseling on medication while ensuring safety and effectiveness	97% of patients was satisfied with consult Time: interview mean 38 min	Moderate

- Table 2.3 continues -

-Table 2.3 continued -

Reference	Type of communication and by whom	Information given by patient to professional	Consultation by professional	Evaluation of patient participation	Quality assessment
Lam 2011	Web-cam enabled video-conferencing by pharmacist	- Actual drug use - Awareness of treatment goals - Perception of disease control and health care needs - Adherence (questionnaire)	- Answering of questions - Patient-centred education - Medication and life-style recommendations - Instructions and confirmation of understanding	All respondents agreed or strongly agreed that answers to their questions were helpful and they had better medication knowledge. Time: interview 45-60 min	Moderate
Niquille 2010	Interview at the pharmacy by community pharmacist	- Medication experiences - Medication knowledge/ skills - Adherence - Attitude towards prevention	Not described	-	Weak
Granas 2010	Interview at the pharmacy by community pharmacist	- Actual drug use - Compliance issues	Medication advice on paper form	- 98% of patients said they benefited from the review - Time: median consultation 60 min	Moderate

- Table 2.3 continues -

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Reference	Type of communication and by whom	Information given by patient to professional	Consultation by professional	Evaluation of patient participation	Quality assessment
Hernandez 2010	Interview in hospital with standardised service questionnaire by hospital pharmacist	- Actual drug use - Adherence - Possible allergies - Adverse drug effects	- Printed: prescription, schedule, indications, (contra-) interactions, ADE - Drugs and usage recommendations (knowledge of disease, treatment and ADE)	- All respondents could ask (almost) all questions - All respondents rated the treatment as (very) good Time: counselling mean 26 min	Moderate
Hugtenburg 2009	Counsel at home , in pharmacy or by phone by pharmacist	- Actual drug use	- Printed: daily medication intake scheme - Counseling	40% of the patients mentioned a medication problem or raised questions	Moderate
Karapinar-Carkit 2009	Counseling at discharge by pharmaceutical consultants	- Actual drug use - Considering continuing need - Practical problems - Adverse drug effects - Forgetting of medication	- Education	-	Moderate
Pindolia 2009	Telephone contact by pharmacist and/or GP	- Actual drug use - Determine health goals - Concerns about treatment	- Explain the drug change(s) - In-depth counselling on medications/ health - Follow-up instructions (lab, GP visit, drugs)	- 90% found the telephone discussion convenient and was provided with the necessary education - Time: 2.5 hrs/ patient, mainly by pharmacist	Strong

- Table 2.3 continues -

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Reference	Type of communication and by whom	Information given by patient to professional	Consultation by professional	Evaluation of patient participation	Quality assessment
Moultry 2008	Home-visit by consultant pharmacist	- Actual drug use - Medical history (self-reported) - Allergies - Adverse effects	- Drug information (verbally and written) - Action plan - Emergency medication-kit and education	- Almost all patients were satisfied or some-what satisfied with the service - All patient felt more knowledgeable after home-visit - Time: Home-visit: 15-60 min	Moderate
MEDMAN 2007	Consultation according to pharmacist-determined patient need	- Actual drug use - Compliance - Lifestyle and social support	Not described	Not described	Weak
Nguyen 2007	Home-visit 2 days after discharge by pharmacist	- Actual drug use - Medication knowledge	- Education on medication knowledge	In 73/98 of identified DRPs the information given by the patient was new to the GP	Weak
Viktil 2006	Interview at hospital by pharmacist	- Actual drug use - Medication handling (adherence, knowledge, practical, efficacy)	Not described	- Only 50% of intended interviews were conducted. Feasibility was difficult. - Time: Interview mean 20.3 min (range 5–60 min)	Moderate
Sorensen 2004	Home-visit by pharmacist and consult with GP	- Actual drug use	Not described	-	Moderate

- Table 2.3 continues -

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Reference	Type of communication and by whom	Information given by patient to professional	Consultation by professional	Evaluation of patient participation	Quality assessment
Griffiths 2004	Interview at unknown location by community nurse	- Actual drug use - Allergies - Side effects	- Educational support (Medilist) - Compliance aid support.	-	Moderate
Naunton 2003	Home-visit 5 days after discharge by pharmacist	- Adherence - Info to identify DRPs	- Education (medications and compliance) - Compliance devices, when needed	94% was satisfied with the home-visit Time: visit median 50 min	Moderate
Gilbert 2002	Home-visit by community pharmacist and follow-up by GP	- Actual drug use - Knowledge on medication - Demo of administration devices	- Dosing instructions - Education - Assisted with dose administration - Informed choice is mentioned	In 31 cases the patient refused to follow-up the advice on which the GP and pharmacist agreed upon	Moderate
Zermansky 2001	Home-visit community pharmacist and follow-up by GP	- Actual drug use - Confirm indications still valid - Adherence - Unadressed problems	Not described, however negotiation with the patient is mentioned in the methods	- Time: mean 20 min for pharmacist	Strong
Jameson 2001	1. telephone questionnaire 2. Interview in GP office by GP 3. Counselling by GP	- Actual drug use - Understanding of medication	- Explain drug changes - Counselling or instructions on medication and lifestyle, when needed	- 70% of consult group patients said that they benefited from the consult - Time: Face-to-face interviews: 45-60 min	Strong

- Table 2.3 continues -

-Table 2.3 continued -

Reference	Type of communication and by whom	Information given by patient to professional	Consultation by professional	Evaluation of patient participation	Quality assessment
Krska 2001	Home-visit by pharmacist	- Actual drug use - Effectiveness	Not described	-	Moderate
Sellors 2001	Interview at GP office by pharmacist	- Actual drug use - Adherence (questionnaire)	Not described	-	Moderate
Grymonpre 2001	Home-visit by trained staff or volunteers Patient counselling by physician	- Actual drug use - Daily routine - Adherence - Adverse drug events - Allergies and intolerances - Other possible DRPs	- Counselling with written information with physician at practice or at home - Follow-up with pharmacist at home to identify and resolve new issues.	-	Moderate
Schneider 1994	Home-visit by community pharmacist	- Actual drug use - Medication knowledge - Medication management and adherence (incl. hoarding) - Adverse drug effects - Practical problems	When needed, advice on medication and follow-up visit	- From qualitative interviews several benefits were identified for patients, GPs and pharmacists due to the home visits - Time: Home visit mean 56 min.	Moderate

ADE= Adverse Drug Effects; DRPs=Drug Related Problems; GP=General Practitioner

Table 2.4 Type of patient participation and evaluation in medication reviews –qualitative studies–

Reference	Type of communication and by whom	Information given by patient to professional	Consultation by professional	Process or evaluation outcomes	Quality assessment
Sheridan 2012	Interview in pharmacy by pharmacist	- Actual drug use - Adherence - Side effects - Effectiveness - Storage - Use of equipment	Education	- All but one patient were happy with the home visit - Nearly all respondents felt that they had enough time to discuss relevant questions, and were responded adequately - Patients did not report specific health gains directly from the MUR, however, knowledge and comfortable to discuss health or medication issues in the future with pharmacists were mentioned - Pharmacists did believe that the MUR could have improved outcomes for patients - The consultation lasted <30 min-1hr	Strong
Latif 2008	Home-visits by pharmacist	- Actual drug use - Medication knowledge	Education	- 40-60% of the patients did not ask any questions during the MUR - Little room for open questions, OTC discussion offered more scope for participation	Strong
Bissel 2008	Consultation with pharmacist	- Actual drug use - Compliance - Lifestyle and social support	Not described	- Majority expressed ambivalent views about the service, overall cautiously more positive than negative - Helpful reassurance on illness and therapy - Positive about the consultation with the pharmacist but reservations about them making recommendations. Many regard the doctor as the health professional in charge. - Patient felt more knowledgeable on their medicines	Strong

- Table 2.4 continues -

-Table 2.4 continued –

Reference	Type of communication and by whom	Information given by patient to professional	Consultation by professional	Process or evaluation outcomes	Quality assessment
Salter 2007	Home-visits by pharmacist	- Actual drug use	Advice, information, and instruction on medicines	- Advice was often resisted or rejected and created interactional difficulties and awkward moments - Almost no patient initiated requests for advice or information - Calling on the higher authority of the doctor was prevalent - Consultation time: mean 45 min	Strong
Petty 2003	Interview in clinic by clinical pharmacist	- Actual drug use - Medication issues	Explanation, not further defined	- Some patients welcomed the opportunity to have questions answered - Healthcare professional must judge who needs more detailed information and who not - Not everybody accepted the advice given by the pharmacist	Strong
Chen 2000	Interview in pharmacy by clinical pharmacist	- Effectiveness perception - Side effects - Adherence	Not described	- Better understanding of patient's perspective, would facilitate concordance - Consultation duration ranged from 15-90 minutes	Moderate
Nathan 2000	Interview in pharmacy by pharmacist	- Actual drug use	Not described	- Expression of satisfaction and gratitude - Better understanding of medicines - Re-assurement (for patients) that they were taking medicines correctly - Learning things about medications that they not knew before	Strong

OTC=Over The Counter medicines; MUR=Medication Use Review

Table 2.5 Effectiveness of patient participation in medication reviews –quantitative studies–

Reference	Type of patient participation	Outcomes	Quality assessment
Olsson 2012	Information giving on actual drug use and compliance, during a home visit from a study nurse. Patients were enabled to participate, they received a current and comprehensive medication record	No difference in QoL between the group that received a medication record to enable participation and the group that did not. Only 8 of 21 returned medication records were used, with accompanying messages listing forgetfulness, feeling unaccustomed to participating and fear to causing trouble.	Weak
Kwint 2012	Information giving on actual drug use, during a home visit from a community pharmacist	27% of all identified DRPs were identified through patient interview and were assigned a higher priority. DRPs identified during patient interviews were more frequently assigned a high priority, associated with recommendations for drug change and were implemented recommendations for drug change.	Moderate
Willoch 2012	Information giving on actual drug use, knowledge, adverse events, and efficacy during hospital stay and follow-up home visit by clinical pharmacist on post-discharge effects	30% of all DRPs at admission were identified through patient interviews, mainly medication chart errors, compliance problems and adverse drug reactions. Many DRPs identified during the home visits were compliance problems; 20% of DRPs was related to patient knowledge and skills (derived from home visit)	Weak
Lam 2011 (34)	Information giving through web-cam enabled video-conferencing on actual drug use, awareness of treatment goals and adherence	Most prevalent patient-centred DRP was lifestyle-related non-adherence (40/43-93%). Non-adherence to medications was present in 32/43 (74.4%), with forgetfulness as most frequently cited.	Weak

- Table 2.5 continues -

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Reference	Type of patient participation	Outcomes	Quality assessment
Karapinar-Carkit 2009	Information giving on actual drug use and DRPs, at a counselling at discharge by pharmacist consultants.	With patient counselling, 8.8% more patients benefited in correction of discrepancies (interventions in 72.5% vs. 63.7%). 9.1% more patients benefited in optimizing the pharmacotherapy (interventions in 76.3% vs. 67.2%).	Moderate
Viktil 2006	Information giving on actual drug use and drug(problem) handling during an interview with the pharmacist in the hospital.	39.9 % of total DRPs were found during the interview, significantly more DRPs were found in interviewed group vs. non-interview group.	Moderate
Gilbert 2002	Information giving on actual drug use and knowledge with the purpose of an informed choice during a home-visit by community pharmacist and follow-up by GP.	On average 2.5 DRPs were identified. Of which 20% related to patient knowledge and skills.	Weak
Jameson 2001	Information giving on adverse events and the understanding of medications during a telephone interview, face-to-face interview with GP and follow-up counselling by the GP.	73% of the interventions were recognized only through patient interview (unplanned outcome of the study).	Moderate
Krska 2001	Information giving on actual drug use and effectiveness during home-visit by pharmacists.	Pharmaceutical Care Issues were in 29.4% of the cases identified during the patient interview. Of all the PCI, 21% were resolved by information found in notes and 8.5% in patient interviews.	Moderate

DRP= Drug Related Problem; GP=General Practitioner; PCI= Pharmaceutical Care Issue; QoL= Quality of Life

Discussion

The type of patient participation commonly practiced in the studies reviewed was information giving and was often the starting point in a medication review. Other types of patient participation were not found. The information given by the patient was mainly on actual drug use and adherence problems. In most studies the professional was a pharmacist who interviewed or counseled patients at home, in the pharmacy or in the hospital. The involvement of patients led to identification of more drug related problems. These DRPs were considered more relevant, had a higher priority and treatment recommendations based on these problems had a better implementation rate. Both patients and professionals indicated to be satisfied with the patient participation. Some studies suggested increased medication knowledge and patients' understanding.

The effects of patient participation is hardly studied and poorly described in current literature. We found no evidence the patient involvement in medication reviews went further than information exchange during dialogues or interviews between patients and caregiver. It remains unclear how patients participate in subsequent stages of the medication review with regard to the sharing of information, decision-making, counseling and implementation of possible medication changes.

The exact contribution of patient participation to the effects of the study was mostly unclear. Studies with higher quality often reported effects of patient participation on the identification of DRPs. Weaker quality studies reported good patients' satisfaction, increased medication knowledge and patients' understanding. These outcomes, however, were measured in surveys with low response rates, which could have led to response bias.

In national and international guidelines, patient participation in a medication review process is a prerequisite for a successful medication review.[5,10,11] However, guideline recommendations to involve patients are not based on evidence but on prevailing societal considerations expert opinions.[11] Apparently, there is a discrepancy between patient-centeredness and evidence-based care. Patient participation is a concept that already arises from the sixties, when the consumer protection rights were introduced in the US

Congress; “the right to safety, the right to be informed, the right to choose and the right to be heard”.[57] This also implicates that patient participation is more a right and largely justified on humane reasons than an evidence-based means to improve treatment outcomes, as is questioned before.[58,59]

The use of medication reviews, particularly with active patient involvement, as an intervention to improve treatment results is a fairly recent development in pharmaceutical care. This may partly explain the absence of good quality literature clearly describing involvement of patients in medication reviews and its effects. Furthermore, implementing patient participation is strongly dependent on overcoming healthcare professionals’ obstacles such as time constraints and finances, societal norms and the tendency of caregiver to maintain control.[1] Particularly, the time investment to involve patients in the medications reviews process is considerable, and hence costly. In this literature review, it varied between 15-90 minutes for patients interviews aimed only to inform caregivers on actual drug use and experiences.

As compared to younger patient, elderly are known to participate less in care and self-management and have different preferences for involvement and decision making.[60] This literature review consisted of studies almost solely in elderly subjects, which is the main target group for medication reviews. This means that the patient group described in this literature study is already less prone to participate and to a lesser extent wants to be involved in medical decisions. Not all patients want to or can be involved and the extent to which involvement is useful may depend on age, disease severity, acuteness of the disease, cognitive state, comorbidity, health literacy, socio-economic status, type and impact of decision, attitudes towards medication and prevention, patient-professional relationships and other personal preferences.[1,7] Previous research also indicated that patients have a desire to participate in the consultation, but do not always feel a need to be involved in medical decision and patient involvement was limited to information sharing.[59,61-63] This means that we may have to reconsider how and which patients should be involved in a medication review.

Data on the gain of patient participation in terms of effects is scarce and existing literature has a weak quality. The evidence for the effects on clinical patient outcomes such as quality of life, hospitalisation and mortality of medication reviews themselves is limited.[64] Although, patient participation in

consultations has been suggested to improve e.g., adherence, long-term effects of pharmacotherapy and thereby indirect patient outcomes.[3,4] However no evidence was found for this in the context of medication reviews.

There are some limitations to discuss. The taxonomy by Thompson[7] used in this study is not very discriminative. There may be other in-between combinations applicable, however others also recognize that labelling these would not be very useful since one always deals with specific situational contexts.[65] This emphasizes the complexity of studying patient participation.

Although an extensive search strategy in four literature databases was used and an additional hand search in reference lists was performed, relevant articles may have been missed.

The complexity of patient participation in medication reviews makes it difficult to design comparative studies. Moreover, it is difficult to measure to specific contribution of patient participation on treatment outcomes. To study whether e.g. shared-decision making is carried out in practice, a qualitative study design may be needed. With qualitative observational research one could study whether patients really influence the content and structure of the interaction of a consultation or decision, like Street and Millays' definition of patient participation.[6]

To study whether patient participations also results in effects, future research should focus on designs, possibly comparative, with a mixed character with relevant, quantitative patient outcomes such as adherence, quality of life, adverse drug events and patient satisfaction and qualitatively on the level of involvement of patients by observing consultations.

Conclusion

To conclude, patient participation in medication reviews is important to gain information about patient preferences and relevant drug related problems. Patient participation is not common and not always desirable in decision making in the last phase of a medication review. As there is often no clear decision as with treatment counselling and the target group for medication reviews, vulnerable elderly, does not always have the wish to be involved in the actual decision. Patient satisfaction and knowledge seem to improve when

patients are more involved, however no effects in health outcomes have been observed.

Patient participation in medication reviews is desirable and may improve patient outcomes, but is presently based on expert opinions and ethical considerations for modern healthcare, rather than on evidence. Considering the time investment and limited evidence of patient participation in medication reviews efficient methods targeted at the right patients seem appropriate. The profit of higher levels of patient communication and shared decision making is until now, not supported by evidence of its effectiveness. Since patient involvement limited to information sharing seems more appropriate, efficient methods to involve patients in medication reviews are topic for future research and practice innovations. In this way, clinical medication reviews will become more feasible for GPs and pharmacists.

Practice implications

Our results may have potential implications for pharmacists, GPs or other physicians who perform medication reviews. Patient participation at the level of information giving, may improve information of the professionals and identification of DRPs and may contribute to improved patient knowledge, understanding and patients' satisfaction. Physicians and pharmacists have to keep in mind that involvement of patients during decision making is not primarily evidence-based to improve the outcomes of both medication review outcomes as well as and patient outcomes and is not always needed in this type of decisions. Based on the literature, information giving participation during medication reviews improves the medication review process and identification of drug related problems, however evidence regarding the effectiveness of higher levels are lacking and might not be needed at all times and at all costs.

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Competing Interests Statement

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: FW had support from a research grant by the Dutch Organization for Health Research and Development (ZonMw) for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

Author contributions

FW, JGH, FGS and PJME designed the study and research questions. FW and PJME performed the title and abstract screening and FW performed the full text selection. FW, JGH, FGS and PJME performed the quality assessment and FW carried out the data extraction. FW, JGH, FGS and PJME prepared the manuscript.

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Supplementary Material I. PubMed search strategy

Carried out on: 08-07-2013

Search: (#1 AND #2) NOT (#3)

#1 Patient participation

"Decision Making"[Mesh] OR “Shared decision”[tiab] OR “Shared decisions”[tiab] OR Concordanc*[tiab] OR "Patient Participation"[Mesh] OR “Patient participation”[tiab] OR “consumer participation”[tiab] OR “Patient interview”[tiab] OR “Patient interviews”[tiab] OR “Patient input”[tiab] OR “Participating patient”[tiab] OR “Participating patients”[tiab] OR “patient contribution”[tiab] OR “patients contribution”[tiab] OR “patient contributions”[tiab] OR “patients contributions”[tiab] OR “Patient involvement”[tiab] OR "Physician-Patient Relations"[Mesh] OR "Professional-Patient Relations"[Mesh] OR “Physician-Patient Relation”[tiab] OR “Physician-Patient Relations”[tiab] OR “Physician-patient communication”[tiab] OR "Patient-Centered Care"[Mesh] OR “Patient-focused care”[tiab] OR “Patient-centered intervention”[tiab] OR “Patient-centred intervention”[tiab] OR “Patient-focused intervention”[tiab] OR “Patient-centered”[tiab] OR “Patient-centred”[tiab] OR “patient centredness”[tiab] OR “Individualized-care”[tiab] OR “person-centered care”[tiab] OR “person-centred care”[tiab] OR “client-centered care”[tiab] OR “client-centred care”[tiab] OR “resident-centered care”[tiab] OR “resident-centred care”[tiab] OR “patient empowerment”[tiab] OR "Home Care Services"[Mesh] OR “Medical Home”[tiab] OR “Medical Homes”[tiab] OR “Home visit”[tiab] OR “Home visits”[tiab] OR “domiciliary care”[tiab] OR “domiciliary pharmaceutical care”[tiab] OR “domiciliary pharmacist visits”[tiab] OR “domiciliary pharmacy visits”[tiab] OR “Patient Information”[tiab] OR “patient counseling”[tiab] OR “patient counselling”[tiab] OR “patient consult”[tiab] OR “patient consults”[tiab] OR “patient communication”[tiab] OR "brown bag"[tiab]

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#2 Medicationreview

"Medication review"[tiab] OR "Medication reviews"[tiab] OR "Drug utilization review"[Mesh] OR "Medication Therapy Management"[Mesh] OR "Drug utilization review"[tiab] OR "Drug utilization reviews"[tiab] OR "Drug utilisation review"[tiab] OR "Drug utilisation reviews"[tiab] OR "Drug utilization evaluation"[tiab] OR "Drug utilisation evaluation"[tiab] OR "Drug utilization evaluations"[tiab] OR "Drug utilisation evaluations"[tiab] OR "Drug use review"[tiab] OR "Drug use reviews"[tiab] OR "Pharmacist intervention"[tiab] OR "Pharmacist interventions"[tiab] OR "Pharmacists intervention"[tiab] OR "Pharmacists interventions"[tiab] OR "pharmaceutical care programme"[tiab] OR "pharmaceutical care program"[tiab] OR "Medication Reconciliation"[Mesh] OR "Medication reconciliation"[tiab] OR "Medication reconciliations"[tiab] OR "Medication assessment"[tiab] OR "Medication assessments"[tiab] OR "Medication evaluation"[tiab] OR "Medication evaluation"[tiab] OR "Drug assessment"[tiab] OR "Drug assessments"[tiab] OR "Drugs assessment"[tiab] OR "Drug assessments"[tiab] OR "Medicines use review"[tiab] OR "Medicines use reviews"[tiab] OR "Medicine use review"[tiab] OR "Medicine use reviews"[tiab] OR "Medication use review"[tiab] OR "Medication use reviews"[tiab] OR "Medicines utilization review"[tiab] OR "Medicines utilization reviews"[tiab] OR "Medicine utilization review"[tiab] OR "Medicine utilization reviews"[tiab] OR "Medication utilization review"[tiab] OR "Medication utilization reviews"[tiab] OR "Medicines utilisation review"[tiab] OR "Medicines utilisation reviews"[tiab] OR "Medicine utilisation review"[tiab] OR "Medicine utilisation reviews"[tiab] OR "Medication utilisation review"[tiab] OR "Medication utilisation reviews"[tiab] OR "Clinical medication review"[tiab] OR "Clinical medication reviews"[tiab] OR "Treatment review"[tiab] OR "Treatment reviews"[tiab] OR "Prescription review"[tiab] OR "Prescription reviews"[tiab] OR "Medication Errors/prevention and control"[Mesh] OR "Inappropriate Prescribing/prevention and control"[Mesh] OR "Pharmacotherapy consultation"[tiab] OR "Pharmacotherapy consultations"[tiab] OR "Medication consultation"[tiab] OR "Medication consultations"[tiab] OR "Medications consultation"[tiab] OR "Medications consultations"[tiab] OR "Medicine consultation"[tiab] OR "Medicine consultations"[tiab] OR "Medicines consultation"[tiab] OR "Medicines consultations"[tiab] OR "Drug consultation"[tiab] OR "Drug consultations"[tiab] OR "medication analysis"[tiab] OR "medication analyses"[tiab] OR "medication management"[tiab] OR "medicine management"[tiab] OR "medicines management" [tiab]

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#3 Publication Types (NOT) ("addresses"[Publication Type] OR "biography"[Publication Type] OR "comment"[Publication Type] OR "directory"[Publication Type] OR "editorial"[Publication Type] OR "festschrift"[Publication Type] OR "interview"[Publication Type] OR "lectures"[Publication Type] OR "legal cases"[Publication Type] OR "legislation"[Publication Type] OR "letter"[Publication Type] OR "news"[Publication Type] OR "newspaper article"[Publication Type] OR "patient education handout"[Publication Type] OR "popular works"[Publication Type] OR "congresses"[Publication Type] OR "consensus development conference"[Publication Type] OR "consensus development conference, nih"[Publication Type] OR "practice guideline"[Publication Type]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms])

3

Information on actual medication use and drug-related problems in older patients: questionnaire or interview?

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Abstract

Background

Information on medication use and drug-related problems is important in the preparation of clinical medication reviews. Critical information can only be provided by patients themselves, but interviewing patients is time-consuming. Alternatively, patient information could be obtained with a questionnaire.

Objective

In this study the agreement between patient information on medication use and drug-related problems in older patients obtained with a questionnaire was compared with information obtained during an interview.

Setting

General practice in the Netherlands

Method

A questionnaire was developed to obtain information on actual medication use and drug-related problems. Two patient groups ≥65 years were selected based on general practitioner electronic medical records in nine practices; I. polypharmacy and II. ≥1 predefined general geriatric problems. Eligible patients were asked to complete the questionnaire and were interviewed afterwards.

Main outcome measure

Agreement on information on medication use and drug-related problems collected with the questionnaire and interview was calculated.

Results

Ninety-seven patients participated. Of all medications used, 87.6% (95% CI 84.7-90.5) was reported identically in the questionnaire and interview. Agreement for the complete medication list was found for 45.4% (95% CI 35.8-55.3) of the patients. On drug-related problem level, agreement between questionnaire and interview was 75%. Agreement tended to be lower in vulnerable patients characterized by ≥4 chronic diseases, ≥10 medications used and low health literacy.

Conclusion
Information from a questionnaire showed reasonable agreement compared with interviewing. The patients reported more medications and drug-related problems in the interview than the questionnaire. Taking the limitations into account, a questionnaire seems a suitable tool for medication reviews that may replace an interview for most patients.

Introduction

Older age is frequently accompanied with an increased prevalence of multiple chronic diseases, often resulting in the use of multiple medications or polypharmacy. Polypharmacy, usually defined as the chronic use of ≥5 prescribed medications, is associated with the occurrence of drug-related problems (DRPs) such as drug-drug interactions, inefficacy of treatment, adverse drug reactions (ADR), prescription errors and non-adherence.[1] A clinical medication review (CMR) can be used to detect potential DRPs and improve the quality of pharmacotherapy and patient outcomes.[2-6] A CMR is defined as a 'structured, critical examination of the patient's medicines with the objective of reaching an agreement with the patient about treatment, optimizing the impact of medicines, and minimizing the number of DRPs.[7]

Preparing a CMR requires insight in actual medication use and knowledge of potential DRPs. Active patient participation is a prerequisite to determine how and which medications are actually used and to identify DRPs for successful medication reviews.[3,8-11] A gold standard for collecting patient-specific information on medication use and DRPs is not available. However, interviewing patients including a medication inspection, preferably during a home visit or the 'brown bag' method[12], seems the best method.[13] The Dutch guideline for polypharmacy in older patients recommends face-to-face interviews, however this is very time-consuming.[14,15] Patient involvement in medication reviews is desirable and may improve patient outcomes, but as yet is not evidence-based and might not be needed at all times and costs.[9]

Alternatively, a self-administered questionnaire could be used to obtain information from patients to conduct a CMR. Self-administered questionnaires are less time-consuming, can reach more people, provide standardized

information and may be preferable for capturing sensitive topics in comparison to face-to-face interviews.

However, existing self-reported questionnaires on DRPs were not developed with the aim to obtain patient information relevant for CMRs.[16,17] Interview protocols have been developed to support a CMR.[13,18] In the present study a self-administered questionnaire was developed using an existing interview protocol and DRP classification system, to report actual medication use and DRPs from the patients' perspective. We were interested in the agreement between the information obtained via the questionnaire and an interview and which patient groups showed better or worse agreement.

Aim of the study

The aims of this study were: 1) to compare information on actual medication use and DRPs obtained by means of a questionnaire with information from a face-to-face interview and 2) to assess whether the extent of agreement for a number of patient and health characteristics differs between subgroups of patients.

Ethical approval

The study was assessed by the Medical Ethics Committee of VU University Medical Centre (2011/408). In accordance with local regulatory guidelines and standards for Dutch human subjects protection (Medical Research Involving Human Subjects Act [WMO], 2005), this study proved to be exempt from further medical ethical review.

Method

Information obtained by means of a questionnaire was compared with a face-to-face interview in 97 older patients with either polypharmacy or geriatric problems.

Participants

Patients were recruited February-June 2013 from nine GP (general practitioner) practices in Haarlem, the Netherlands. Two patient groups aged ≥65 years were

included: polypharmacy patients and patients with geriatric problems. Both groups were selected because there is no consensus on the best target group for medication reviews. Patients were identified based on information in the GP's Electronic Medical Records (EMR) and the following criteria:

1. Polypharmacy was defined as the use of ≥5 chronic prescribed medications;
2. Geriatric problems were immobility, falls, dizziness, urine incontinence and impaired cognition.[19] Geriatric problems were identified on the basis of a selection of International Classification of Primary Care (ICPC) coded diagnoses[20] recorded in 2012 in the patients' EMRs. To ensure that patients had an actual geriatric problem questions about current complaints were included in the questionnaire to be scored on a 3-point Likert scale; none, some or a lot problems (respectively 1, 2 or 3). Patients were included if they scored at least '2' for at least one geriatric problem or if they reported ≥1 falls in the previous six months. Patients were eligible if they used ≥1 prescribed medication chronically.

Chronic medication use was defined as ≥3 prescriptions in the last 12 months recorded in the EMR.

Patients with a dementia diagnosis were not eligible. The GPs reviewed the list of eligible patients for exclusion criteria: terminally ill patients, recent severe psychiatric problems, or other personal issues making it not desirable to invite patients. Participants were asked to sign informed consent form. Patients who did not want to participate could return a no-participation form.

Development of the questionnaire

A questionnaire to obtain information on actual medication use and DRPs to support CMR was developed on the basis of a previously developed interview to identify DRPs[18] and the Pharmaceutical Care Network Europe Classification for DRPs.[21] The questionnaire consisted of two parts; Part A: actual medication use and medication knowledge and Part B: patient experiences of DRPs (Supplementary Material I). Ten experts (GPs, pharmacists, elderly care specialist, researchers) reviewed the questionnaire using a systematic scoring system in two rounds to obtain face- and content validity. All experts had content, textual and/or lay-out suggestions for the questionnaire and manual.

In part A, five questions were deleted and one changed, in part B, two questions were deleted, two added and three were changed. The questionnaire was pilot-tested in two phases by seven and four patients, all ≥75 years using ≥8 medications recruited from one pharmacy. Each patient was asked to fill out the questionnaire in the presence of a researcher, who asked the patients to verbalise their thoughts ('think aloud'). The patient's behaviour was observed, such as skipping questions or hesitation. After the first round, the lay-out of part A on actual medication use was changed thoroughly and the sequence of questions of part B was changed. Following these revisions, a second pilot test confirmed that the questionnaire was suitable for older patients.

Interview

Interviews were performed using a structured interview protocol by trained researchers using the same questions as the questionnaire. The interviewers received half a day of interview training and the first three interviews were conducted in pairs. To obtain information about actual medication use, the medication name, dosage and frequency were noted from the boxes and bottles, including any over the counter (OTC) medications. For each medication the patient was asked for the indication. A distinction was made between oral and non-oral medications based on ATC codes. There were eleven questions on DRPs and four main groups could be distinguished: possible adverse events, effectiveness, non-adherence, and user problems.

Measurements

First, patients were asked to complete the questionnaire, second, patients were visited at home for an interview by a researcher. Information on gender, age, socio-demographics, self-perceived health status and geriatric problems was obtained from the questionnaire. Health literacy was measured using the REALM-D test, a score of ≤59 indicates low health literacy.[22] The number of chronic diseases per patient was calculated using the ICPC coded diagnoses in the EMRs based on a list of the most common chronic diseases in general practice.[23]

Statistical analyses

Descriptive statistics were used to describe patient characteristics. The agreement of the medication's name and potential DRPs (dichotomous answers) between the questionnaire and the interview were presented in percentages and 95% confidence intervals. Percentages were calculated for the reporting of medication and DRPs either only in the questionnaire or only in the interview. Agreement was assessed both at individual drug and DRP level as well as at patient level.

Independent t-tests and Chi-square tests were performed to analyze differences in agreement in actual medication and DRPs for gender, age, living situation, education level, self-perceived health, health literacy, number of medications and number of chronic diseases.

Non-responder analyses were performed to detect differences in patient characteristics between participants and non-participants; descriptive and Chi-square statistics were used. All data was analyzed anonymously and carried out using IBM SPSS statistics version 20 software).

Results

Patient characteristics

Of the 255 patients that were selected from the EMR records, 39 were excluded by the GP. Of the remaining 216 patients, 131 (61%) were willing to participate in the study (figure 3.1). Complete data was obtained from 97 patients (44 polypharmacy patients and 53 geriatric problem patients). The mean duration of the interview was 16 [sd 7] minutes, excluding travelling and introduction time. The mean period between the receipt of the questionnaire and the interview was 9 [sd 5.2] days.

The mean age of the patients was 75.9 [sd 7.1] years and 72% were women. The mean number of medications per patient according to the interview was 7.3 [sd 3.2] and 6.8 [sd 2.7] according to the questionnaire. The most common geriatric problems were mobility problems (73%), followed by urine incontinence (50%) and cognitive problems (40%). Multimorbidity was common, the mean number of chronic diseases was 4.0 [sd 2.4]. 19% of the patients had inadequate health literacy. (table 3.1)

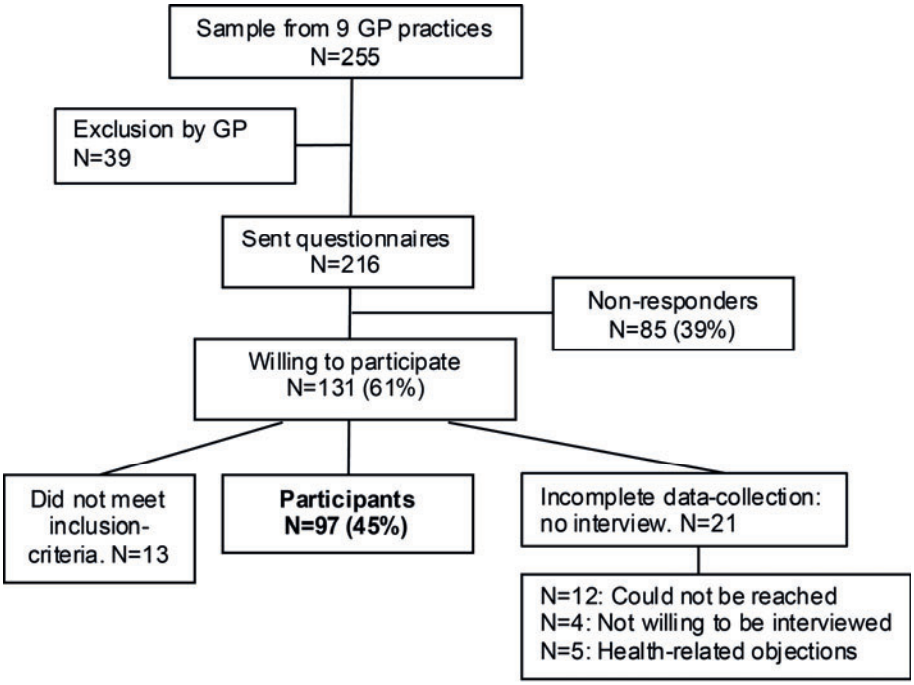

Figure 3.1 Flow diagram of participants

Table 3.1 Patient characteristics

Patient characteristics	Total
Patients, n	97
Women (%)	72%
Mean age in years (sd) [range]	75.9 (7.1) [65-90]
Education level [1]	
Low %	53%
Middle %	37%
Upper %	10%
Low health literacy [2]	18 (19%)

- Table 3.1 continues -

-Table 3.1 continued -

Patient characteristics	Total
Living alone	44 (45%)
Mean no medications (sd) [range] in questionnaire	6.8 (2.7) [1-13]
Mean no medications (sd) [range] in interview	7.3 (3.2) [1-16]
% Reported ≥5 medications in either questionnaire or interview	80 (83%)
Use of one or more OTC medications (%)	76 (88%)
Self-perceived health	
Good to excellent	48 (50%)
Fair to poor	49 (50%)
Mean no chronic diseases (sd) [range][3]	4.02 (2.4) [0-10]
Geriatric problems, n (%)	
Falling (≥1 last 6 months)	31 (32%)
Mobility problems	71 (73%)
Dizziness	33 (34%)
Incontinence problems	48 (50%)
Cognitive problems	39 (40%)
Fear to fall	37 (39%)

sd=standard deviation; OTC=Over the Counter

1 low education level: No education, primary education or first stage of basic education
middle education level: Lower secondary education or second stage of basic education
upper education level: Upper secondary education or higher

2 REALM score ≤59[22]

3 Chronic diseases according to set list[23]

Comparison of participants and non-participants

Of the 85 patients not willing to participate, 27 indicated the reason for non-participation. Main reasons were no interest (N=13), personal reasons/no reason (N=11) or the use of few medications (N=3). There were significantly more females among the participants (72%), compared to non-participants (46%). There were no significant differences between participants and non-participants in age and multimorbidity.

Agreement on actual medication use

Table 3.2 shows the observed agreement on the level of medication and table 3.3 on the patient level, which represents the agreement on the complete medication list.

The total number of used medications according to the interview was 705, mean 7.3 [sd 3.2] per patient and according to the questionnaire 662, mean 6.8 [sd 2.7] per patient. The observed overall agreement was 87.6% for all medications. Medications were more frequently mentioned only in the interview (8.8%), than only in the questionnaire (3.3%). The observed agreement for information on dosage and frequency was both 76%. Of all medications reported, 12% was non-oral. The agreement for non-oral medications was significantly lower than for oral medications (67.4% versus 88.7%).

Agreement of knowledge of medications indication was not assessed.

Table 3.2 Agreement for medication use in questionnaire compared with interview at medication name level by patient characteristics

Patient characteristics	Agreement at medication name level (95% CI)
All patients	87.6% (84.7-90.5)
Gender	
Male	88.7% (82.7-94.7)
Female	87.2% (83.8-90.5)
Age	
<80 years	88.5% (85.1-92.0)
>80 years	85.8% (80.4-91.2)
Living situation	
Alone	87.7% (83.7-91.6)
With partner	87.5% (83.3-91.8)

- Table 3.2 continues -

-Table 3.2 continued -

Patient characteristics	Agreement at medication name level (95% CI)
Level of education	
Low	88.4% (84.4-92.3)
Middle	87.1% (82.6-91.6)
High	85.5% (71.6-99.4)
Health literacy	
Low	83.5% (76.6-90.4)
Adequate	88.6% (85.3-91.9)
Self-perceived health	
Good to excellent	85.6% (81.2-90.0)
Fair to poor	89.7% (85.9-93.4)
Number of medications*	
<10	91.1% (88.4-93.9)
≥10	78.4% (71.9-84.9)
Chronic diseases	
0-3 chronic diseases	90.5% (86.6-94.3)
≥4 chronic diseases	85.2% (81.0-89.4)

CI=Confidence Interval
*p-value: <0.05

The agreement for patients using ≤10 medications was 91% (95% CI 88.4-93.9), significantly higher compared to 78% (95% CI 71.9-84.9) for patients using ≥10 medications (p<0.001). There were no other significant differences in agreement on medication use between subgroups of patients (table 3.2).

45.4% of the patients had complete agreement for their total medication list (table 3.3). There were no significant differences in agreement between subgroups based on gender, age, living situation, education level, or self-perceived health. The complete list agreement for patients using ≤10 medications was significantly higher (p=0.01), 56% compared to 18.5% for patients using ≥10 medications. Participants with inadequate health literacy

and ≥4 chronic diseases had a slightly lower complete list agreement (respectively 28% and 38%) compared to participants with adequate health literacy and <4 chronic diseases (respectively 49% and 55%), however no significant differences were found (both p=0.099).

Table 3.3 Agreement for medication use in questionnaire compared with interview at patient level by patient characteristics (N=97)

Patient characteristics	Complete medication list agreement at patient level % (95% CI)
All patients	45.4% (35.8-55.3)
Gender	
Male	55.6% (37.3-72.4)
Female	41.4% (30.6-53.1)
Age	
<80 years	46.9% (35.2-58.9)
>80 years	42.4% (27.2-59.2)
Living situation	
Alone	43.2% (29.7-57.8)
With partner	47.2% (34.4-60.3)
Level of education	
Low	47.1% (34.1-60.5)
Middle	41.7% (27.1-57.8)
High	50.0% (23.7-76.3)
Health literacy**	
Low	27.8% (12.5-50.9)
Adequate	49.3% (38.3-60.4)
Self-perceived health	
Good to excellent	40.8% (28.2-54.8)
Fair to poor	50.0% (36.4-63.6)

- Table 3.3 continues -

-Table 3.3 continued -

Patient characteristics	Complete medication list agreement at patient level % (95% CI)
No of medications*	
<10	55.7% (44.1-66.8)
≥10	18.5% (8.2-36.7)
Chronic diseases**	
0-3 chronic diseases	54.5% (40.1-68.3)
≥4 chronic diseases	37.7% (25.9-51.2)

CI=Confidence Interval

* value: <0.05

** p-value: <0.10

Agreement on drug-related problems

The DRPs were categorized in adverse events, effectiveness problems, non-adherence, and user or practical problems (table 3.4). There were more DRPs identified in the interview than with the questionnaire, respectively 116 and 76 DRPs. The best overall agreement was found for adverse events and effectiveness problems, (78% and 79%). For non-adherence and user problems the agreement was 71% and 68%, respectively. For 31% of all patients there was agreement for all DRPs.

In total, 17% of the patients reported to experience adverse events in the questionnaire and 24% in the interview. Non-adherence problems were the most common DRP mentioned in the patient questionnaire and interview, respectively 26%, and 41%. Not all reported non-adherence problems may be serious, many patients reported to forget medicine(s) only once or twice per month. In total 23% of the DRPs for non-adherence were only reported in the interview, compared to 7% that was only mentioned in the questionnaire.

Effectiveness problems, defined as doubts about the effect of the medication by the patient, were also more frequently mentioned in the interview (25%) than the questionnaire (14%).

Finally, user and practical problems were also identified by both tools, 29% in the interview and 22% in the questionnaire. Patients indicated in the questionnaire that they had e.g. difficulties to using their medications due to fear of side effects (n=3) or were experiencing practical problems such as the

time of the day (n=4) and difficulties with swallowing (n=3). In the interview problems like opening a medication strip (n=9) and difficulties with swallowing (n=6) were the most frequently reported practical problems. The user and practical problems were in 20% only reported in the interview, and 12% was only reported in the questionnaire.

There were no significant differences in the agreement on DRPs between subgroups based on patient and health characteristics (results not shown). Most subgroups were too small for valid analyses. There were no significant differences for all covariates at patient level for total DRP agreement.

Table 3.4 Observed agreement for drug-related problems

Drug-related problems	Prevalence Questionnaire n (%)	Prevalence Interview n (%)	Agreement % (95% CI)	DRP only in questionnaire %	DRP only in interview %
Adverse events [1]	16 (17%)	23 (24%)	78.4% (70.0-86.7)	7%	14%
Adherence [2]	25 (26%)	41 (41%)	71.1% (60.8-79.4)	7%	23%
Effectiveness [3]	14 (14%)	24 (25%)	79.4% 71.2-87.6)	5%	16%
User and practical problems [4]	21 (22%)	28 (29%)	68.1% 58.6-77.4)	12%	20%

DRP=Drug-Related Problem; CI=Confidence Interval

[1] Adverse events; self-reported suspected adverse drug events

[2] Effectiveness; doubts about the effect of the medications

[3] Adherence problems; either forgetting medications, under- and overuse or not taking medications

[4] User and practical problems; unable to use medications and practical problems

Discussion

In this study we used a questionnaire on actual medication use and DRPs from the patient's perspective as instrument for the use in daily practice of clinical medication reviews and compared this with face-to-face interviews. Information on actual medication use obtained by a patient interview had good agreement with information obtained by the questionnaire. There was complete agreement for the total medication list for almost half of the patients. For orally used medications there was better agreement between questionnaire and the interview as compared to non-oral medication. Agreement for DRPs was reasonable, the interview provided more information compared to the questionnaire.

In current guidelines face-to-face contact with the patient is recommended when preparing medication reviews. These activities are time-consuming and undermine the feasibility or implementation of medication review activities in daily GP and pharmacist practice. However, an overview of actual medication use is essential for medication reviews. It is known that GPs' and pharmacists' medication records and actual intake often mismatch.[24,25] Results from an Australian study showed that medication use obtained by means of a telephone interview had good agreement with those obtained by means of an interview.[26] In this study agreement percentages were somewhat higher, up to 100%, than ours. This suggests that more efficient tools, like a questionnaire or self-reports by phone, may be a surrogate for face-to-face interviews.

We were interested in differences in agreement between different subgroups according to patient and health characteristics. We found no differences in agreement on DRPs between subgroups. For actual medication use, there was a slightly better agreement for patients with fewer medications, fewer chronic diseases and adequate health literacy, suggesting that the use of a questionnaire is the best option for these patients. For a subgroup of vulnerable older patients and patients with limited (health) literacy a face-to-face interview is probably preferable. In addition, not all older patients will be able to fill out a questionnaire. However the good response rate indicates that many older patients are capable and willing to complete a questionnaire. Unfortunately, we could not trace whether the questionnaire was completed

by the patients themselves or with support, however we know some patients were assisted by informal carers.

Dichotomous answers about the existence of DRPs were analysed. However, the preparation of a CMR requires additional qualitative information on DRPs for use in daily practice. This additional information may include signals for potential DRPs and their causes and can be addressed by the physician or pharmacist when discussing the results of a medication review.

Some limitations may have influenced the outcomes. First, the interviews were not performed by pharmacists or GPs, as the result, information might have been less complete. However, the interviews have been conducted by trained interviewers using a structured protocol. Second, there were relatively more women among the participants than among the non-participants, which might question their representativeness. However, a higher participation rate by women is common in healthcare and questionnaire research.[27] The similar age and number of chronic diseases between participants and non-participants and the good response rate (61%) suggests good representativeness of the sample while female gender was not related to agreement levels. Third, the order of the questionnaire and the interview may have influenced the results. All patients started with the questionnaire which may partly explain that patients reported more medication and DRPs in the interview than the questionnaire. The effects of the different measuring methods cannot be distinguished from asking a second time similar questions by a different method. Finally, the GPs were asked to exclude patients for who an invitation for the study would not be desirable at this moment. In total 15% of the sample was excluded. GPs may have excluded more vulnerable or complex patients, a target group for medication reviews, but may have more difficulties with written questionnaires. As stated above, this is a group of patients for which another approach appears more appropriate.

The questionnaire is intended for use in GP or pharmacy practices as preparation for a CMR, instead of more elaborate history taking. Information from the patient on actual medication use and potential DRPs clearly is the appropriate starting point for a CMR. Answers on the questionnaire can be particular signals to address in the CMR and requiring further exploration by questioning the patient. Since more information on its usefulness in practice is

needed, the questionnaire is currently evaluated in an ongoing trial on CMR in elderly with geriatric problems.[15]

Conclusion

Overall, the information from the questionnaire showed reasonable agreement compared with the interview. Actual medication use as assessed from questionnaire data had good agreement with the interview-based assessment, especially for oral medication. Although more DRPs were identified by means of the patient interview than with the questionnaire, there was a reasonable agreement. Taking the limitations into account, a questionnaire seems a suitable tool to replace a face-to-face interview and may increase the feasibility and standardization of conducting CMRs in daily practice. More patients can be reached with a questionnaire and it is less time-consuming. However, for more vulnerable older patients an interview may be still needed.

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Conflict of Interest Statement

All authors declare that they have no conflict of interest.

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Supplementary Material I: Translated questionnaire

Part A

Explanation:

We would like to know which medication you are using the last month, how often per day, how many and for what condition. Medications are tablets or capsules, but also (eye) drops, sprays, creams, drinks, inhaler puffs, suppositories etc.
You can use your medication overview from the pharmacy and the boxes or bottles from the pharmacy of the last month to fill in part A. Of course, you can ask somebody to help you with the questionnaire.

The following questions you can fill in for each medication separately.

Medication 1

A. Name and dosage (in mg/g/ml): .....
B. How often do you use this medication? . . . . . *per day / week / as needed*
C. How much do you use per time? *(e.g. 2 tablets)* .....
D. What is this medicine for? .....

Medication 16

A. Name and dosage (in mg/g/ml): .....
B. How often do you use this medication? . . . . . *per day / week / as needed*
C. How much do you use per time? *(e.g. 2 tablets)* .....
D. What is this medicine for? .....

Do you also use medications or supplements that you purchase yourself at e.g. the local drugstore? E.g. paracetamol, ibuprofen, vitamins, homeopathic or herbal medications?

❑ No
❑ Yes

If yes, which ones and how often?.....
.....
.....
.....

Part B

In this part of the questionnaire we ask you about possible drug-related problems. If you want you can explain more about you answer.

1. **Do you experience in the last month any side effects due to you medications?**

❑ No → Continue with question 2

❑ Yes → Continue with the table below

If yes, which side effects did you experience?

Side effect (type of complaint)	By which medication(s)? If you do not know, fill in '?'	Since how long do you have this complaint?
1……	……	……
2……	……	……
3……	……	……

2. **Are you worried about possible side effects of your medications?**

❑ No

❑ Yes

If yes, which side effects from which medication(s) do you worry about?

.....

3. **Do you use medication(s) for which you have doubts that they really work for you?**

❑ No

❑ Yes

If yes, for which medication(s)?

.....

4. **Did you forget to take one or more of your medications last month?**

❑ No

❑ Yes

If yes, how often and for which medication(s)?

.....

5. At what moments of the day you take your medication?

(*You can check multiple boxes*)

- ❑ Before breakfast
- ❑ During or after breakfast
- ❑ During or after lunch
- ❑ During or after diner
- ❑ Before bedtime
- ❑ As necessary
- ❑ Otherwise, namely.....

6. How do you take care not to forget your medication?

(*You can check multiple boxes*)

- ❑ Use on regular times, such as before or after a meal
- ❑ Pill box
- ❑ Pre-packed bags per day/ medication-roll (Baxter), from the pharmacy
- ❑ Alarm, phone reminder
- ❑ Help of partner or family member
- ❑ Help of home care or nurse
- ❑ None of the above
- ❑ Otherwise, namely.....

7. Did you, in the last month, intentionally skip or take less of a medication as prescribed?

- ❑ No
- ❑ Yes

If yes, which medication? And why did you skip or take less?

.....

8. Did you, in the last month, intentionally take more of a medication as prescribed?

- ❑ No
- ❑ Yes

If yes, which medication? And why did you take more?

.....

9. Did you, in the last month, stopped with a prescribed medication, without consulting the physician?

- ❑ No
- ❑ Yes

If yes, which medication? And why did you stop?

.....

10. Do you know for all your medications how to use it?

- ❑ No
- ❑ Yes

If no, what would you like to know?

.....

11. Do you ever have difficulties to use your medications as you physician prescribed?

(You can check multiple boxes)

- ❑ No
- ❑ Yes, because of the multitude of medications .....
- ❑ Yes, because one or more of the medications are not effective for me .....
- ❑ Yes, because I do not know why I take the medications .....
- ❑ Yes, because I experience side effects.....
- ❑ Yes, because I worry about possible side .....
- ❑ Yes, because I do not feel to take the medications .....
- ❑ Yes, because I forget to take the medications.....
- ❑ Yes, because I cannot oversee and differentiate between all the different medications.....
- ❑ Yes, due to other reasons, namely .....

12. Do you ever have practical issues to use your medications?

(*You can check multiple boxes*)

- ❑ No
- ❑ Yes, because I have troubles with the times of the day.....
- ❑ Yes, because I have difficulties with swallowing the tablet or capsule.....

- ❑ Yes, because I have difficulties with the medication strip or opening the package or bottle .....
- ❑ Yes, because I cannot read or understand the label on the medication package .....
- ❑ Yes, because the medication has a bad taste .....
- ❑ Yes, because I have difficulties to administer the medication(s) (e.g. inhaler, eye drops) .....
- ❑ Yes, due to other reasons, namely.....

13. **Do you have any additional comments, problems. questions, or preferences about your medications or health?**

.....
.....
.....
.....
.....
.....

4

Opti-Med: The effectiveness of optimised clinical medication reviews in older people with 'geriatric giants' in general practice; study protocol of a cluster randomised controlled trial

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Abstract

Background

Inappropriate drug use has been identified as one of the most important problems affecting the quality of care in older people. Inappropriate drug use may increase the risk of the occurrence of 'geriatric giants' such as immobility, instability, incontinence and cognitive impairment. There are indications that clinical medication reviews (CMR) can reduce inappropriate drug use. However, CMRs have not yet been implemented at a large scale in primary care. An innovative medication review program in primary care will be developed which tackles the most important obstacles for a large scale implementation of CMRs. The aim of this study is to assess whether this CMR program is (cost-) effective compared with usual general practice care for older patients with geriatric symptoms with regard to quality of life and geriatric symptoms.

Methods

A cluster randomised controlled trial will be performed in 20 Dutch general practices including 500 patients. Patients of 65 years and older are eligible if they newly present with pre-specified geriatric symptoms in general practice and chronic use of at least one prescribed drug. GP practices will be stratified by practice size and randomly allocated to control (n=10) or intervention group (n=10). The intervention consists of CMRs which will be facilitated and prepared by an expert team consisting of a GP and a pharmacist. Primary outcome measures are patient's quality of life and the presence of self-reported geriatric symptoms during a follow-up period of 6 months. Secondary outcomes are costs of healthcare utilisation, feasibility, number of drug related problems, medication adherence and satisfaction with medication.

Discussion

This study is expected to add evidence on the (cost-) effectiveness of an optimally facilitated, prepared and structured CMR in comparison with usual care in older patients who present a geriatric symptom to their GP. The strength of this study is that it will be conducted in daily clinical practice. This improves the possibilities to implement the CMRs in the primary care setting on a large scale.

Background

Inappropriate drug use has been identified as one of the most important problems affecting the quality of care in older people. Appropriate drug use and prescribing in older people is difficult, because of the variability of age-related changes in the metabolism, multimorbidity and polypharmacy.[1,2] In addition, undertreatment of especially preventive medication as well as poor treatment adherence are frequently occurring problems in older people.[3] Because of changes in pharmacokinetics and pharmacodynamics, older people are more prone to reduced effectiveness of drugs and they may be at higher risk of adverse events and other drug related problems (DRP).[4] Several studies have shown associations between inappropriate drug use and clinical outcomes such as hospital admissions, falling, adverse drug reactions and functional decline.[3,5-8]

Inappropriate drug use may increase the risk of the occurrence and persistence of geriatric problems.[3,5,6,9-15] The most common major impairments that appear in older people, also referred to as "geriatric giants" are immobility, instability, including falls and dizziness, incontinence and cognitive impairment.[16] The atypical, silent, non-specific disease presentation of a geriatric giant is a common type of symptom presentation in the older adult and associated with limitations of activities of daily living (ADL).[7] The multi-factorial causes of geriatric giants often include DRPs which can be prescriber-related (e.g. medically non-indicated medication or inappropriate dosage), but also patient-related, e.g. ineffectiveness of drugs, adverse effects, lack of knowledge and usage of the drugs, and non-adherence.[6]

There are indications that clinical medication reviews (CMR) can reduce inappropriate drug use in older people. A CMR is 'a structured, critical examination of the patient's medicines with the objective of reaching an agreement with the patient about treatment, optimising the impact of medicines, and minimising the number of drug related problems'.[17] It has been shown that specific subgroups can benefit from a CMR during or immediately after hospital admissions.[18,19] In several countries guidelines are developed for CMRs in older and polypharmacy patients.[17,20-22] However, CMRs have not yet been implemented at a large scale because of several obstacles.

First, the evidence for the effectiveness of CMRs is not very extensive and convincing. Several studies have shown positive effects of CMRs on intermediate outcomes such as the number of DRPs, medication adherence and patient satisfaction with medication. However, these effects are heterogeneous and so far, few effects have been established on clinical outcome measures as quality of life, hospital admissions or mortality.[23-26] This lack of evidence hinders the provision of financial incentives and motivation of healthcare professionals for further implementation of CMRs.

Second, the best target group for CMRs may be unclear. At present, patients in primary care are often selected based the number of medications, the polypharmacy criteria, which is a large group and not every polypharmacy patient may need a CMR. The current study addresses the appropriateness of medication use in patients who newly present themselves with "geriatric giant" symptoms in general practice. The patients will be selected irrespective of the number of drugs used. Previous research has shown that in many of these geriatric giants, suboptimal pharmacotherapy plays an important role in the occurrence and/or persistence of the problems. Undertreatment in these patients is just as often a problem as overtreatment.[27]

The third obstacle of CMR implementation is its feasibility. A CMR requires a considerable time investment for each review varying from 15 to 60 minutes for a physician and from 30 to 120 minutes for a pharmacist.[28] The current Dutch guideline for polypharmacy in older people recommends in addition to obtain the patient's input preferably by a home visit and follows the Systematic Tool to Reduce Inappropriate Prescribing (STRIP) method, which includes at least two patient contacts.[20,29] In addition, both lack of knowledge as well as insufficient training of both the GPs as well as the pharmacists hinder the implementation of CMRs. Finally the lack of comprehensive organisation of medical data infrastructure and exchange between professionals are hindering factors.

In this study an innovative CMR program (Opti-Med) will be developed to tackle these obstacles in a primary care setting. This Opti-Med study aims at providing scientific evidence for the effectiveness on quality of life and geriatric symptoms of an optimally facilitated, prepared and structured CMR in comparison with usual care in older patients presenting with a new geriatric

giant to their GP. The feasibility of implementing the program in the daily routine of several GP practices will be evaluated.

Methods

The Opti-Med study protocol was approved by the Medical Ethics Committee of the VU University Medical Centre Amsterdam (reference 2011/408). For the description of the design of the Opti-Med intervention, the Consolidated Standards of Reporting Trials (CONSORT) statement with extension to cluster randomised trials is followed.[30]

Study design

A cluster randomised clinical trial will be performed in 20 general practices including 500 patients (see figure 4.1). Allocation of the intervention and control condition will be carried out randomly at practice level. Eligible patients will be invited to participate in the study and the medication of the patients listed in the intervention practices will be reviewed. Patients listed in the control practices will receive usual care, with no systematic attention for their medication. The effects of this intervention will be assessed after a follow-up period of 6 months. The rationale to use a cluster design at practice level is to prevent contamination of structural attention to CMR activities within the GP practice.

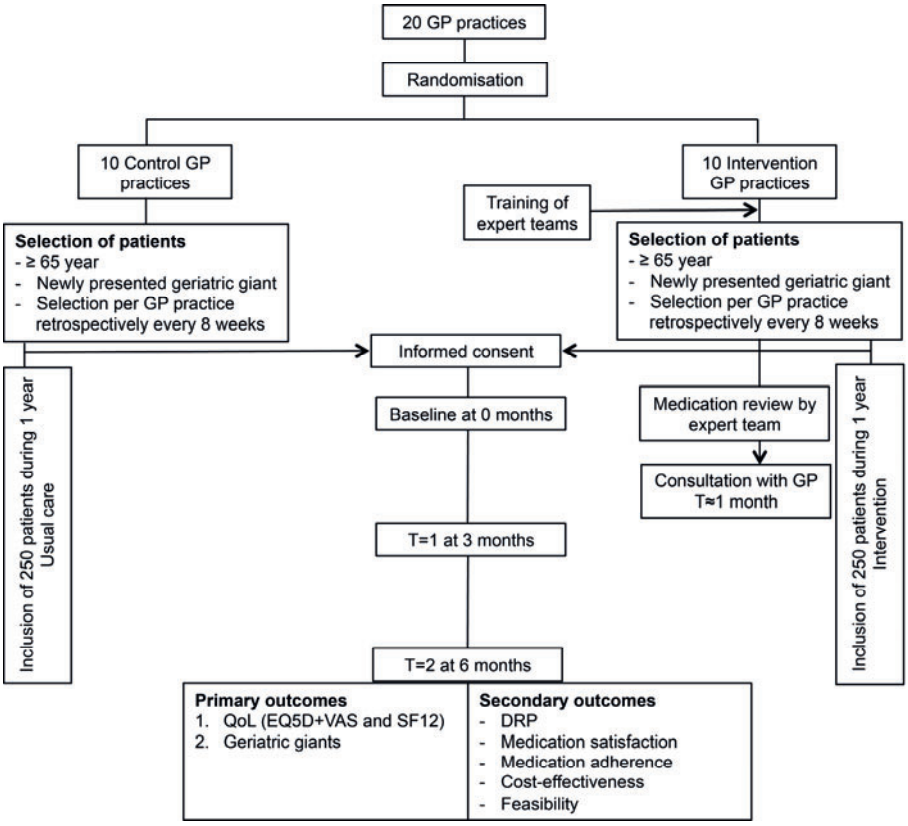

Figure 4.1 Study design of Opti-Med

Setting

The study will be embedded in the Academic Network of General Practices of the VU University Medical Centre (ANH-VUmc) that consists of 20 GP practices in Amsterdam, the Netherlands. Similar to almost all GPs in the Netherlands, the GPs in this network use electronic medical record systems in which all patients contact diagnoses are coded using the International Classification of Primary Care first edition (ICPC-1).[31] All practices employ practice nurses who can assist with the implementation of the intervention, have not yet systematically implemented structured CMR and are therefore eligible for this trial.

This CMR program is tuned to the Dutch healthcare setting where patients are listed with a general practice and their GP is the first contact point for a patient with healthcare problems. Only in case of emergency or after

referral by the GP, patients visit secondary care professionals. Moreover, in the Netherlands it is common to visit one main pharmacy which provides all prescription medication. As such, the pharmacist has the most accurate and complete medication data.

Randomisation

Randomisation will be performed by a statistician blinded to characteristics of the practices using a computer generated list of random numbers. The practices are stratified by practice size (two strata), to ensure equally sized groups. Before patients are recruited, participating practices will be randomly allocated to the intervention, or control condition. Patients will be allocated to either one of the treatment conditions, based on the practice where they are listed. Blinding of patients, GPs and practice nurses to treatment allocation is not possible due to the nature of the intervention.

Participants

Patients of 65 years and older are eligible if they newly present with a geriatric giant in general practice use at least one prescription drug chronically. A new geriatric giant is defined as being a first episode if the problem has not been noted in the patients' medical file during the previous 12 months. Patients with geriatric giants are identified on the basis of the ICPC coded diagnoses[31] (see Additional file 1) in their electronic medical record. Chronic use of at least one drug is defined as at least three prescriptions in the last 12 months in the GP practice. In The Netherlands, prescriptions are always for a maximum of three months of treatment.

Screening questionnaire

Together with the invitation for participation in the study, both intervention and control patients receive a screening questionnaire. The questionnaire consists of four parts:

I. Questions on the presence and self-perceived severity of geriatric giants using visual analogue scales (VAS) (0-10).The geriatric problems that are evaluated are 1. Mobility problem; 2. Dizziness; 3. Urinary incontinence; 4. Problems with cognition; 5. Fear of Falling[32]; Also a question is formulated regarding the number of falls in the previous 6 months.

II. Questions regarding body weight (kg), length (m) and pain (VAS 0-10);
III. Actual drug use including OTC drugs;
IV. Questionnaire aimed at the identification of DRPs from the patient perspective.

Part III and IV of the questionnaire are developed by the authors of this study and have been shown to have good agreement with a patient interview during a home visit.[33,34]

Inclusion procedure

For identifying potential participants in the practices a two-step approach will be applied.

Step 1. Eligible patients will be identified retrospectively every 8 weeks on the basis of a selected set of ICPC codes (see Supplementary Material I), age and chronic use of at least one drug, through a predefined search strategy in the GP electronic medical records. Only patients who consulted the GP with one of these diagnoses in this time period and who did not present with this problem to the GP during the previous 12 months are eligible to participate.

Step 2. Identified potential participants in step 1 will be invited to fill out the above described screening questionnaire. If needed, the patient will be offered support at home to fill out the screening questionnaire. Patients will be included in the trial if they indicate to currently have a score of five or higher on one of the VAS scales of the geriatric problems or have indicated to have one fall or more in the previous 6 months. Additionally they have to indicate that they are willing to participate in the trial by signing an informed consent form.

Exclusion criteria

Patients are not eligible when they have a diagnosis of dementia in their medical record. In addition, patients with a Mini Mental State Examination (MMSE) score of 18 or less will be excluded from the trial, since this is the cut off for serious cognitive impairment.[35,36] An MMSE interview is only carried out when patients indicated they needed help to fill out the screening questionnaire. Each 8 weeks, the GPs will receive a list of all eligible patients and they will exclude patients who received a structured CMR in the last 6

months or are according to the GP unable to participate (e.g. due to terminal illness or severe psychiatric problems).

Intervention

Preparatory steps

The research assistant prepares together with the practice nurse the CMRs for the expert teams (see below). The required information from the electronic medical files from the GP practice, the pharmacy and the screening questionnaire is collected. This information consists of the actual drug use of the patient including OTC drugs, drug delivery history, potential DRPs, the medical problems of the patient, laboratory test results, e.g. renal function and other measurements such as blood pressure.

Clinical medication review by expert team

An expert team consisting of a GP (not the patient's GP) and a pharmacist (not the patient's pharmacist) will review the medication. The team will carry out a systematic assessment aimed at identifying drug related problems (DRP) experienced by the patient as indicated in the screening questionnaire and at optimising the medication of the patient. The medication will be structurally reviewed according to the Dutch Systematic Tool to Reduce Inappropriate Prescribing (STRIP) method including the translated Screening Tool of Older Person's Prescriptions (STOPP) and Screening Tool to Alert doctors to Right Treatment (START) criteria.[20,29] A computer assisted version of the STRIP method, the STRIP-assistant will be used by the team.[37] First, the medications are linked to the diseases or symptoms. Then the following steps will be systematically followed:

1. Undertreatment
2. Effectiveness of treatment
3. Overtreatment
4. Potential adverse events
5. Interactions and contra-indications
6. Dosing problems
7. Other problems, such as user problems, knowledge or adherence

Finally, the result of this CMR analysis is a pharmacotherapeutic treatment plan that will be sent to the patient's GP (see Supplementary Material II) Three expert teams will be formed for the Opti-Med study.

Implementing the pharmacotherapeutic treatment plan
Patients will be invited for a consultation with the GP in which both the pharmacotherapeutic treatment plan and the patient's perspective as previously assessed with the screening questionnaire are discussed and definitive changes in the prescribed medication will be implemented.

Monitoring the medication use
Six months after inclusion a check will be carried out by the researchers to identify medication changes compared to the outcome of the CMR (intervention group) and/or compared to baseline drug use of all participating patients. The patients' GPs will receive a signal if new DRPs are identified. The follow-up of this signal is outside the scope of this study.

Training
Expert teams will follow accredited online courses for medication reviews and pharmacology in elderly and two medication review workshops. Participating GPs and practice nurses of the intervention practices will be instructed how to carry out the study protocol and will receive a handbook.

Control condition
Eligible patients who are listed in a control practice will be identified and selected in exactly the same manner as in the intervention group. They will be asked to give informed consent and to fill in the same questionnaires at inclusion, baseline, 3 and 6 months. Patients in control practices receive usual care, which means that no structured attention will be paid to their medication.

Outcome measures
Measurements by means of patient questionnaires and proxy assessments will be carried out at baseline, after 3 and 6 months It is expected that some patients will develop either cognitive problems or other difficulties precluding

that they fill out the questionnaires adequately during the study. Self-assessment in these patients might therefore be less reliable or become not feasible. Proxy assessment could be a substitute for self-assessment of quality of life.[38] Therefore, patients will be asked to indicate two proxies: an informal care giver and a professional care giver who will fill out a proxy assessment questionnaire of the patient's quality of life. Data on morbidity and laboratory test results will be collected using medical records in the GP practices. Characteristics of medication, changes in medication and adherence to medication will be assessed using dispensing data from the patient's pharmacist. All outcomes will be assessed at patient level.

Primary outcome measures

Quality of life (QoL) will be assessed using both the SF-12 and the EuroQol (EQ-5D-3L) at baseline, and after 3 and 6 months. The SF-12 covers eight dimensions of health with two summary scores; physical health (PHS) and mental health (MHS), and has been validated in many different countries and populations.[39-42] The PHS will be used as outcome measure because of its superior responsiveness compared to the MHS.[43] The EQ-5D-3L is a generic preference based health status measure that has been shown to be valid and reliable in a variety of populations and patient groups.[44,45] The EQ-5D-3L will be assessed using information from the patient and by proxy assessment by an informal carer and a healthcare professional. The proxies will be asked to report on QoL from the patients' perspective.[46] The EQ-5D scores will be used to calculate utilities using the Dutch tariffs. Quality-adjusted life years (QALYs) will be calculated using linear interpolation between time points. Higher QALY scores indicate more improvement in quality of life.[47]

The presence of geriatric giants will be assessed at baseline with the screening questionnaire. At 3 and 6 months, presence of geriatric giants will be assessed with the same questions as in the screening questionnaire enabling to assess changes compared to baseline.

Secondary outcome measures

The prevalence of DRPs in patients will be determined at baseline and after 6 months in both groups. The 6 month questionnaire will be similar to the screening questionnaire omitting questions that only need to be asked at the

beginning of the study. An independent clinical pharmacologist and GP will assess the DRPs on the basis of the screening questionnaire and the pharmacist's medication overview using the DOCUMENT checklist.[48] DOCUMENT stands for Drug selection, Over- or underdose prescribed, Compliance, Untreated indications, Monitoring, Education or information, Non-clinical and Toxicity or adverse reaction and has multiple subcategories.

Research suggests that greater treatment satisfaction is associated with better compliance.[49] Patient satisfaction about medication in general will be assessed by the single-item Medication Satisfaction Questionnaire (MSQ) "Overall, how satisfied or dissatisfied are you with your current medication?" with a written response assessed on a seven point Likert like scale at baseline, 3 and 6 months.[50]

Medication adherence will be measured in two ways; 1. Check for at least one pharmacy delivery in the last six months for all chronically used medication and 2. Self-reported adherence as questioned in the screening and follow-up questionnaires at baseline and 6 months. Self-reported adherence is part of the developed screening questionnaire.

Costs will be measured from a societal perspective. To calculate the costs of the intervention, information will be recorded by the expert team, the GP, the pharmacist and the practice nurse in terms of time and material spent on performing the CMR and the monitoring of the patients. Healthcare costs made by the patient will be assessed from a societal perspective using an slightly adapted version of the Dutch Medical Consumption Questionnaire (*i*MTA) questionnaire on care consumption, including informal care after 3 months (t=1) and after 6 months.[51] Information on prescribed medication will be derived from the pharmacy administration information system (PAIS). Lost productivity costs will not be included since almost all patients will be retired. Healthcare utilisation will be valued according to guidelines for economic evaluation in healthcare in the Netherlands.[52]

Pilot study

Based on the experiences of two small pilot innovation programs, the intervention program was developed. [[33] and unpublished results Elders and Bleeker 2009] An Opti-Med pilot study was conducted in two intervention and two control practices for eight weeks including 10 patients. An evaluation was

conducted to test the logistics, baseline measurements, questionnaires, and the feasibility and functioning of the expert team of the study. The pilot study resulted in minor changes in the questionnaire instructions, improvements in logistics and communication with the GP practices.

Process analysis

The process evaluation involves assessing the extent to which the intervention is performed according to the protocol of the study, the time that is spent by the professionals to perform the activities of the protocol, the nature of the recommendations made to the patients by the GP, compliance with these recommendations, the judgment of the GPs, pharmacists and practice nurses about the intervention program. Data on these topics are collected using structured registration forms during the intervention. In addition, semi-structured interviews will be held with the participating practice nurses, GPs and members of the expert teams at the end of the intervention period in order to record their experiences and opinions on the CMR program. The presence and influence of possible contamination in both intervention and control practices will also be assessed by interviewing GPs or practice nurses at the end of the trial on their opinions to what degree structured attention to medication was an issue during the study period in general or with regard to specific patients.

Sample size

The size of the study groups is based on the difference in change over 6 months between the intervention and control group of the EQ-5D VAS score (score range 0-100). A difference of 7.4 in the EQ-5D VAS is considered as a clinically relevant difference.[53] The average score among persons with osteoarthritis, a comparable group, is 64.8 (standard deviation 26.5). To establish a difference of 7.4 points as statistically significant with alpha=0.05 and beta=0.20, a group size of 225 is sufficient, taking the clustered design into account. To adjust for loss to follow up of 10% we will include 500 patients.

Statistical analyses

Descriptive statistics will be used to describe the study population. Dropout and loss to follow up will be described. Effect analyses will be performed

according to both 'intention to treat' and per protocol principles. Differences between intervention and usual care patients on the outcome measures will be compared between the intervention and control group by both univariate and multivariate techniques. Multilevel linear and logistic regression analyses will be performed to study differences between the intervention and the control patients. Multilevel analysis is needed in order to take clustering on the GP level and repeated measurements in one patient into account. We will adjust for possible confounders, such as gender, age, education level, number of medications and multi-morbidity.

Possible future subgroup analyses will be exploratory, due to lack of power.

Economic evaluation

For the economic evaluation, missing cost and effect data will be imputed using multiple imputation according to the Multivariate Imputation by Chained Equations (MICE) algorithm developed by van Buuren using predictive mean matching and fully conditional specification.[54] The number of imputed datasets will be increased until the fraction of missing information is below 5%.[55] The imputed datasets will be analysed separately as described below and subsequently pooled using Rubin's rules.

The effect measures that will be taken into account in the cost-effectiveness are QALYs, and changes in the VAS scores of the geriatric giant symptoms. For effects and costs, linear multilevel regression models will be estimated. Clustering at the level of GP practice will be included in these multilevel models. Incremental cost-effectiveness ratios (ICERs) will be calculated by dividing the difference in mean total costs between the treatment and control groups by the difference in mean effects between the groups. Costs generally have a highly skewed distribution; therefore, bootstrapping with 5,000 replications will be used to estimate bias-corrected and accelerated confidence intervals around cost differences.[56] To account for the clustering of data, bootstrap replications will be stratified for practice.[57] The uncertainty surrounding the ICERs which will be graphically presented on cost-effectiveness planes. Cost-effectiveness acceptability curves and net monetary benefits will also be calculated. Cost-effectiveness acceptability curves show the probability that the medication review programme is cost-

effective in comparison with usual care for a range of different ceiling ratios thereby showing decision uncertainty.

Discussion

This study is expected to add evidence on the effectiveness and cost-effectiveness of an optimally facilitated, prepared and structured CMR in comparison with usual care in older patients presenting with a geriatric giant to their GP.

Geriatric giants are highly prevalent among older people and represent a major cause of impaired quality of life. Optimising the patient's medication in addition to treating these geriatric problems or delaying their worsening by treatment, is expected to have a positive additional impact on the patient's perceived health. Moreover, optimising drug use will also improve the effectiveness of drug treatment, prevent adverse drug reactions and potentially harmful drug interactions, and consequently hospital admissions or even death.

For healthcare professionals, handling DRPs in older people is a challenge. The burden of aging on the healthcare sector, care efficiency is an important issue.

The streamlining of the process, the experienced expert teams and minimising the contact moments with the patients due to the written questionnaire as proposed in this study increases the feasibility that CMRs can be implemented successfully in usual care. In practice, after this study, expert teams could be implemented in a GP cooperation or another regional care settings in which pharmacists and GPs should be trained and form expert groups.

The strength of this study is that it will be conducted in daily clinical practice and will resemble daily clinical practice as much as possible. This improves the possibilities to implement CMRs in the primary care setting.

The most important innovations compared to previous programs are:

1. The CMR will not focus primarily on polypharmacy patients, instead the selection of older patients is based on episodes related to a geriatric giant.

2. The CMR is prepared by a trained expert team consisting of an external GP and an external pharmacist who formulate a pharmacotherapeutic treatment plan for the patient's GP;
3. The coordination of the CMR at the primary care level is performed by a case manager, usually the practice nurse or assistant.
4. The number of contacts with the patient is reduced by assessing the patient's perspective by a written questionnaire instead of a home visit.

Quality of life is the primary outcome measure. This may not be sensitive enough to capture the changes induced by the intervention. However, we have chosen to use generic health measures as primary outcome measures because we include patients in this study that might have a variety of geriatric symptoms with a heterogeneous treatment effect. Also we think that in this population quality of life is the most important outcome.

In addition, the study is not blinded and there is a possibility of contamination between the intervention and control group. We counter possible contamination between treatments groups by using a cluster randomised controlled design. That way, caregivers cannot unintentionally apply aspects of the Opti-Med study into their usual care for patients. Patients in the control condition also fill out the screening questionnaire on actual drug use and medication related problems, this is needed for the study, but could underestimate the effectiveness of Opti-Med by increasing awareness of possible drug related problems in these control participants. Furthermore, we suppose that current activities on older people care and possible future pharmacist's polypharmacy projects are minimally interfering with the study. This assumption about possible contamination will be checked during the process analysis.

Implementation of structured CMR and monitoring will raise the awareness about the importance of optimising medication use in general, and especially in older patients among healthcare professionals. In this study, we will evaluate a form of a structured CMR that can easily be implemented in a GP cooperation or care group. If the CMR is shown (cost-) effective and feasible it could also be extrapolated to other groups of patients in the future in whom inappropriate medication use is suspected as well. If proven cost-effective, this

will support the nationwide implementation of this structured approach. The first results of the study will be expected at the end of 2015.

Competing interests

F. Willeboordse reports a governmental grant from the Dutch Organisation for Health Research and Development (ZonMw), for the conduct of the study. Dr. L. van Dijk reports grants from BMS/Pfizer and Astra Zeneca, outside the submitted work. All other authors declared no conflicts of interest.

Authors' contributions

FW constructed the design of the study and drafted the manuscript. JH, PE and FS developed the study, constructed the design and revised the manuscript. LvD, JB and OdV participated in the design of the study and revised the manuscript. All authors read and approved the final manuscript.

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Supplementary Material I. ICPC codes for the selection patients with geriatric giants in the Opti-Med study

Category	Code	Description
General	A05	Feeling ill
Instability / immobility	A06	Fainting/syncope
	A10	Bleeding-haemorrhage not otherwise specified
	A28	Limited function/disability not otherwise specified
	A80	Trauma/injury not otherwise specified
	H82	Vertiginous syndrome / labyrinthitis
	K88	Postural hypotension
	L02	Back symptom/complaint
	L03	Low back symptom/complaint without radiating pain
	L13	Hip symptom/complaint
	L14	Leg/thigh symptom/complaint
	L15	Knee symptom/complaint
	L16	Ankle symptom/complaint
	L17	Foot/toe symptom/complaint
	L28	Limited function/disability
	L72	Fracture: radius/ulna
	L73	Fracture: tibia/fibula
	L74	Fracture: hand/foot bone
	L75	Fracture: femur
	L76	Fracture: other
	L77	Sprain/strain of ankle
	L78	Sprain/strain of knee
	L79	Sprain/strain of joint not otherwise specified
	L80	Dislocation/subluxation
	L81	Injury musculoskeletal not otherwise specified
	L86	Low back symptom/complaint with radiating pain
	L96	Acute internal damage knee

-Table continues -

- Table continued -

Category	Code	Description
Instability / immobility *(continued)*	N17	Vertigo/dizziness
	N18	Paralysis/weakness
	N79	Concussion
	N80	Head injury other
	S16	Bruise/contusion
	S17	Abrasion/scratch/blister
	S18	Laceration/cut
	S19	Skin injury other
Cognitive impairment	P20	Memory / concentration / orientation disturbance
	P71	Organic psychosis other
	P73	Affective psychosis
	P01	Feeling anxious/nervous/tense
	P03	Feeling depressed
	P05	Senility, feeling/behaving old
	P74	Anxiety disorder/anxiety state
	P76	Depressive disorder
Urine incontinence	U04	Incontinence urine

Supplementary Material II. Format Pharmacotherapeutic Treatment Plan Opti-Med

Pharmacotherapeutic Treatment Plan Opti-Med		
Date consultation		
Name GP		
Time investment (incl. preparation)	Minutes | Home visit: YES / NO	

Name patient:	**Date of birth:**	**Follow-up number (Opti-Med):**
Medicationreview date:	**Medication review executed by team no:**	**GP practice:**
Geriatric giant(s):		
Diseases and symptoms based on ICPC	**New medication list *(new items are bold)***	**Problems/questions/signals from patient:**

- Table continues -

- Table continued –

Pharmacotherapeutic Treatment Plan Opti-Med	
Date consultation	
Name GP	
Time investment (incl. preparation)	Minutes | Home visit: YES / NO

Priority	**No**	**Proposed changes/advices**	**Explanation / reason:**	**Follow up? Yes/No/NA + explain:**
		Start:		**YES/NO/NA**
		Stop:		**YES/NO/NA**
		Changes (frequency, dosing):		**YES/NO/NA**
		Ask/discuss with patient:		**YES/NO/NA**
		Additional laboratory results/physical assessment:		**YES/NO/NA**
		Other advice:		**YES/NO/NA**
Other changes (related to the medication regime) by GP?				

FINALLY:

- Communicate all changes with the local pharmacy
- When needed, provide the patient with written information on changes in medication

5

The effectiveness of optimised clinical medication reviews for geriatric patients: Opti-Med a cluster randomised controlled trial

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Abstract

Background

Inappropriate drug use is a frequent problem in older patients and associated with adverse clinical outcomes and an important determinant of geriatric problems. Clinical medication reviews (CMR) may reduce inappropriate drug use.

Objective

The aim of this study is to investigate the effectiveness of CMR on quality of life (QoL) and geriatric problems in comparison with usual care in older patients with geriatric problems in the general practice.

Methods

We performed a cluster randomised controlled trial in 22 Dutch general practices. Patients of ≥65 years were eligible if they newly presented with pre-specified geriatric symptoms in general practice and the chronic use of ≥1 prescribed drug. The intervention consisted of CMRs which were prepared by an independent expert team and discussed with the patient by the general practitioner. Primary outcomes: QoL and the presence of self-reported geriatric problems after a follow-up period of 6 months.

Results

518 patients were included. No significant differences between the intervention and control group and over time were found for QoL, geriatric problems, satisfaction with medication and self-reported medication adherence. After six months the percentage of solved Drug Related Problems (DRPs) was significantly higher in the intervention group compared to the control group [B 22.6 (95% CI 14.1-31.1), p <0.001].

Conclusion

The study intervention did not influence QoL and geriatric problems. The higher percentage of solved DRPs in the intervention group did not result in

effects on the patient's health. CMRs on a large scale seem not meaningful and should be reconsidered.

Background

Inappropriate drug use is a frequent problem in older patients. It is influenced by patient, prescriber, healthcare provider and system related factors[1] and is associated with adverse clinical outcomes such as functional decline, falling, adverse drug reactions, and hospital admissions. This has a negative impact on quality of life (QoL)[2-4] and may also increase the risk of the occurrence and persistence of the most common major impairments that appear in older people , also referred to as "geriatric giants", such as immobility, instability, incontinence and cognitive impairment.[5-9]

Clinical medication reviews (CMRs) may reduce inappropriate drug use. A CMR is a structured, critical examination of the patient's medicines with the objective of reaching an agreement with the patient about treatment, optimising the impact of medicines, minimizing the number of drug related problems (DRPs) and reducing waste.[10] Several studies have shown positive effects of CMRs on intermediate outcomes such as DRPs, medication adherence and knowledge. Although cost reduction might be an important motivation to CMRs, patient related effects are the most important. However, few effects have been established on clinical outcomes such as QoL, hospital admissions or mortality.[11]

At present, CMRs have not yet been fully implemented because of lack of evidence for effectiveness and doubts about the target group who are assumed to benefit most. The feasibility in clinical practice and the consumption of time are barriers for implementation.[12]

This study addresses the effects of CMRs on quality of life and geriatric problems in patients who newly present with geriatric problems in general practice, including immobility, instability, incontinence and impaired cognition, who use ≥1 drug chronically. Inappropriate drug use is considered an important determinant of geriatric problems and primary care is usually problem-oriented. We used a structured program for CMR, that was designed to increase the feasibility of CMRs in primary care.[13] In this paper we report on

the effects of CMRs on QoL and geriatric problems in comparison with usual care. A process evaluation of the intervention and a cost-effectiveness evaluation will be published separately.

Methods

Study design and setting

We performed a cluster randomised clinical trial in 22 general practices (mean 3,890 listed patients) in Amsterdam, The Netherlands. The rationale to use a cluster design at practice level was to prevent contamination of structural attention to CMR activities within the GP practice. Non-institutionalised Dutch inhabitants are obligatory listed at a general practice and most patients are registered with one community pharmacy. We included participants between November 2013 and February 2015 and followed them for 6 months. Randomisation of the intervention and control condition was carried out at practice level and was done before the patients were recruited. Randomisation was performed by a statistician blinded to characteristics of the practices using a computer generated list of random numbers. The practices were stratified by practice size (two strata), to ensure equally sized groups. Blinding to treatment allocation was not possible due to the nature of the intervention. The study protocol has been described elsewhere.[13]

Practices

All 22 participating GP practices were member of the Academic Network Of General Practitioners of the VUmc Medical Centre. When the study started, most GP's used a electronical medical record system that warned for medication interactions. Pharmacies that filled the prescriptions would also check for interactions only. The inclusion criterion was that the practice was not performing CMRs on a regular basis and would not start doing so if randomized in the control group. All approached practices were willing to participate.

Study participants

Patients ≥65 years were eligible if they newly presented with a geriatric problem in general practice and used ≥1 prescribed drug chronically (i.e. ≥ 3 months). Patients with geriatric problems were identified based on ICPC coded diagnoses in their primary care electronic medical record (EMR) by an automated search strategy and an additional screening questionnaire. This questionnaire included questions on geriatric problems, actual medication use and DRPs. The geriatric problems included mobility problems, dizziness, fear of falling, falls, urinary incontinence and cognitive impairment. Patients were included if they scored ≥5 on the VAS scales (range 1-10) of the geriatric problems or reported ≥1 fall in the preceding 6 months.

We excluded those with a recorded dementia diagnosis and the GP excluded patients who had a recent CMR or were deemed unable to participate. All participants returned an informed consent form together with the screening questionnaire.

Intervention

The intervention consisted of the following components:

1. *Preparation:* Information from EMRs, the pharmacy and a screening questionnaire was collected, including the actual drug use of the patient, medication history, potential DRPs, the medical problems of the patient, recent laboratory test results and non-laboratory measurements. The questionnaire showed good agreement with a patient interview.[14]
2. *Clinical medication review:* Four trained independent expert teams consisting of a GP or nursing home physician and a community pharmacist performed the CMR analysis. They performed the medication review according to the adapted Systematic Tool to Reduce Inappropriate Prescribing (STRIP) method including the Screening Tool of Older Person's Prescriptions (STOPP) and Screening Tool to Alert doctors to Right Treatment (START) criteria.[15] A computerised version of STRIP, the STRIP-assistant was used.[16]
3. *Pharmacotherapeutic treatment plan (PTP):* The expert team made a PTP which was sent to the patient's GP by fax or encrypted e-mail.

4. *Implementation of the PTP:* Patients were invited for a consultation with their GP in which the PTP was discussed and determined together with the patient. Changes in the medication were implemented usually by electronic communication from the practice to the pharmacy.

Usual care

The patients in control practices were identically selected as in the intervention practices but only received usual care. The expert teams also performed CMR analyses for control patients, but the GPs and patients did not receive the results.

Outcome measures

Measurements were administered at baseline, after 3 and 6 months through patient questionnaires. We chose the two most generally used generic measures for Qol: SF-12 and the EuroQol (EQ-5D-3L) and the presence and severity of geriatric problems. This was assessed with questions on the presence and self-perceived severity of geriatric problems using VAS (1-10). The primary geriatric problem per patient and two dichotomous outcome measures were defined (figure 5.1).

The number of DRPs per patient was determined at baseline and the number of solved DRPs after 6 months. Contrary to the study protocol **(**due to capacity problems) only one researcher (FW), rather than an independent expert team, only one categorised the DRPs after 6 months based on the results of the CMR analyses by the expert team using the DOCUMENT checklist[17] and the EMR information. In case of doubt this was discussed with another researcher (JH).

Patient satisfaction about medication was assessed by the single-item Medication Satisfaction Questionnaire (MSQ) on a 7-point Likert scale at baseline, 3 and 6 months. The MSQ has acceptable reliability and validity. A 1-point change on the MSQ score was considered clinically meaningful.[18]

Self-reported medication adherence was measured in the screening and follow-up questionnaires after 6 months.

Definition primary geriatric problem based on decision rules:
1. Two or more falls in the previous 6 months
2. Highest VAS for the geriatric problems Dizziness, Mobility, Cognition problems or Incontinence. When equal VAS:
    1. Check with EMR for matching ICPC code for identification
    2. Dizziness>Mobility>Cognition problems>Incontinence
3. One fall in the previous 6 months
4. Fear of falling

The geriatric problem outcome measure was operationalised in two ways (dichotomous);
1. improvement versus worsening or stabilization of the primary geriatric problem
    - A difference after 6 months of two or more points on the VAS was considered as either an improvement or worsening.
    - For falls an improvement or worsening was absolutely more or less falls in the previous 6 months (T1 and T2 combined).

2.'Resolved' geriatric problem: Absence of the geriatric problem versus the presence of the primary geriatric problem;
    - Resolved: Absence of the primary geriatric problem is defined as a VAS of two or less after 6 months or no falls in the previous 6 months
    - Unsolved: Presence of the primary geriatric problem is a VAS or three or more after 6 months or at least one fall.

Figure 5.1 Definition and operationalization of geriatric problems outcome measure based on the information in the patient questionnaires.

Sample size

A sample size calculation, as described in the study protocol, was performed based on a clinically relevant change of 7.4 in the EQ-5D VAS (score range 0-100).[19] Two groups of 225 patients were required.[13]

Statistical analyses

We used descriptive statistics to describe the patient characteristics and compared baseline values between study groups using independent sample t-tests, chi-squared tests and Mann-Whitney-U tests. We performed effect analyses according to the 'intention to treat' principle. Multilevel linear and logistic regression analyses were performed to establish differences between the intervention and the control group taking clustering on the GP level and repeated measurements in patients into account Imputation methods for missing data were not applied, because this is not needed in multi-level analyses as the total number of missings was low (max 15%). Fixed effects were time (baseline, 3 and 6 months) and the study group x time interaction. We assumed a random intercept for the second level (patients). Adjustment for baseline values was done by retaining baseline as part of the outcome vector and by assuming that the group means are equal at baseline, as appropriate in

RCTs.[20] Regression coefficients and odds ratios are shown adjusted for baseline and adjusted for baseline and number of chronic diseases, because this number differed significantly between intervention and control group.

The addition of the GP as third level variable and the interaction of the different expert teams were analysed. For DRPs solved after six months a linear multilevel regression analyses was performed with a random intercept at the second level and a random slope for the number of DRPs at baseline. Residuals were checked for normal distribution.

Two per protocol analyses were performed; 1. all intervention patients that had a consultation with the GP and 2. all intervention patients that had the consultation within 1.5 months. We also performed subgroup analyses for polypharmacy patients and for each geriatric problem separately.

The data was analysed using IBM SPSS statistics version 22 software and MLWIN v2.28 for the multilevel analyses.

Results

Baseline characteristics

Figure 5.2 provides an overview of randomisation, recruitment and follow-up. In total 518 patients were included. Apart from more frequent use of multidose dispensing systems, more chronic diseases and DRP's there were no significant differences for patient characteristics between intervention and control group at baseline. (table 5.1) The distribution of DRP types did not differ between the two groups, with the most frequent DRPs being drug selection and undertreatment. (table 5.2)

Fifty nine GP's worked in the 22 practices. There were no significant differences between the intervention and control practices for practice and GP characteristics (practice size, number of GPs, gender and years of working experience).

Table 5.1 Patient characteristics of the participants at baseline of the Opti-Med study

Demographic characteristics	Intervention	Usual care	Total	p-value
Number of participants	275	243	518	
Women n (%)	177 (64.4)	159 (65.4)	336 (64.9)	0.80
Age, mean (sd) [range]	77.8 (7.7)	77.8 (8.0)	77.7 (7.9) [65-102]	0.94
≥80 year,%	38.8	40.6	39.6	0.67
≥90 year,%	5.8	7.4	6.5	0.47
Country of Birth				0.43
Dutch and other European,%	91.7	93.6	92.6	
Non-Western,%	8.3	6.4	7.4	
Education level[1]				0.25
Low, %	26.6	20.5	23.7	
Middle, %	44.9	46.6	45.7	
High, %	28.5	32.9	30.6	
Living situation				0.60
Alone, %	59.4	57.1	58.3	
Together, %	40.6	42.9	41.7	
Health characteristics	**Intervention**	**Usual care**	**Total**	**p-value**
EQ-5D-3L utility, mean (sd)	0.72 (0.22)	0.75 (0.20)	0.73 (0.21)	0.15
EQ5D VAS (0-100), mean (sd)	68.5 (15.6)	68.5 (14.5)	68.5 (15.1)	0.93
SF12 PCS, mean (sd)	47.9 (24.0)	47.2 (25.7)	47.6 (24.8)	0.76
SF12 MCS, mean (sd)	63.4 (23.1)	64.0 (22.6)	63.7 (22.9)	0.78
Mean chronic diseases (sd)[2]	2.77 (1.76)	3.23 (2.19)	2.99 (1.98)	**0.01**
≥2 chronic diseases[2], %	73.8	78.6	76.1	0.20
≥3 chronic diseases[2], %	48.4	53.9	51.0	0.21
≥4 chronic diseases[2], %	30.9	41.6	35.9	**0.01**
≥5 chronic diseases[2], %	17.5	26.7	21.8	**0.01**
BMI, mean (sd)	26.7 (5.4)	26.8 (5.4)	26.7 (5.4)	0.86
Pain VAS (0-10), mean (sd)	3.7 (3.0)	3.6 (2.9)	3.7 (3.0)	0.82

- Table 5.1 continues –

- Table 5.1 continued –

Geriatric problems	**Intervention**	**Usual care**	**Total**	**p-value**
Mobility problems, % ≥5 VAS	57.9	62.6	60.1	0.28
Falling				0.70
% ≥1 times last 6 months	33.9	33.3	33.7	-
% ≥2 times last 6 months	17.4	20.1	18.7	-
Fear of falling, % ≥5 VAS	36.6	41.2	38.7	0.29
Dizziness, % ≥5 VAS	17.2	15.8	16.5	0.67
Incontinence, % ≥5 VAS	22.9	25.2	24.0	0.54
Cognition problems, % ≥5 VAS	25.5	26.9	26.1	0.72
≥ 2 geriatric problems, %	56.5	61.3	58.8	0.27
≥ 3 geriatric problems, %	32.3	35.7	33.9	0.54
Primary geriatric problems	**Intervention**	**Usual care**	**Total**	**p-value**
Mobility**, %,** mean VAS (sd)	41.4 [7.1 (1.7)]	37.3 [7.1 (1.6)]	39.2 [7.1 (1.7)]	
Falling ≥1 times last 6 months, **%**	18.5	12.8	15.8	
Falling ≥2 times last 6 months, %	17.4	20.1	18.7	
Fear of falling**, %,** mean VAS (sd)	1.6 [6.4 (1.8)]	2.9 [5.5 (1.0)]	2.3 [6.1 (1.6)]	
Dizziness**, %,** mean VAS (sd)	6.5 [7.1 (1.7)]	4.9 [7.1 (1.9)]	5.8 [7.1 (1.7)]	
Incontinence**, %,** mean VAS (sd)	8.7 [7.8 (1.7)]	9.8 [7.0 (1.4)]	9.2 [7.4 (1.6)]	
Cognitive problems**, %,** mean VAS (sd)	9.0 [6.8 (1.4)]	8.7 [6.1 (1.2)]	8.8 [6.5 (1.3)]	

- Table 5.1 continues –

- Table 5.1 continued –

Medication characteristics	Intervention	Usual care	Total	p-value
No of drugs in pharmacy records, mean (sd)	6.2 (3.2)	5.8 (3.3)	6.0 (3.2)	0.22
No of drugs reported by patient, mean (sd)	6.1 (3.1)	5.6 (3.2)	5.9 (3.2)	0.12
No of chronic drugs GP EMR, mean (sd)	5.6 (3.4)	5.5 (3.2)	5.6 (3.3)	0.74
Polypharmacy %[3]	58.0	55.7	56.9	0.60
OTC medication use %	81.3	83.1	82.1	0.62
Multidose drug dispensing system use %	13.0	7.0	10.2	**0.02**
Self-reported adverse event %	28.7	19.9	24.6	**0.02**
Adherence problems %	34.8	29.1	32.2	0.17
Effectiveness problems %	18.8	16.6	17.8	0.51
User or practical problems %	23.5	21.3	22.5	0.54
MSQ score (1-7)[4], mean (sd)	5.4 (0.9)	5.3 (0.9)	5.3 (0.9)	0.43

P values <0.05 in bold are considered statistically significant

BMI= Body Mass Index; EMR=Electronic Medical Record; MSQ=Medication Satisfaction Questionnaire ; NA=Not Applicable; OTC= Over The Counter; SF-12= Short Form 12-item health survey; SF12-Physical Health Summary Scales; SF-12 MCS = SF12 Mental Health Summary Scales ;

[1] low education level: No education, primary education or first stage of basic education; middle education level: Lower secondary education or second stage of basic education; high education level: Upper secondary education or higher

[2.] Chronic diseases according to set list of 29 diseases[21]

[3] Definition of polypharmacy is the use of ≥5 indicated for the treatment of a chronic disease at the ATC-5 level in in the four months preceding baseline. ATC codes were derived from prescription data from the EMR records. Excluded were anti-infectives (ATC-class J,G01,S01A,C,S02A,C), topical products (ATC-class M02 and dermatologicals (ATC-class D) and preparations for sensory organs, except drugs intended for long-term use were included (ATC-class S01E,F,G)

[4] Range is 1 (extremely dissatisfied) to 7 (extremely satisfied) with all medications in general.[18]

Table 5.2 Drug Related problems identified by the expert team at baseline according to the DOCUMENT classification.

	Intervention	Usual care	Total	p-value
DOCUMENT DRP Category				0.44
Drug selection, %	38.6	37.0	37.9	
Over or underdose prescribed, %	8.0	9.9	8.8	
Compliance, %	3.8	3.1	3.5	
Un(der)treated indications, %	28.5	29.0	28.7	
Monitoring, %	11.9	13.8	12.7	
Education or Information, %	3.2	2.1	2.7	
Not classifiable, %	1.4	1.5	1.5	
Toxicity or ADR, %	4.5	3.7	4.1	
Total number of DRPs, mean (sd)	4.4 (1.9)	3.7 (1.9)	4.1 (2.0)	**<0.01**
Total number of DRPs, median (IQR)	4 (3-5)	4 (2-5)	4 (2-5)	**<0.01**

ADR= Adverse Drug Reaction; DRP= Drug Related Problem; IQR-Inter Quartile Range

DRPs were identified by the expert team at baseline and classified by the researchers according to the validated DOCUMENT classification system to categorize DRPs into 8 categories[17]

Declined to participate and non-responders

378 (18.6%) subjects declined to participate. They did not differ in age from participants, but among them were significantly fewer women (p=0.02) and they used fewer drugs (p<0.001). Indicated reasons for non-participation included no interest or no time, older age, health problems or the patient deemed the CMR not useful. Age and gender of the non-responders (n=840) were similar to the participants.

Performed intervention

A CMR was performed for 274 of 275 participants in the intervention group (one drop-out before expert team started). N=247 (90%) of the CMR's were discussed with the patient. The median (IQR) number of days between inclusion and the consultation was 33.0 (15-51) days and 42% of the patients had their consultation within the planned one month after inclusion. The implementation rate of the proposed interventions was 47.8%.

Primary outcomes

No significant differences between the intervention and control group and over time were found for QoL at three and six months, with either the EQ5D-3L and

SF-12. There were also no significant differences in improvement of the primary geriatric problem. (table 5.3) In the intervention group, for 24.8% of the patients the primary geriatric giants was resolved and for 44.7% this was improved, compared to 23.0% and 41.5% in the control group.

Per protocol and subgroup analyses did not show different results. For EQ5D utility scores and SF12 MCS, we found a statistical significant intervention effect after three months among intervention patients who had their consultation within 1.5 months, this effect was absent at 6 months.

Adding general practice as a third level and the expert team as interaction term did not significantly improve the models and were not added to the final model.

Secondary outcomes

The percentage of solved DRPs after six months was significantly higher in the intervention group compared to the control group B:22.6 (95% CI 14.1-31.1). (table 5.3) A higher number of DRPs at baseline decreased the difference between the two groups. Subgroup analyses with only polypharmacy patients gave lower regression coefficients, but the effect remained highly significant 19.3 (95% CI 10.6-27.4).

Patient satisfaction with medication and self-reported medication adherence did not change over time, nor in the intervention nor in the control group. (table 5.3) General practice as second level had no effect. Per protocol analyses and subgroup analyses did not show different results. The effect on the percentage solved DRPs after six months was higher in the per protocol analyses, in favor of the intervention group.

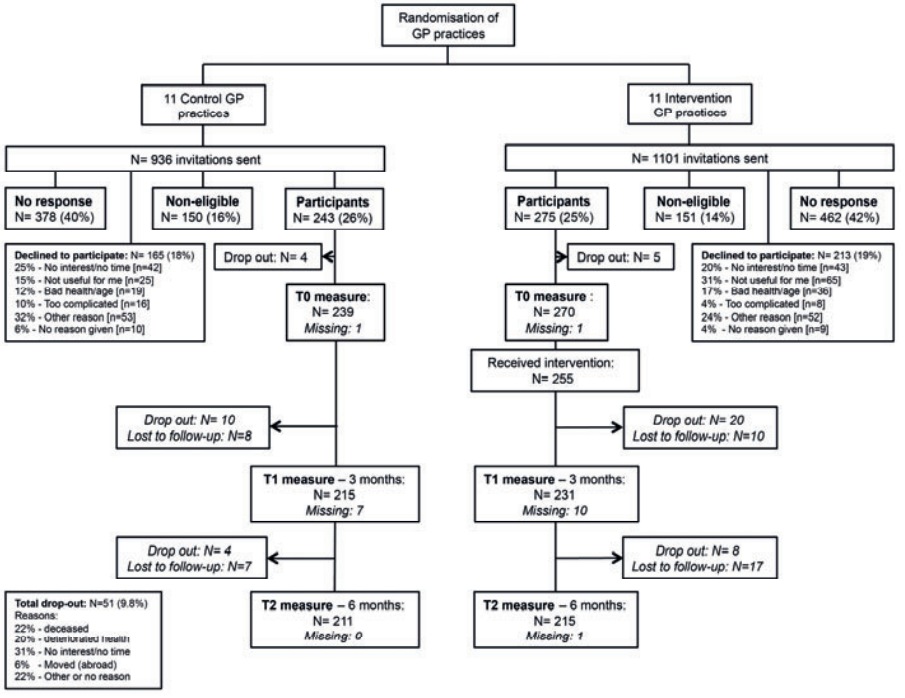

Figure 5.2 Flowchart of the Opti-Med study participants

GP=General Practitioner

Table 5.3 Intervention effects from multilevel linear and logistic regression analyses

		3 months				6 months		6 months	
Continuous outcome measures	**obs/total[1]**	**Adjusted for T0** ***B (95% CI)***	**p-value**	**Adjusted#** ***B (95% CI)***	**p-value**	**Adjusted for T0** ***B (95% CI)***	**p-value**	**Adjusted#** ***B (95% CI)***	**p-value**
Quality of Life (EQ5D-3L utility -0.20-1)	1338/1554	0.03 (0.00-0.06)	0.06	0.02 (-0.00-0.05)	0.14	0.02 (-0.02-0.05)	0.32	0.01 (-0.02-0.04)	0.53
Quality of Life (EQ5D-3L VAS 0-100)	1332/1554	0.91 (-1.69-3.43)	0.51	0.38 (-2.03-2.80)	0.76	2.30 (-0.16-4.76)	0.06	1.82 -0.55-4.18)	0.13
Quality of Life (SF-12 MCS 0-100)	1319/1554	3.33 (0.35-6.32)	0.03	2.76 (-0.19-5.73)	0.07	0.16 (-2.89-3.22)	0.92	-0.39 (-3.43-2.65)	0.81
Quality of Life SF-12 PCS (0-100)	1305/1554	2.36 (-0.67-5.4)	0.13	1.88 (-1.13-4.89)	0.22	-0.06 (-3.19-3.06)	0.96	-0.58 (-3.69-2.53)	0.72
Medication Satisfaction MSQ (1-7)	1344/1554	0.01 (-0.17-0.20)	0.89	0.00 (-0.19-0.18)	0.97	0.11 (-0.08-0.30	0.25	0.09 (-0.10-0.28)	0.35
Percentage of solved DRPs after six months	470/507	-	-	-	-	20.2 (12.2-28.1) ## [1] *ICC: 0.08*	**<0.001**	19.9 (12.0-27.9) ## [1] *ICC: 0.08*	**<0.001**

- Table 5.3 continues -

- Table 5.3 continued -

						6 months		6 months	
Dichotomous outcome measures	***N***					**OR (95% CI)**	**p-value**	**OR# (95% CI)**	**p-value**
Resolved primary geriatric problem[2]	406	-	-	-	-	1.10 (0.69-1.74)	0.68	0.99 (0.62-1.57)	0.96
Improved vs worsened/ unchanged primary geriatric problem[3]	406	-	-	-	-	1.14 (0.77-1.69)	0.52	1.09 (0.73-1.63)	0.67
Persistence of self-reported adherence problems	406	-	-	-	-	0.83 (0.54-1.27)	0.38	0.81 (0.53-1.25)	0.35

P values <0.05 in bold are considered statistically significant

B=Regression Coefficient; CI=Confidence Interval; DRP=Drug Related Problem; ICC= Intraclass Correlation Coefficient; MSQ=Medication Satisfaction Questionnaire; OR = Odds Ratio; SF-12= Short Form 12-item health survey; SF12-Physical Health Summary Scales; SF-12 MCS = SF12 Mental Health Summary Scales ; VAS=Visual Analogue Scale

Adjusted for T0 and number of chronic diseases at baseline

Adjusted for number of DRPs at baseline

[1] Total observations is 1554 (3 times 518) for QoL and MSQ. For solved DRPs after six months total is 507, no DRPs at baseline and deceased were excluded from analyses.

[2] A 'solved' primary geriatric problem is defined as a VAS of two or less after 6 months or no falls in the previous 6 months.

[3] A difference after 6 months of two or more points on the VAS was considered as either an improvement or worsening. For falls an improvement or worsening was absolutely more or less falls in the previous 6 months (T1 and T2 combined).

Discussion

We investigated the effectiveness on QoL and geriatric problems of an optimally facilitated, prepared and structured CMR in comparison with usual care in older patients presenting their GP with a new geriatric problem. No significant effects were found for QoL and improvement in geriatric problems. The secondary outcomes patient satisfaction with medication and self-reported medication adherence did not show any effects either. However, after six months significantly more DRPs were solved in the intervention group compared to the control group. Subgroup analyses showed no other effects of the intervention, in the per protocol analyses a small significant difference in favour of the intervention group after three months for QoL was found. This effect disappeared after six months. The capability of CMRs to solve DRPs did not result in an improved QoL or a reduction of geriatric problems.

Our results are comparable to findings of other studies.[11,22] The recent Cochrane review concluded that CMRs demonstrated improvements in appropriate prescribing, however it remains unclear whether such interventions can improve clinical outcomes on the patient level, no effects were found for QoL.[23] Apparently, expert opinion and guideline recommendations[10,15,24] do not match with available evidence.

There are several explanations for the absence of effects. First, the selected target group for Opti-Med may have been not complex. Other studies showed some effects of medication reviews on patient outcomes in specific more complex subgroups such as patients having more than five comorbidities[25] or patients with heart failure.[26] Because of the large number of patients that did not respond (41%) or declined to participate (18.5%) we cannot exclude selection bias. In our study only 57% had polypharmacy and a mean of 3 chronic diseases, however subgroup analyses showed no differences. Since our inclusion criterion was a cut-off value on a VAS regarding geriatric problems, one could argue that the scores and cut-off value for the VAS for geriatric problems might have been too low. However over half of the participants had multiple geriatric problems and all contacted their GP for their complaints. Our target group is very heterogeneous, which could partially explain the absence of effects.

Another explanation for the lack of effects could be related to the outcome measures. QoL is difficult to measure in elderly people due to the diversity of problems in multimorbidity. The EQ5D-3L and SF12 questionnaires appear unresponsive measures and the VAS for geriatric problems are limited. Ideally CMRs should lead to less hospitalizations and mortality, for which much larger sample sizes are needed and one previous attempt failed[25] More specific outcomes might be more appropriate, such as Medication related QoL or exposure to specific high-risk medications[27,28], however these are still intermediate outcomes.

Another explanation could be the intensity and implementation of intervention. Only one face to face contact with the patient was performed, since we chose to replace the patient interview with a questionnaire. Our previous study showed reasonable agreement between a patient interview and a questionnaire.[14] The level of implementation of the intervention was good, with 90% having had a consultation with the GP and 47.8% of the proposed interventions was implemented by GP and patients, which is also high for an intervention with an external expert team. The number of DRPs identified by the expert teams is within the range found in other studies.[29,30] The non-published process evaluation of Opti-Med including a patient survey and qualitative interviews among healthcare workers showed that all those involved were satisfied with the intervention and thought it was useful. This suggests that low fidelity is not the explanation for the absence of effects.

Finally, the follow-up may have been too short to detect changes in QoL due to changes in medication. Resolved DRPs related to e.g. preventative medication are not expected to influence QoL in the short term.

A limitation was that the external expert teams that performed the medication reviews were not blinded, for practical reasons and as result of the protocol deviation as described earlier. This might be the explanation that more DRPs were identified in intervention than the control group. However, we corrected for this in in the analyses. Moreover, we think that the protocol deviation did not influence the results.

Our study indicates that there are no (measurable) effects of medication reviews on QoL or geriatric problems in this population or that the effects of CMR in the selected population are so small that the number needed to review is very high. The study had sufficient power, with a representative primary care

population, the implementation of the intervention was good and patients were involved through a questionnaire and during a consultation with the GP. An additional factor might be that the quality of usual primary care in the Netherlands is high leaving only limited room for improvement.

Implications for practice and research

Intervention studies to reduce inappropriate medication and prescribing so far have not resulted in measurable changes in clinical patient outcomes. The evidence for medication reviews is mainly based on expert opinions and not on the evidence for the effectiveness of medication reviews. However, in clinical practice and guidelines, patients and policymakers demand CMRs, based on ethical considerations regarding possible future medication complications. Therefore future initiatives for implementation in clinical practice should focus on efficient and less costly methods, in which the Opti-Med intervention elements such as the questionnaire to evaluate patients' medication use and DRPs[13] and the use of external expert teams seem suitable.

Future research initiatives should focus on the characteristics of high risk patient groups for whom medication reviews might be of added value.

Conclusions

The Opti-Med study intervention did not influence QoL and geriatric problems. The higher percentage of solved DRPs in the intervention group did not translate into effects on the patient level. Clinical medication reviews on a large scale seem not meaningful and should be reconsidered.

Ethics

The Opti-Med study is registered in the Netherlands Trial Register (NTR4264), and was approved by the Medical Ethics Committee of the VU University Medical Center (2011/408).

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Disclosures

None of the authors report conflicts of interest.

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Cost-effectiveness of optimised clinical medication reviews as compared to usual care in general practice

Submitted

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Abstract

Background

Costs related to inappropriate medication use contribute importantly to total healthcare costs for older patients. Therefore, reducing these costs can substantially lower the expanding healthcare costs for these patients. The aim of this study was to evaluate the cost-effectiveness of clinical medication reviews (CMR) as compared to usual care in older patients with a new geriatric problem in general practice.

Methods

An economic evaluation alongside a cluster randomized controlled trial was performed. The intervention tested comprised a CMR. Outcome measures included societal costs, quality-adjusted life years (QALYs) based on the EQ-5D, drug-related problems (DRPs), quality of life (QoL) measured with the Short-Form Survey (SF12) and changes in geriatric problems (immobility, instability, incontinence and impaired cognition). Missing cost and effect data were imputed using multiple imputation techniques. Bootstrapping was used to estimate the uncertainty around the differences in costs and incremental cost-effectiveness ratios.

Results

After six months of follow-up, there were no statistically significant differences in QoL and geriatric problems between intervention and control group. In the intervention group, significantly more DRPs were solved as compared to the control group (mean difference 1.13 (95% CI 0.92 ; 1.35). Total societal costs in the intervention group were € 684 higher than in the control group, but this difference was not statistically significant (95% CI € -1142 ; 2387). Cost-effectiveness acceptability curves showed that for solved DRPs, the probability of the intervention being cost-effective compared to usual care reached 0.95 at a willingness-to-pay WTP of €2.100 per solved DRP. For all other outcomes, the probability was low at all WTP values (i.e. range 0.25 ; 0.49).

Discussion
CMRs were not considered cost-effective as compared to usual care. Implementation of CMRs is, therefore, not recommended for this patient group on a large scale.

Introduction

Inappropriate medication use is a common problem among older people. The rate of inappropriate medication use among older people in primary care settings is estimated to be around 20% (range 2.9-38.5%).[1] Adverse effects resulting from inappropriate medication use, especially unscheduled hospitalizations, induce high costs for healthcare and society. In a large cross-sectional study, gross costs of potentially inappropriate medication use were estimated to be around €6 million in Northern Ireland.[2] In the light of the expanding costs of healthcare for older patients, it is essential to reduce costs associated with inappropriate medication use.

Clinical medication reviews (CMRs) are a potential tool to reduce inappropriate medication use, and prevent and reduce drug related problems (DRPs) such as drug interactions, inefficacy of treatment, adverse drug reactions, non-adherence with treatment, and drug use patient related problems. However, evidence for the effect of medication reviews on various outcomes, including costs, is limited.[3] Despite the limited evidence on the effectiveness and cost-effectiveness of CMRs, CMRs are now widely implemented in daily practice.

In previous studies, the cost-effectiveness of CMRs as compared to usual care is often not or not fully evaluated.[4] Available cost-effectiveness, cost-utility, and cost-consequence analyses showed heterogeneous results. Some recent studies showed that a CMR can be cost-effective in comparison with usual care, mainly due to avoided drug-related hospital readmissions.[5,6] A UK study concluded that CMRs have a low probability to be cost-effective as compared to usual care.[7] Two reviews on cost evaluations of CMRs concluded that it was difficult to pool results, but that CMRs might be cost-effective as compared to usual care.[8,9] Another conclusion was that there is a need for large clinical trials with carefully chosen interventions and more robust

methodology that include comprehensive outcomes such as utility scores to determine whether CMRs can be cost-effective.[8,9] A rigorous evaluation of cost-effectiveness of CMRs in large RCTs is essential to determine future policy.

Our recently completed cluster randomized controlled trial (RCT) testing the effectiveness of an optimised CMR in comparison with usual care showed a reduction in inappropriate medication use in terms of more solved DRPs compared to usual care.[10] To optimise the feasibility of CMRs in primary care in terms of organisation, target group and patient participation, a structured program to conduct the CMR was designed. Alongside this RCT, we evaluated the cost-effectiveness of CMRs compared with usual care from a societal perspective in older patients presenting with a new geriatric problem in general practice. Since the aim of our intervention was to provide a more efficient and less time-consuming CMR, the analyses on its cost-effectiveness as compared to usual care are highly relevant.

Methods

Design and setting

An economic evaluation from a societal perspective was performed alongside a cluster RCT, the Opti-Med study, evaluating optimised CMRs as compared to usual care in general practice. Details of the Opti-Med study design have been described elsewhere.[11] In short, the study was performed in 22 general practices in The Netherlands between November 2013 and August 2015. Randomisation of practices was performed using a computer-generated list of random numbers. The practices were stratified by practice size (two strata), to ensure equally sized groups. The Opti-Med study is registered in the Netherlands Trial Register (NTR4264), and was approved by the Medical Ethics Committee of the VU University Medical Center (2011/408). The present cost-effectiveness study follows the reporting guidelines as specified in the CHEERS statement. [12]

Participants

Patients ≥65 years were eligible if they n presented a new geriatric problem in a general practice and used ≥1 prescribed drug chronically (i.e. ≥ 3 months).

Patients with geriatric problems were identified based on ICPC coded diagnoses in their electronic medical record (EMR) and an additional screening questionnaire on geriatric problems including mobility problems, dizziness, fear of falling, falls, urinary incontinence and cognitive impairment, and excluded if diagnosed with dementia. Patients rated these problems using a visual analogue scale (VAS) with a range from 1 (no problem) to 10 (severe problem). Patients were included if they scored ≥5 on the VAS for one or more geriatric problems or reported ≥1 fall in the preceding six months. The GP (general practitioner) excluded patients who had had a CMR recently or were deemed unable to participate.

Intervention

Within the Opti-Med study, external expert teams performed the CMRs for all patients. The expert teams consisted of a trained GP or elderly care physician and a community pharmacist. The CMRs were carried out as follows:

1. The CMRs were prepared using the GP's pharmacy's electronic records to obtain the medication history and the actual medication use, and information on geriatric problems and potential DRPs on the basis of patients' responses in a questionnaire.[13]
2. The expert teams reviewed medication use according to the adapted Systematic Tool to Reduce Inappropriate Prescribing (STRIP) method.[14]
3. The expert teams made a pharmacotherapeutic treatment plan (PTP) which was sent to the patient's GP.
4. Patients were invited for a consultation with their GP in which the PTP was discussed and the medication regimen was determined together with the patient. Changes in the medication were implemented and communicated to the pharmacy.

Usual Care

Patients in the control practices received care as usual with no systematic attention paid to pharmacotherapy. The expert team performed a CMR according to the same protocol as for the intervention group; however, the results were not communicated.

Outcome measures

Clinical outcomes

Measurements were administered at baseline, and after three and six months by means of patient questionnaires. The primary outcome was quality of life (QoL) as measured by the 12-item Short-Form Health Survey (SF-12) and the EuroQol (EQ-5D-3L). The SF-12 was used to calculate physical (PCS) and mental component summary (MCS) scores. Based on the EQ-5D-3L, quality-adjusted life years (QALYs) were calculated by multiplying the utilities according to the Dutch tariff [15] with the amount of time participants spent in a particular health state (6 months follow-up). Transitions between health states were linearly interpolated.

Geriatric problems were assessed with questions on the presence and self-perceived severity of geriatric problems using VAS (1-10). Figure 6.1 shows the operationalization of resolved and improved geriatric problems.

The number of DRPs per patient was determined at baseline and the number of solved DRPs after six months. One researcher (FW) categorised the DRPs after six months based on the results of the CMR analyses by the expert team using the DOCUMENT checklist [16] and the EMR information. In case of doubt this was discussed with another researcher (JH).

Definition primary geriatric problem based on decision rules:

1. Two or more falls in the previous 6 months
2. Highest VAS for the geriatric problems Dizziness, Mobility, Cognition problems or Incontinence. When equal VAS:
    1. Check with EMR for matching ICPC code for identification
    2. Dizziness>Mobility>Cognition problems>Incontinence
3. One fall in the previous 6 months
4. Fear of falling

The geriatric problem outcome measure was operationalised in two ways (dichotomous);

1. improvement versus worsening or stabilization of the primary geriatric problem
    - A difference after 6 months of two or more points on the VAS was considered as either an improvement or worsening.
    - For falls an improvement or worsening was absolutely more or less falls in the previous 6 months (T1 and T2 combined).

2.'Resolved' geriatric problem: Absence of the geriatric problem versus the presence of the primary geriatric problem;

- Resolved: Absence of the primary geriatric problem is defined as a VAS of two or less after 6 months or no falls in the previous 6 months
- Unsolved: Presence of the primary geriatric problem is a VAS or three or more after 6 months or at least one fall.

Figure 6.1 Definition and operationalization of geriatric problems outcome measures

Costs

All costs were indexed for the year 2014 and in Euros. Lost productivity costs were not considered relevant in this retired older population.

Health utilization costs

The iMCQ questionnaire was used to assess the utilization of formal healthcare services at three and six months after baseline.[17] Healthcare cost categories included primary care (visits to GP, nurse practitioner, therapists), secondary care (emergency room visits, outpatient visits, hospital admissions), institutional care (institutional day treatments and institutional stay) and homecare.

Costs were calculated by multiplying the units of resource utilization by the standard cost prices of these services as reported in the Dutch costing guideline, diagnostic treatment combinations (DBC) or by using a standard price of € 276 per treatment if prices were not available.[18]

Medication costs

Type and units of prescribed medication was obtained from the patients' EMR. Corresponding medication prices were obtained from the Z-index and the National Healthcare Institute (ZiN).[19,20] Total costs were calculated by multiplying the price per unit.

Informal care costs

Informal care was also assessed with the iMCQ questionnaire at three and six months after baseline.[17] Informal care costs were calculated using prices for a legally employed housekeeper (hourly rate € 14) and total costs were calculated by multiplying the number of hours of informal care with this price.[18]

Costs of the intervention

A cost price for the Opti-Med medication review was calculated using a bottom-up approach. The total cost price was €127.28 per patient. The mean costs of selection, invitation and preparation of the CMR per patients were €11.35, consisting of 15 minutes of time by a practice nurse and porto costs. The mean costs for the expert team to conduct the CMR analysis were € 59.36, consisting of two times a mean time expenditure 21.7 minutes for a GP and

pharmacist. The mean costs for a GP consultation were € 56.57, mean 34 minutes per patient, including preparation of the consultation.[21]

Missing data

Missing data on cost and effects were imputed using multiple imputation according to the Multivariate Imputation by Chained Equations (MICE) algorithm using predictive mean matching in STATA 12.1 and stratified for treatment group.[22,23] An imputation model was created that included variables that differed between groups at baseline, variables that differed between participants with and without complete follow-up, variables that were related to the outcome variables, and all variables in the analysis models. The number of imputed datasets was increased until the loss of efficiency was below 5%. The imputed datasets were analysed separately as described below and results were subsequently pooled using Rubin's rules.[24]

Statistical analyses

All analyses were conducted according to the intention-to-treat principle, unless stated otherwise. A p-value of 0.05 was considered statistically significant. Clustering at the level of general practice was not adjusted for, because the intra-class correlation for all outcome measures was below 8%. Differences in costs and effects were estimated using seemingly unrelated regression analyses.[25] Incremental cost-effectiveness ratios (ICERs) were calculated by dividing the difference in mean total costs between the treatment and control groups by the difference in mean effects between the groups. Bias-corrected and accelerated bootstrapping with 5,000 replications was used to estimate 95% confidence intervals around cost differences and to estimate the statistical uncertainty surrounding the ICERs. The uncertainty surrounding the ICERs is graphically presented on cost-effectiveness planes (CE plane). In addition, cost-effectiveness acceptability curves (CEAC) were estimated. CEACs show the probability that the medication review programme is cost-effective in comparison with usual care for a range of different willingness-to-pay (WTP) values thereby showing decision uncertainty.[26]

Sensitivity analyses

Three sensitivity analyses were performed. First, the analysis was done from the healthcare perspective, meaning that informal care costs were excluded. Second, in a per protocol analysis, only intervention patients who had a consultation with the GP as part of the intervention were included. Finally, in a post-hoc subgroup analysis only patients were included who used five or more chronic medications at baseline.

Results

Participants

Figure 6.2 shows the participant flow in the Opti-Med study. Of the 2,037 invited patients, 14.8% was not eligible, 18.6% declined to participate and 41.2% did not respond at all. In total, 518 patients were included and signed an informed consent: 275 in the intervention group and 243 in the control group.

In table 6.1, baseline characteristics are shown for all participants per study group. There was a clinically relevant and significant difference in the number of chronic diseases between intervention and control group. Complete effect data was available for 426 (82%) participants and complete cost data was available for 407 (79%) participants. The probability of missing cost or effect data was significantly higher in participants who were not Dutch, living alone, with lower QoL (EQ5D and SF12MCS), and had higher VAS scores for fear of falling and cognitive problems.

Table 6.1 Patient characteristics of the participants at baseline of the Opti-Med study

Demographic characteristics	Intervention	Usual care	Total	p-value
Number of participants	275	243	518	-
Women n (%)	177 (64.4)	159 (65.4)	336 (64.9)	0.80
Age, mean (sd) [range]	77.8 (7.7)	77.8 (8.0)	77.7 (7.9) [65-102]	0.94
≥80 year,%	38.8	40.6	39.6	0.67
≥90 year,%	5.8	7.4	6.5	0.47
Country of Birth				0.43
Dutch and other European,%	91.7	93.6	92.6	-
Non-Western,%	8.3	6.4	7.4	-
Education level[1]				0.25
Low, %	26.6	20.5	23.7	-
Middle, %	44.9	46.6	45.7	-
High, %	28.5	32.9	30.6	-
Living situation				0.60
Alone, %	59.4	57.1	58.3	-
Together, %	40.6	42.9	41.7	-

- table 6.1 continues -

- table 6.1 continued -

Health characteristics	Intervention	Usual care	Total	P-value
EQ-5D-3L utility, mean (sd)	0.72 (0.22)	0.75 (0.20)	0.73 (0.21)	0.15
EQ5D VAS (0-100), mean (sd)	68.5 (15.6)	68.5 (14.5)	68.5 (15.1)	0.93
SF12 PCS, mean (sd)	47.9 (24.0)	47.2 (25.7)	47.6 (24.8)	0.76
SF12 MCS, mean (sd)	63.4 (23.1)	64.0 (22.6)	63.7 (22.9)	0.78
Mean chronic diseases (sd)[2]	2.77 (1.76)	3.23 (2.19)	2.99 (1.98)	**0.01**
≥2 chronic diseases[2], %	73.8	78.6	76.1	0.20
≥3 chronic diseases[2], %	48.4	53.9	51.0	0.21
≥4 chronic diseases[2], %	30.9	41.6	35.9	**0.01**
≥5 chronic diseases[2], %	17.5	26.7	21.8	**0.01**
BMI, mean (sd)	26.7 (5.4)	26.8 (5.4)	26.7 (5.4)	0.86
Pain VAS (0-10), mean (sd)	3.7 (3.0)	3.6 (2.9)	3.7 (3.0)	0.82
Geriatric problems	**Intervention**	**Usual care**	**Total**	**p-value**
Mobility problems, % ≥5 VAS	57.9	62.6	60.1	0.28
Falling				0.70
% ≥1 times last 6 months	33.9	33.3	33.7	-
% ≥2 times last 6 months	17.4	20.1	18.7	-
Fear of falling, % ≥5 VAS	36.6	41.2	38.7	0.29
Dizziness, % ≥5 VAS	17.2	15.8	16.5	0.67

- table 6.1 continues -

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Geriatric problems	**Intervention**	**Usual care**	**Total**	**p-value**
Incontinence, % ≥5 VAS	22.9	25.2	24.0	0.54
Cognition problems, % ≥5 VAS	25.5	26.9	26.1	0.72
≥ 2 geriatric problems, %	56.5	61.3	58.8	0.27
≥ 3 geriatric problems, %	32.3	35.7	33.9	0.54
Primary geriatric problems	**Intervention**	**Usual care**	**Total**	**p-value**
Mobility**, %,** mean VAS (sd)	41.4 [7.1 (1.7)]	37.3 [7.1 (1.6)]	39.2 [7.1 (1.7)]	-
Falling ≥1 times last 6 months, **%**	18.5	12.8	15.8	-
Falling ≥2 times last 6 months, %	17.4	20.1	18.7	-
Fear of falling**, %,** mean VAS (sd)	1.6 [6.4 (1.8)]	2.9 [5.5 (1.0)]	2.3 [6.1 (1.6)]	-
Dizziness**, %,** mean VAS (sd)	6.5 [7.1 (1.7)]	4.9 [7.1 (1.9)]	5.8 [7.1 (1.7)]	-
Incontinence**, %,** mean VAS (sd)	8.7 [7.8 (1.7)]	9.8 [7.0 (1.4)]	9.2 [7.4 (1.6)]	-
Cognitive problems**, %,** mean VAS (sd)	9.0 [6.8 (1.4)]	8.7 [6.1 (1.2)]	8.8 [6.5 (1.3)]	-

- table 6.1 continues -

- table 6.1 continued -

Medication characteristics	Intervention	Usual care	Total	p-value
No of drugs in pharmacy records, mean (sd)	6.2 (3.2)	5.8 (3.3)	6.0 (3.2)	0.22
No of drugs reported by patient, mean (sd)	6.1 (3.1)	5.6 (3.2)	5.9 (3.2)	0.12
No of chronic drugs GP EMR, mean (sd)	5.6 (3.4)	5.5 (3.2)	5.6 (3.3)	0.74
Polypharmacy, %[3]	58.0	55.7	56.9	0.60

BMI= Body Mass Index; EMR=Electronic Medical Record; NA=Not Applicable; OTC= Over The Counter; SF-12= Short Form 12-item health survey; SF12-PCS = Physical Health Summary Scales; SF-12 MCS = SF12 Mental Health Summary Scales ;

[1] low education level: No education, primary education or first stage of basic education; middle education level: Lower secondary education or second stage of basic education; high education level: Upper secondary education or higher

[2] Chronic diseases according to set list of 29 diseases[35]

[3] Definition of polypharmacy is the use of ≥5 indicated for the treatment of a chronic disease at the ATC-5 level in in the four months preceding baseline. ATC codes were derived from prescription data from the EMR records. Excluded were anti-infectives (ATC-class J,G01,S01A,C,S02A,C), topical products (ATC-class M02 and dermatologicals (ATC-class D) and preparations for sensory organs, except drugs intended for long-term use were included (ATC-class S01E,F,G)

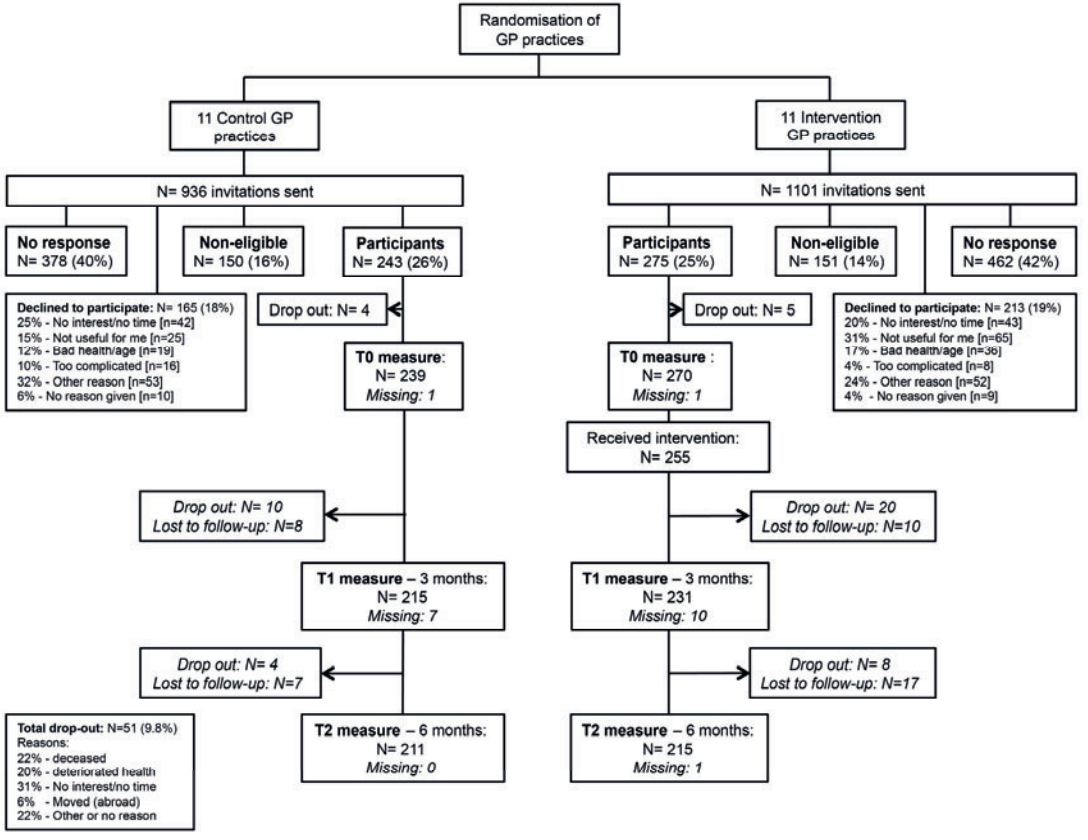

Figure 6.2 Flowchart of Opti-Med study participants

Clinical outcomes

There were no statistically significant differences in SF12 scores, QALYs and geriatric problems between the intervention and control group after six months adjusted for number of chronic diseases (see table 6.2). In the intervention group, significantly more DRPs were solved during follow-up compared to the control group (adjusted mean difference 1.13 (95% CI 0.92 ; 1.35)) (see table 6.2).

Costs

The mean difference in total societal costs between intervention and control group was €684 (95% CI: -1,142; 2,387) after six months adjusted for number of chronic diseases (see table 6.2). Medication costs were the largest contributor to total societal costs. There were no statistically significant differences in costs between the groups for any of the cost categories.

Table 6.2 Group estimates and differences for clinical outcomes and costs over 6 month follow-up

	Intervention Crude mean (se)	Control Crude mean (se)	Unadjusted difference (95% CI)	Adjusted[1] mean difference (95% CI)
Clinical outcomes				
QALYs	0.37 (0.01)	0.40 (0.02)	-0.03 (-0.07 ; 0.01)	-0.02 (-0.06 ; 0.01)
SF12-PCS	48.6 (1.7)	48.9 (1.8)	-0.35 (-5.12 ; 4.42)	-1.38 (-5.21 ; 2.44)
SF12-MCS	64.6 (1.7)	64.5 (1.6)	0.15 (-4.35 ; 4.66)	-0.44 (-4.22 ; 3.33)
Resolved PGP[3]	0.25 (0.03)	0.22 (0.03)	0.03 (-0.05 ; 0.11)	0.01 (-0.07 ; 0.09)
Improved PGP[4]	0.45 (0.03)	0.41 (0.03)	0.04 (-0.05 ; 0.13)	0.03 (-0.06 ; 0.12)
Solved DRPs[5]	2.03 (0.09)	0.92 (0.07)	1.11 (0.90 ; 1.33)	1.13 (0.92 ; 1.35)
Cost categories (2014, €)	**Intervention Crude mean (se)**	**Control Crude mean (se)**	**Unadjusted difference (95% CI)**	**Adjusted[2] mean difference (95% CI)**
Total healthcare costs	5529 (684)	5309 (792)	219 (-1704 ; 2006)	676 (-1145 ; 2378)
Primary care[6]	499 (33)	499 (41)	1 (-92 ; 89)	28 (-62 ; 114)
Secondary care[7]	832 (118)	728 (125)	104 (-217;415)	159 (-135;460)
Home care	1528 (431)	1940 (621)	-411 (-1712 ; 743)	-226 (-1386 ; 887)
Institutional care[8]	537 (248)	186 (121)	351 (-10 ; 994)	421 (65 ; 1162)
Medication	2005 (417)	1957 (418)	48 (-1072 ; 1029)	166 (-940 ; 1161)
Intervention costs	127 (NA)	0 (NA)	127 (NA)	127 (NA)

- table 6.2 continues -

- table 6.2 continued -

Cost categories (2014, €)	Intervention Crude mean (se)	Control Crude mean (se)	Unadjusted difference (95% CI)	Adjusted[2] mean difference (95% CI)
Informal care	49 (15)	46 (12)	3 (-28 ; 35)	8 (-21 ; 42)
Total societal costs	5578 (685)	5356 (795)	222 (-1709 ; 2013)	684 (-1142 ; 2387)

CI=Confidence Interval; DRP=Drug Related Problem; NA=Not Applicable; PGP=Primary Geriatric Problem; QALY=Quality Adjusted Life Year; se=standard error; SF12-PCS = Physical Health Summary Scales; SF-12 MCS = SF12 Mental Health Summary Scales ;

[1] Adjusted for number of chronic diseases and T0

[2] Adjusted for number of chronic diseases

[3] A 'resolved' primary geriatric problem is defined as a VAS score of two or less after 6 months or no falls in the previous 6 months.

[4] A difference after 6 months of two or more points on the VAS score was considered as either an improvement or worsening.

[5] Adjusted for number of DRPs at baseline

For falls an improvement or worsening was absolutely more or less falls in the previous 6 months (T1 and T2 combined).

[6] Includes general practitioner, nurse practitioner, therapists.

[7] Includes emergency room visits, outpatient visits and hospital stay.

[8] Includes institutional day treatments and institutional stay.

Cost-effectiveness

The results of the cost-effectiveness analyses are presented in table 6.3 and figure 6.3a and 6.3b. The ICERs for the SF12-PCS and SF12-MCS were respectively -€493 and -€1,548, indicating that the change in QoL between six months and baseline in the intervention group was smaller than in the usual care group at higher costs. This is confirmed by the CE plane in which the majority of the SF12-PCS and SF12-MCS cost-effect pairs were located in the northwest quadrant (less effective and more expensive). The CEACs showed that for both the SF12-PCS and SF12-MCS, the probability that the intervention was cost-effective in comparison with usual care was 0.25 at WTP values of 0 €/point improvement. For the SF-12 PCS, this probability remained stable at increasing ceiling ratios, while for SF-12 MCS this slowly increased to 0.40 at a willingness-to-pay (WTP) of 20,000 €/point improvement.

The ICER for resolved and improved geriatric problems were €58,716 and €21,136, respectively. This means that the investment needed per additional resolved geriatric problem is €58,716 and per improved geriatric problem €21,136 in the intervention group as compared to the usual care group. For both geriatric problem measures, the majority of cost-effect pairs were located in the northeast quadrant (more effective and more expensive) of the CE plane. The CEACs showed that for both resolved and improved geriatric problems, the probability that the intervention was considered cost-effective in comparison with usual care was 0.25 at WTP values of 0 €/resolved or improved geriatric problem, and that this slowly increased to 0.36 and 0.49 at a WTP of 20,000 €/resolved geriatric problem and improved geriatric problem, respectively.

The ICER for solved DRPs was €603, meaning that the investment needed per extra solved DRP is €603. The majority (approximately 75%) of cost-effect pairs were located in the northeast quadrant (more effective and more expensive) of the CE plane and the remaining cost-effect pairs were located in the southeast quadrant (more effective and less expensive). The probability that the intervention was considered cost-effective in comparison with usual care was 0.25 at WTP values of 0 € per solved DRP, and increased quickly to a probability of 0.95 at a WTP of €2,100 per solved DRP.

Cost-utility

The results of the cost-utility analysis are presented in table 6.3 and figure 6.3a and 6.3b. The ICER for QALYs was **-**€31,816, meaning that the loss of one QALY in the intervention group as compared to usual care is associated with an increase in costs of €31,816. The majority of the QALY cost-effect pairs were located in the northwest quadrant (less effective and more expensive) of the CE plane. The CEAC showed that for QALYs, the probability that the intervention was considered cost-effective in comparison with usual care was 0.25 at a WTP value of 0 €/QALY and this decreased to 0.13 at a WTP of 20,000 €/QALY.

Sensitivity analyses

Table 6.3 shows the results of the three sensitivity analyses. The results of the healthcare perspective analysis, excluding informal care costs, were comparable to the main analysis. In the per protocol analysis, the mean cost difference was smaller than in the main analysis, €567 (95% CI -1,197 ; 2,382). However, this did not affect the cost-effectiveness and cost-utility outcomes.

The analyses for patients using five or more chronic medications produced different results. Total societal costs in the intervention group were €1,792 lower than in the control group which was statistically significant (95% CI - 4732 ; -28); this was mainly due to lower institutional care and medication costs. The ICERs for QALYs, SF12-M/PCS and SF12-M/PCS were €44,747, €723 and €984, respectively. Cost-effectiveness acceptability curves showed that for all outcomes the probability of the intervention being cost-effective was 92% at all willingness-to-pay (WTP) value of €0. These values decreased to 0.20 and 0.26 at a WTP of €20,000 for the SF12-MCS and SF12-PCS, respectively. For QALYs and resolved geriatric problems, the probability of being cost-effective decreased to 0.76 and 0.88, respectively at a WTP of €20,000. For solved DRPs, the probability reached 0.92 at a WTP of €0 per solved DRP and this increased to 1.00 at a WTP of €20,000. (see table 6.2)

Table 6.3 Differences in outcomes and costs over 6 months between Intervention and Control group, ICER, % CE planes quadrants

Analysis	Δ Costs	Δ Effects	ICER	Cost-effectiveness plane				Probability that the intervention is cost-effective compared to usual care	
Main analyses ITT $^{n=518}$				**NE**	**SE**	**SW**	**NW**	**WTP=0€**	**WTP=20,000€**
QALYs[1]	684 (-1142 ; 2387)	-0.02 (-0.06 ; 0.01)	-31816	10%	2%	23%	66%	0.25	0.13
SF12-PCS[1]	684 (-1142 ; 2387)	-1.38 (-5.2; 2.4)	-493	16%	8%	17%	60%	0.25	0.23
SF12-MCS[1]	684 (-1142 ; 2387)	-0.44 (-4.2 ; 3.3)	-1548	28%	11%	13%	47%	0.25	0.40
Resolved PGP[2]	684 (-1142 ; 2387)	0.01 (-0.07 ; 0.09)	58716	47%	14%	9%	29%	0.25	0.36
Improved PGP[3]	684 (-1142 ; 2387)	0.03 (-0.06 ; 0.12)	21136	58%	18%	6%	18%	0.25	0.49
Solved DRPs[4]	684 (-1142 ; 2387)	1.13 (0.92 ; 1.35)	603	76%	24%	0%	0%	0.25	1.00

- table 6.3 continues -

- table 6.3 continued -

Analysis	Δ Costs	Δ Effects	ICER	Cost-effectiveness plane				Probability that the intervention is cost-effective compared to usual care	
Per protocol[5] n=490 (94%)									
QALYs[1]	567 (-1203 ; 2373)	-0.02 (-0.06 ; 0.02)	-27005	10%	2%	26%	62%	0.29	0.17
SF12-PCS[1]	567 (-1203 ; 2373)	-1.72 (-5.61 ; 2.18)	-330	12%	7%	21%	60%	0.29	0.19
SF12-MCS[1]	567 (-1203 ; 2373)	-1.12 (-4.71 ; 2.47)	-506	18%	9%	19%	54%	0.29	0.27
Resolved PGP[2]	567 (-1203 ; 2373)	0.002 (-0.08 ; 0.09)	285213	37%	15%	13%	35%	0.29	0.35
Improved PGP[3]	567 (-1203 ; 2373)	0.02 (-0.08 ; 0.11)	30623	48%	18%	10%	24%	0.29	0.44
Solved DRPs[4]	567 (-1203 ; 2373)	1.20 (0.97 ; 1.42)	474	72%	28%	0%	0%	0.29	1.00

- table 6.3 continues -

- table 6.3 continued -

Analysis	Δ Costs	Δ Effects	ICER	Cost-effectiveness plane				Probability that the intervention is cost-effective compared to usual care	
Subgroup (≥5 medications) n=271 (52%)									
QALYs[1]	-1792 (-4732 ; -28)	-0.04 (-0.09 ; 0.01)	44747	0%	4%	89%	6%	0.92	0.76
SF12-PCS[1]	-1792 (-4732 ; -28)	-2.48 (-8.05; 3.10)	723	1%	18%	76%	5%	0.92	0.26
SF12-MCS[1]	-1792 (-4732 ; -28)	-1.89 (-7.49; 3.71)	948	1%	22%	71%	5%	0.92	0.20
Resolved PGP[2]	-1792 (-4732 ; -28)	0.02 (-0.09 ; 0.12)	-99562	4%	61%	33%	2%	0.92	0.88
Improved PGP[3]	-1792 (-4732 ; -28)	0.007 (-0.12 ; 0.13)	-272872	3%	51%	42%	3%	0.92	0.84
Solved DRPs[4]	-1792 (-4732 ; -28)	1.04 (0.72 ; 1.36)	-1717	6%	93%	0%	0%	0.92	1.00

- table 6.3 continues -

- table 6.3 continued -

Analysis	Δ Costs	Δ Effects	ICER	Cost-effectiveness plane				Probability that the intervention is cost-effective compared to usual care	
Healthcare system perspective [n=518]									
QALYs[1]	676 (-1145 ; 2378)	-0.02 (-0.06 ; 0.01)	-31406	10%	2%	22%	66%	0.25	0.14
SF12-PCS[1]	676 (-1145 ; 2378)	-1.38 (-5.21 ; 2.44)	-488	16%	8%	17%	60%	0.25	0.23
SF12-MCS[1]	676 (-1145 ; 2378)	-0.44 (-4.20 ; 3.32)	-1531	28%	11%	13%	48%	0.25	0.40
Resolved PGP[2]	676 (-1145 ; 2378)	0.01 (-0.07 ; 0.09)	58019	46%	15%	9%	30%	0.25	0.37
Improved PGP[3]	676 (-1145 ; 2378)	0.03 (-0.06 ; 0.12)	20886	57%	18%	6%	18%	0.26	0.49
Solved DRPs[4]	676 (-1145 ; 2378)	1.14 (0.93 ; 1.36)	591	76%	24%	0%	0%	0.25	1.00

CE=Cost-effectiveness; DRP=Drug Related Problem; ICER= Incremental cost effectiveness ration; ITT=Intention to Treat; NE=North-East quadrant; NW=North-West quadrant; PGP=Primary Geriatric Problem; SE=South-East quadrant; SW=South West quadrant; WTP=Willingness to pay

[1] Adjusted for number of chronic diseases and T0

[2] A 'resolved' primary geriatric problem is defined as a VAS score of two or less after 6 months or no falls in the previous 6 months.

[3] A difference after 6 months of two or more points on the VAS score was considered as either an improvement or worsening. For falls an improvement or worsening was absolutely more or less falls in the previous 6 months (T1 and T2 combined).

[4] Number of solved DRPs, adjusted for baseline number of DRPs

[5]Definition per protocol: all intervention patients that had a consultation with the GP

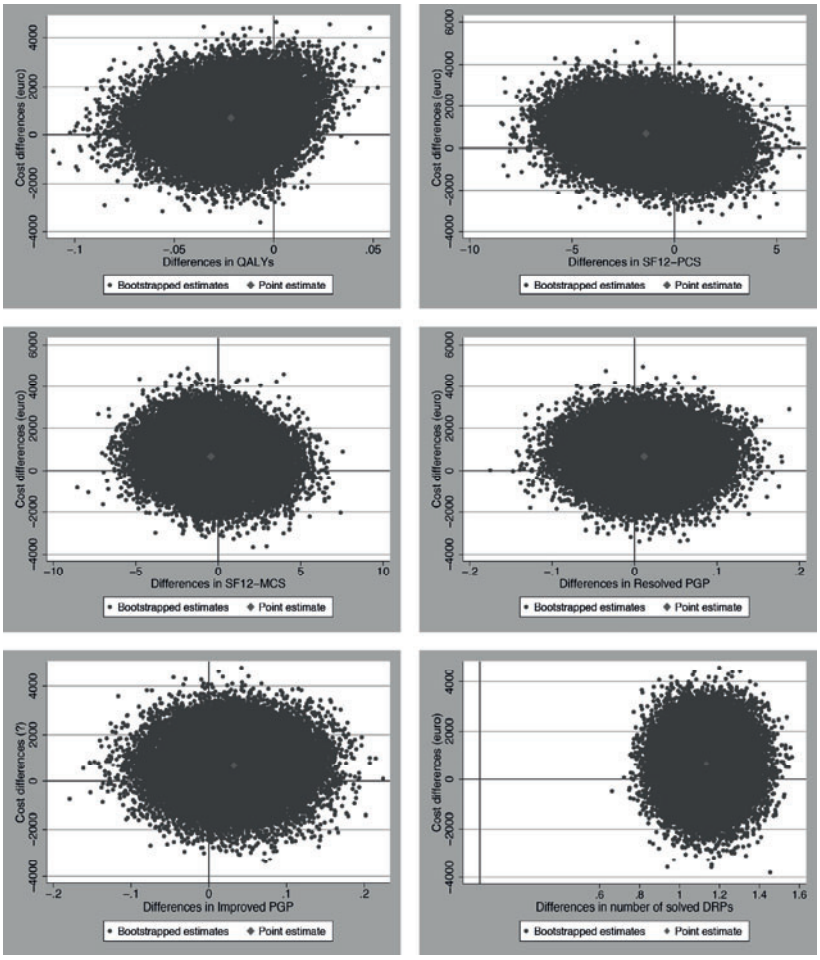

Figure 6.3a Cost-effectiveness planes

Visualization of the uncertainty around the ICER defined by the difference in costs between the Opti-Med intervention and usual care, divided by the difference in health effects.

[1] A difference after 6 months of two or more points on the VAS score was considered as either an improvement or worsening. DRP=Drug Related Problem; ICER=incremental cost-effectiveness ratio, QALY=Quality-Adjusted Life Years, SF12-PCS = Physical Health Summary Scales; SF-12 MCS = SF12 Mental Health Summary Scales; PGP=Primary Geriatric Problem.

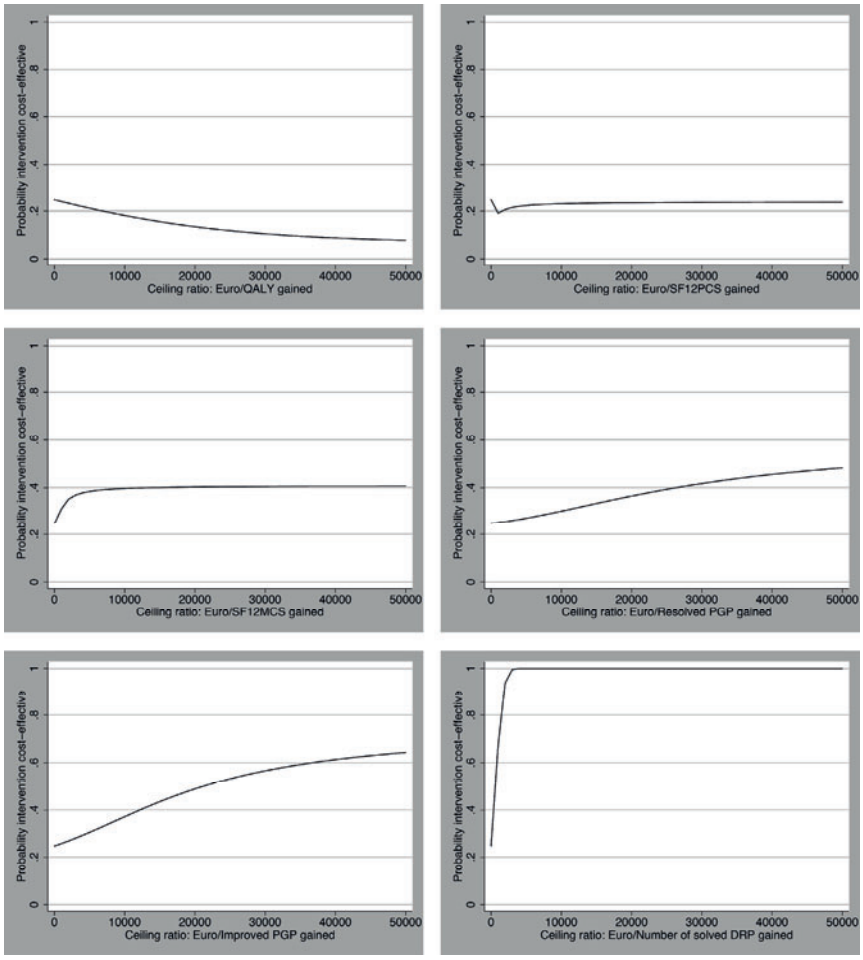

Figure 6.3b Cost-effectiveness acceptability curves

Visualization of the probability that care provided according to the Opti-Med intervention was more cost-effective than usual care using different ceiling ratios. The ceiling ratios represent the maximum amount that the society is willing to pay for a 1-point improvement in the outcome scales.

[1] A difference after 6 months of two or more points on the VAS score was considered as either an improvement or worsening. DRP=Drug Related Problem; ICER=incremental cost-effectiveness ratio, QALY=Quality-Adjusted Life Years, SF12-PCS = Physical Health Summary Scales; SF-12 MCS = SF12 Mental Health Summary Scales; PGP=Primary Geriatric Problem.

Discussion

The Opti-Med intervention aimed to optimise the conduct of CMRs in clinical practice and to reduce inappropriate medication use, but there were no significant differences in societal costs, QoL or reduction in geriatric problems as compared to usual care. However, the intervention significantly reduced DRPs at an estimated incremental cost of € 603 per DRP and had a 95% probability of being cost effective as compared to usual care for DRPs at a WTP of 2,100 Euro's. Depending on the willingness to pay for one solved DRP, this may be considered cost-effective by decision makers. For the subgroup of patients using five or more chronic medications, the costs per patients were significantly lower in the intervention group as compared to the usual care group, but the effectiveness was lower or similar. Again, the intervention may potentially be considered cost-effective in comparison with usual care with regard to resolved DRPs.

In a systematic review by Loh et al.[8] of pharmacy-based medication reviews on economic outcomes with studies until 2015, 13 studies were included. The majority of these studies also did not find any significant differences between intervention and usual care groups in costs. Only three studies reported QALYs; these results were inconsistent, overall medication reviews were not considered cost-effective as compared with control conditions. None of the studies in the systematic review or any other recent studies, as far as we know, reported results on costs per DRP solved.

There are several explanations for the lack of effect on both QoL and presentation of geriatric problems. First, the selected target group for the Opti-Med study may not have been complex enough in terms of age, number of medications or multimorbidity. The more positive findings in the subgroup with five or more chronic medications support this explanation. Second, the outcome measures may not have been sufficiently sensitive.[10] Currently used QoL measures focus on somatic health primarily, whereas cure in older adults is not always possible. New outcome measures like the Adult Social Care Outcomes Toolkit (ASCOT)[27] and the ICEPOP Capability measure for Older people (ICECAP-O)[28], both preference-based measures, may be more suitable for use in these groups.

After adjustment for the number of chronic diseases, societal costs in the intervention group were €684 higher than in the usual care group. This difference was not statistically significant, nor was any of the other differences in costs, except for the costs of institutional care. There is no specific explanation for this difference between the two groups for institutional care.

The slightly higher medication costs in the intervention group may have been the consequence of the changes due to the intervention. Previous studies have shown that a medication review does not always lead to substantial changes with respect to the number of drugs taken [29], which was confirmed in this study. Consequently no decrease in the subcategory medication costs could be observed, the costs were even slightly higher in the intervention group. Overall, medication costs were the largest contributor to the total healthcare costs in both groups.

The lack of effect in clinical outcome measures in combination with the higher societal costs in the intervention group, led us to conclude that the intervention is not cost-effective in comparison with usual care as shown in the cost-effectiveness planes and acceptability curves.

This is the first Dutch study on CMRs that includes a cost-effectiveness evaluation. A strength of this study was the large study population. Because costs generally have a highly skewed distribution, large sample sizes are needed.[30] A second strength of this study was the relatively low percentage of missing data (ranging from 0-21%). Moreover, to prevent bias due to missing data multiple imputation techniques were used, which is generally considered the most appropriate technique to handle missing data in economic evaluations.[31]

Another strength is the societal perspective of the study. Thus, not only healthcare costs were included, but also costs of informal care. However, the utilization and accompanying costs of informal care amounted to only 1% of the total costs. This percentage is very low as compared to other Dutch studies in older patients.[32,33] A possible explanation for this difference, and possibly a limitation of our study is that we included less frail older people than in other studies. A second limitation of our study was the relatively short follow-up of six months; possibly effects on QoL and costs might only become apparent after this period. Loh et al.[8] also suggest that unlike clinical outcomes, economic outcomes, and possibly also QoL outcomes may be realized only

much later. Third, healthcare service use was questioned over a recall period of three months. Although there is evidence that people can reliably recall health care utilization up to six months[34], this is possibly less reliable in older people. Finally, medication data from the GPs' EMRs may not always accurately reflect changes in the medication regime. However, considering the large number of medications participants used, it was expected that self-report would have been burdensome for participants and less accurate than the GP's record data.

Conclusion and recommendations

CMRs according to the Opti-Med protocol were not considered cost-effective compared to usual care over a six month follow-up period. Costs were lower in the intervention subgroup that used five or more chronic medications. However, patient health outcomes did not improve. Thus, improvement in intermediate outcomes of CMRs, such as reducing inappropriate medication use which was operationalized as DRPs in the current study, does not automatically improve health outcomes for patients and reduce costs as well. Despite the lack of evidence on the effectiveness and cost-effectiveness of CMRs, CMRs are now widely conducted and considered more and more as part of usual practice. However, based on these results, performing CMRs on a large scale is not recommended. Future research should first identify the optimal method and target groups for effective and efficient CMRs before starting further implementation of CMRs.

Compliance with Ethical Standards

This study was supported by a research grant by the Dutch Organization for Health Research and Development (ZonMw). The Opti-Med study is registered in the Netherlands Trial Register (NTR4264), and was approved by the Medical Ethics Committee of the VU University Medical Center (2011/408) and in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.
None of the authors report conflicts of interest.

Acknowledgements

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7

Implementation fidelity of a clinical medication review intervention: process evaluation

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Abstract

Background

Implementation of clinical medication reviews in daily practice is scarcely evaluated. The Opti-Med intervention applied a structured approach with external expert teams (pharmacist and physician) to conduct medication reviews. The intervention was effective with respect to resolving drug related problems, but did not improve quality of life.

Objective

The objective of this process evaluation was to gain more insight into the implementation fidelity of the intervention.

Setting

Process evaluation alongside a cluster randomized trial in 22 general practices and 518 patients of 65 years and over.

Method

A mixed methods design using quantitative and qualitative data and the conceptual framework for implementation fidelity was used. Implementation fidelity is defined as the degree to which the various components of an intervention are delivered as intended.

Main outcome measure

Implementation fidelity for key components of the Opti-Med intervention

Results

Patient selection and preparation of the medication analyses were carried out as planned, although mostly by the Opti-Med researchers instead of practice nurses. Medication analyses by expert teams were performed as planned, as well as patient consultations and patient involvement. 48% of the proposed changes in the medication regime were implemented. Cooperation between expert teams members and the use of an online decision-support medication evaluation facilitated implementation. Barriers for implementation were time

constraints in daily practice, software difficulties with patient selection and incompleteness of medical files. The degree of embedding of the intervention was found to influence implementation fidelity. The total time investment for healthcare professionals was 94 minutes per patient.

Conclusion
Overall, the implementation fidelity was moderate to high for all key components of the Opti-Med intervention. The absence of its effectiveness with respect to quality of life could not be explained by insufficient implementation fidelity.

Introduction

Implementation fidelity is defined as the degree to which the various components of an intervention are delivered as intended [1]. Convenience of use and degree of implementation exert considerable influence on the applicability of a complex healthcare intervention in daily practice. Implementation fidelity gives researchers and practitioners a better understanding of how and why an intervention is effective or ineffective, and the extent to which health outcomes can be improved. Implementation fidelity reflects the adherence to content, frequency, duration and coverage of the intervention. In addition, there may be moderating factors that influence the degree of implementation fidelity [1,2]. As long as the evaluation of the implementation fidelity has not been performed, it remains unclear whether ineffectiveness is due to a poor implementation of the intervention or inadequacies inherent to the intervention itself.

In this study, the complex intervention of a clinical medication review (CMR) has been evaluated. A CMR is a structured, critical examination of the patient's medicines with the objective of reaching an agreement with the patient about treatment, optimising the impact of medicines, minimising the number of drug related problems (DRPs) and reducing waste [3]. CMRs can improve the appropriateness of drug prescribing and medication use and are increasingly used and recommended in primary care [4-7]. However, in daily practice the implementation of CMRs is difficult and time consuming. [8,9] A

recent review highlights the need for research on intervention development and process evaluations to improve the understanding of how effective interventions to prevent potentially inappropriate prescribing can be sustained and ultimately be translated into improvements in patient outcomes [10]. Therefore, the Opti-Med randomised controlled trial (RCT) was recently carried out in a primary care population to test the effectiveness of CMRs on the quality of life and DRPs.

The Opti-Med study design and its results have been published separately [11,12]. In short, The Opti-Med study was designed as a cluster RCT in 22 general practices (figure 7.1) [11]. We studied the effects of CMRs on quality of life and DRPs in 518 older patients (≥65 year). Patients were selected and invited when they chronically used one or more prescribed drugs and newly presented themselves to the general practitioner (GP) with one or more geriatric problems (immobility, instability, incontinence and impaired cognition). Patient selection was facilitated by software specifically developed for the Opti-Med study based on electronic medical records (EMRs). CMRs were conducted by the expert teams according to a structured program using the STRIPA tool [13]. Patients in control practices received usual GP care with no specific attention to their medication use.

The Opti-Med study included three innovative CMR elements. First, medication analyses were carried out by trained external expert teams consisting of a pharmacist and a physician, not being the patient's own GP and pharmacist.

The second innovative element was a new target group. We included patients of 65 years and over who chronically used ≥1 prescribed drug and had one or more geriatric problems, also called geriatric giants (immobility, instability, incontinence and impaired cognition) instead of polypharmacy patients, which is the usual target group. Inappropriate medication use may be associated with a higher risk on the occurrence and persistence of these geriatric problems. The nature of this association is complex, as the causes of these problems are multifactorial; however these geriatric problems are among the most common adverse drug reactions [14-19].

The third innovative element was the method of patient involvement. Patients gave input for the medication analyses by means of completing a

questionnaire and discussed the results of the analyses during a consultation with their GP.

We hypothesized that these three elements would facilitate the implementation of CMRs in daily practice and thereby increase their effectiveness. The results of our effectiveness study showed that the Opti-Med CMRs indeed improved appropriate prescribing, i.e. more DRPs were identified and solved after six months of follow-up compared to usual GP care, but there was no effect on patients' quality of life [12]. A process evaluation of the Opti-Med intervention could clarify whether the limited impact of the Opti-Med intervention was due to a poor implementation or due to inadequacies inherent to the intervention itself.

Aim of the study

The aim of this process evaluation study is to gain more insight into the implementation fidelity of the Opti-Med CMR intervention in daily practice.

Ethics approval

This study was approved by the Medical Ethics Committee of the VU University Medical Center (approval reference 2011/408) Informed consent was obtained from all individual participants included in the study.

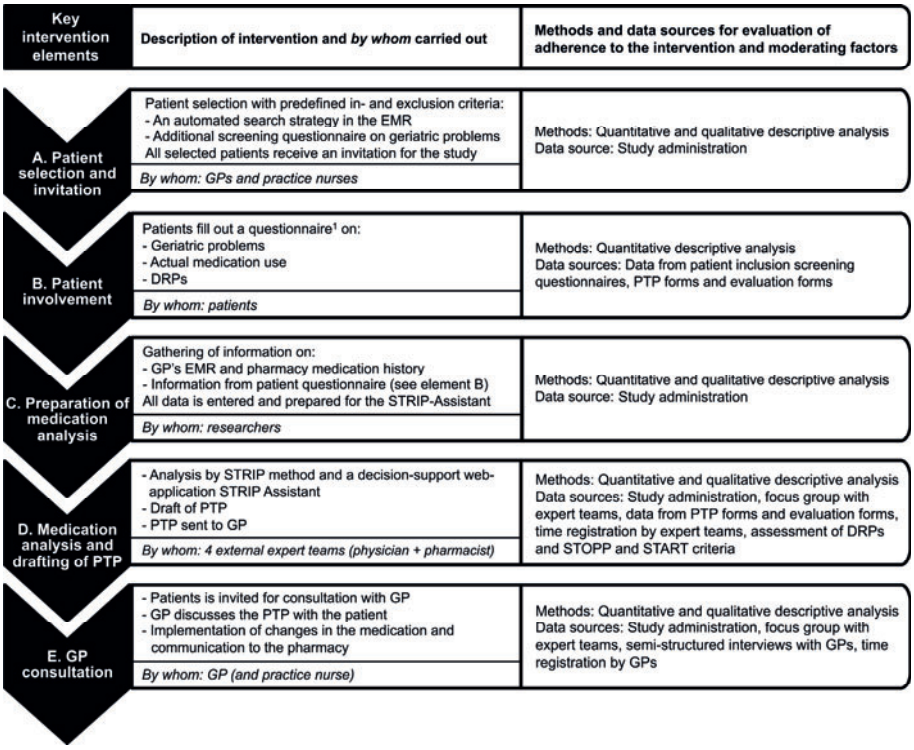

Figure 7.1 Overview of the Opti-Med intervention and important elements for the process evaluation

DRPs=Drug Related Problems; EMR=Electronic Medical Record; GP=General Practitioner; PTP=Pharmacotherapeutic Treatment Plan; START=Screening Tool to Alert doctors to Right Treatment; STOPP= Screening Tool of Older Person's Prescriptions; STRIP=Systematic Tool to Reduce Inappropriate Prescribing; STRIPA= Systematic Tool to Reduce Inappropriate Prescribing Assistant

[1] Questionnaire by Willeboordse et al. 2016 [20]

Method

Study design

This process evaluation was conducted alongside the Opti-Med RCT. Within the present study, the implementation fidelity of the Opti-Med intervention was evaluated. Quantitative data was collected from the start of the study and qualitative data was collected at the end of the study. For the evaluation we distinguished five key intervention components:

A. Patient selection and invitation by GPs and practice nurses to participate using EMRs through a newly developed software;
B. Patient involvement through a patient questionnaire [20];
C. Preparation of the medication analysis by practice nurses and Opti-Med researchers;
D. Medication analysis and drafting of a Pharmacotherapeutic Treatment Plan (PTP) by an expert team. The expert teams followed accredited online courses for CMRs and two face-to-face CMR workshops. An electronic medication evaluation tool, the Systematic Tool to Reduce Inappropriate Prescribing Assistant (STRIPA)[13] was used for the medication analysis;
E. GP consultation with the patient and implementation of the PTP.

Conceptual framework for implementation fidelity

The adapted Conceptual Framework for Implementation Fidelity was used (figure 7.2). [1,2] The framework allows to evaluate both adherence to the intervention and to assess moderating factors for adherence to the intervention.

Adherence to the intervention includes the dimensions content, frequency, duration and coverage.

Moderating factors for adherence to the intervention include the dimensions participant responsiveness, strategies to facilitate implementation, quality of delivery and context.

Specific research questions and outcomes per key intervention component (A-E) for each dimension of the conceptual framework are presented in table 7.1 and 7.2. A subjective rating was used to evaluate the implementation fidelity and the researchers assigned the ratings for each

dimension of the framework using four categories: very low, low, moderate, high. 'Very low' means that almost none of the intervention elements were carried out as planned, 'low' means that some elements have been carried out as planned, 'moderate' means that the majority of the elements have been carried out as planned and 'high' means that almost all elements have been carried out as planned.

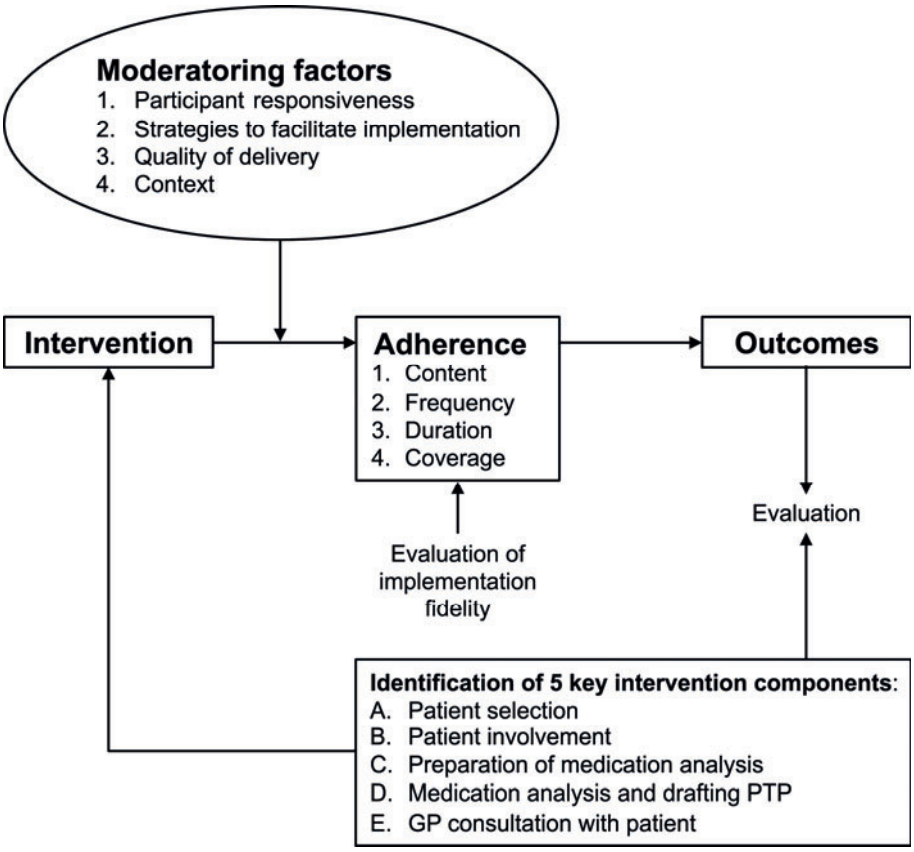

Figure 7.2 Adapted conceptual framework for implementation fidelity for the Opti-Med process evaluation

The measurement of implementation fidelity is the measurement of adherence of the categories content, frequency, duration and coverage.

Data sources

The following data sources were used to address the specific research questions.

I. *Study administration*

Data on selection, inclusion and drop-out of participants, time planning, performing medication analyses by the expert teams, and consultations with the GP were recorded by the researchers alongside the RCT.

II. *Focus group with experts*

A focus group was held with seven members (one GP, two elderly care specialists and four pharmacists) of the four expert teams to collect data on their experiences with conducting the medication analyses. The meeting lasted 70 minutes and was audio recorded. To facilitate the discussion a topic list was developed beforehand (Supplementary Material I).

III. *Interviews with the patients' GPs*

From each intervention practice that performed more than ten consultations, a GP was invited for an semi-structured interview; all participated. The interviews were held by the researchers, lasted 15-30 minutes and were audio-recorded. The objective of the semi-structured interviews was to discuss the experiences of the GPs with this method of conducting CMRs. To facilitate the interview a topic list (Supplementary Material I) was developed.

IV. Evaluation of the implementation of the results of the medication analyses

An evaluation form was used by the GPs to record the follow-up of the changes in the medication regime as proposed by the expert team, including the reason(s) why (part of) these proposals were not implemented. The expert team also indicated for each proposal whether this was influenced by the input of the patient via the questionnaire.

V. Classification and assessment of DRPs

The changes in the medication regime as proposed by the expert teams were classified by the researchers (FW, JH) into DRPs using the DOCUMENT DRP classification system [21].

For a random sample of 21 (8%) of all patients a medication analysis was performed by two different expert teams to assess reproducibility.

Subsequently, the STOPP and START criteria were applied to these DRPs to establish their external validity. STOPP (Screening Tool of Older Person's Prescriptions) is a list of medications that are potentially inappropriate for older people. START (Screening Tool to Alert doctors to Right Treatment) is a list of medications that should be prescribed for older people for a number of conditions. The assessment was carried out by one researcher (HvD) by means of an iterative process. Eventual difficulties were discussed with a second researcher (FW) until consensus was reached. A random sample of 10% of the patients was independently assessed by a second researcher (FW).

VI. Patient questionnaire

At inclusion, patients completed a questionnaire about their actual medication use and experienced problems with their medication. The patients indicated whether they filled out the questionnaire independently or whether they received help.

VII. Time registration

The time investment of the expert teams and the GPs in the intervention practices for completing the respective elements of the intervention was calculated by the researchers.

VIII. Electronic medical records

Data on gender and age from the GPs' EMRs was used for the non-responder analysis.

IX. Patient survey

The intervention patients completed a survey three months after baseline. The survey assessed the preparation and usefulness of the CMR and satisfaction about the consultation with the GP.

X. Survey among GPs in control practices

GPs from the control practices received a short survey to assess whether CMRs were conducted unintentionally during the study period for patients of the control group.

Analyses

Descriptive statistics were used for quantitative data using SPSS Statistics 23, using t-tests for continuous variables and chi square statistics for categorized variables.

For qualitative analyses, audio files were transcribed verbatim. Transcripts of the focus group and interviews were coded by two independent researchers (respectively FW and MD, and FW and SY) top-down with a pre-defined code-list which was formulated based on the topic lists and knowledge of the intervention. Differences in coding were discussed until consensus was reached, a few codes were added retrospectively. Citations and coded transcripts were arranged to broader themes using Atlas.ti software[22].

Table 7.1 Research questions for the evaluation of adherence, data sources and outcomes for the implementation fidelity of the Opti-Med intervention

Key intervention components	Data source[1]	Specific research questions	Outcomes	Rating*
1. Evaluation of adherence: content				
1.a Patient selection	I	To what extent was the patient selection implemented as planned?	Patient selection was carried out as planned according to the inclusion criteria. However, in practice it was not fully carried out by practice nurses but researchers provided extensive support or carried it out completely.	Moderate
1.b Patient involvement	IV	To what extent did the patient questionnaire information influence and tailor the PTP?	Patient questionnaire information was often used to tailor the PTP. Face-to-face patient contact might have resulted in more useful information according to the expert teams, e.g. compliance problems.	High
1.c Preparation of medication analysis	I	To what extent was the preparation of the medication analyses implemented as planned?	The preparation of the medication analyses was carried out by the researchers, therefore not fully implemented as planned. The gathering of information (medical EMR data and medication data from pharmacy) was planned to be carried out by the practice nurses. Medication analysis preparation was deemed sufficient by the expert teams.	Moderate
1.d Medication analysis	II	To what extent was the medication analysis implemented as planned? (structure, cooperation, STRIPA, knowledge and drafting the PTP)	Medication analysis by the expert team was carried out in a structured manner due to the use of the IT application STRIPA. Cooperation was good and complementary knowledge helpful. All expert teams formed fixed couples which improved cooperation and efficiency. Frequency, often once per month, also improved cooperation, efficiency and knowledge. All expert teams used primary care guidelines and applied STOPP and START criteria. The drafting of the PTP was deemed easy due to the structured STRIPA format but the lay-out and overview could be improved.	High

- Table 7.1 continues -

- Table 7.1 continued -

Key intervention components	Data source[1]	Specific research questions	Outcomes	Rating*
1. Evaluation of adherence: content				
1.e GP consultation	II, III	To what extent were patient consultations delivered and prepared as planned?	GPs differently performed the consultation: most GPs planned double consultation time and used a few minutes to prepare the consultations using the PTP form. In one practice, consultations were thoroughly prepared and discussed by phone, in another practice over half of the patients were visited at home. In two practices, the practice nurse did the consultation with the patient and only discussed major changes with the GP. As the result there was more attention for patient knowledge, compliance and preferences. According to GPs the use of external expert teams brought advantages such as efficiency and feasibility (as needed when conducting CMRs for larger numbers of patients), objectivity, expertise, and extra convincing power towards the patient. However, they also considered a final evaluation by the GP always necessary but requiring a certain time-investment. The expert teams mentioned advantages like objectivity. Not knowing the patient may also circumvent preconceptions by the patients' GP.	High

- Table 7.1 continues -

- Table 7.1 continued -

Key intervention components	Data source[1]	Specific research questions	Outcomes	Rating*
2. Evaluation of adherence: frequency				
2.a Patient selection	I	How many times a patient selection was performed?	Patients were selected approximately every 2-3 months and a list with eligible patients was composed. Out of 112 possible lists, 105 (94%) lists were successfully processed. In total 3 lists could not be produced due to software problems and 4 lists were produced but not processed by the GP due to time constraints.	High
2.b Patient involvement	IV, VI	How many patient questionnaires were completed and completed by the patient themselves? What was the influence of the patient input on the identified DRPs?	All questionnaires were filled in by the participants. 17% of the patients did not fill out the questionnaire independently but were assisted by family or other informal carers or visited at home by the researchers. 19% of all DRPs were identified on the basis of patient questionnaire specific data on actual medication use, DRPs, geriatric problems and pain.	High
2.c Preparation of medication analysis	I	How many CMRs were prepared?	All 518 CMRs were prepared as planned. For 11 patients the medication list from the community pharmacy was not received (in time), and the medication list provided by the patient and/or the GP was used.	High

- Table 7.1 continues -

- Table 7.1 continued -

Key intervention components	Data source[1]	Specific research questions	Outcomes	Rating*
2.d Medication analysis	I, IV, V	How many medication analyses were performed? How many proposed interventions and DRPs were formulated? To what extent were the proposed interventions implemented as planned? Were there differences in implementation rate for different type of proposed interventions?	A medication analysis was performed for 274 of 275 participants in the intervention group (one drop-out before expert team started) and for all 243 control patients. See figure 7.3 for the frequency, nature and implementation rate of the proposed interventions and drug related problems, including reasons for not follow-up the interventions. For 275 intervention patients, 1282 interventions were proposed by the external expert teams and documented on the pharmacotherapeutic treatment plans. Retrospectively, the researchers identified 1212 drug related problems with the DOCUMENT tool, out of these proposed interventions. In total, there were 8 patients without any DRPs. The implementation rate was higher for non-pharmacological interventions than pharmacological interventions, 69.2% compared to 42.6% (t-test $p<0.001$). The implementation rate for addition of drug was higher than for cessation of drug, 46.7% compared to 34.7% (t-test, $p=0.002$).	High
2.e GP consultation	I	How many GP consultations were performed?	90% (247) of the PTPs were discussed with the patient by the GP	High

- Table 7.1 continues -

- *Table 7.1 continued* -

Key intervention components	Data source[1]	Specific research questions	Outcomes	Rating*
3. Evaluation of adherence: duration				
3.a Patient selection	I	What was the estimated duration to select a patient?	About 1 minute per patient.	NA
3b. Patient involvement	-	NA	NA	
3.c Preparation of medication analysis	I	What was the estimated duration to prepare a medication analysis? How many days were there between inclusion and GP consultation date?	15 minutes per patient (including gathering of information, enter data and process the PTP). Median (IQR) number of days between inclusion and the consultation was 33.0 (15-51) days. 42% of the patients had their consultation within the planned one month after inclusion.	NA
3.d Medication analysis	VII	What was the mean duration of a medication analysis by the expert team?	Mean [sd] 22 [17] minutes per expert team member per patient	NA
3.e GP consultation	VII	What was the mean duration of a GP consultation?	Mean [sd] 34 [19] minutes per patient.	NA

- *Table 7.1 continues* -

- Table 7.1 continued -

Key intervention components	Data source[1]	Specific research questions	Outcomes	Rating*
4. Evaluation of adherence: coverage				
4. General	I, VIII	What proportion of the selected patients was invited to participate? What proportion of the invited patients participated and how was the drop-out and follow-up? Were there differences between GP practices? Were there differences in patient characteristics between the responders and non-responders?	2401 patients were initially selected on the basis of their GP EMR, 2037 (85%) patients were invited to participate. 364 (15%) patients were excluded after selection by the GP because they were terminally ill or due to a specific reason why it was not desirable to invite the patient (range 4-33% between GP practices). 25% were included (range 12-33% between GP practices) 15% was considered not eligible (range 0-22% between GP practices) 41% did not respond at all (range 26-64% between GP practices) 19% declined to participate (range 8-31% between GP practices) See figure for the patient flow in the Opti-Med study in Supplementary Material II. Patients who declined to participate did not differ in age as compared to participants, but among them there were significantly less women ($Chi^{2,}$ p=0.02) and they used less medication (t-test, p<0.001). Patients who did not respond did not differ in age and gender as compared to participants.	High

CMR=Clinical Medication Review; DRP=Drug Related Problem; EMR=Electronic Medical Record; GP=General Practitioner; IT= Information Technology; NA=Not Applicable; PTP=Pharmacotherapeutic Treatment Plan; START= Screening Tool to Alert doctors to Right Treatment; STOPP= Screening Tool of Older Person's Prescriptions; STRIPA= Systematic Tool to Reduce Inappropriate Prescribing Assistant

[1] I. Study administration
II. Focus group with expert teams
III. Semi-structured interviews with GPs
IV. PTPs and evaluation forms
V. Assessment of DRPs and STOPP and START criteria
VI. Inclusion patient questionnaire
VII. Time registration by expert teams and GPs
VIII. GP EMR data
IX. Patient survey after 3 months
X. Short survey among GPs of control practices

*Rating of implementation fidelity (very low, low, moderate, high)

Table 7.2 Research questions for the evaluation of moderating factors, data sources and outcomes for the implementation fidelity of the Opti-Med intervention

Key intervention components	Data source[1]	Specific research questions	Outcomes
1. Moderating factors: participant responsiveness			
1. General	I, III, IX	How were patients informed about, and engaged in the intervention?	Patients received an information letter including a customized leaflet to prepare for the GP consultation. GPs found most patients were well informed and pleased with the extra attention for their medication.
		How was the patient recall of consultation?	231 intervention patients filled out the questionnaire at 3 months: 14% of the patients that had a consultation with their GP did not recall the consultation.
		How did patients prepare for the consultation?	48% did not prepare particularly for the consultation, 23% brought or studied his/her medication overview, 24% thought of or noted down questions beforehand and 4% brought someone to the consultation.
		How did patients perceive the intervention?	88% of the patients perceived the consultation as pleasant or very pleasant. 72% thought the consultation was useful or very useful.
2. Moderating factors: strategies to facilitate implementation			
2.a Patient selection	I	What strategies were used to support patient selection?	Patient selection was carried out using a specially designed ICT application that searched GP EMR records on the basis of the study inclusion criteria. Due to difficulties in applying the application and time restraints only a few practice nurses were able to carry out the patient selection independently. The majority needed help from the researchers.

- Table 7.2 continues -

- *Table 7.2 continued* -

Key intervention components	Data source[1]	Specific research questions	Outcomes
2.b Patient involvement	I	What were strategies to support implementation of the intervention and patient involvement?	The patient questionnaire and the customized leaflet to prepare patients for the consultation were strategies to involve patients in their own CMR and tailor it to their needs. Patients could ask for assistance in filling out the patient questionnaire on actual medication use and DRPs as needed to prepare the medication analysis. Only a very limited number of patients used this option.
2.c Preparation of medication analyses	I	What strategies were used to support the preparation of the medication analysis?	Although time-consuming and prone to error, convenient use was made of the STRIPA. Collecting information from the GP EMR and pharmacy was also convenient but time-consuming due to limitations of the GP IT systems.
2.d Medication analysis	I, II	What strategies were used to support expert teams in implementing the medication analyses? How were these strategies perceived by the expert teams?	Expert teams followed an online course, 5 hours professional training to prepare for the medication analyses and a 2 hour feedback meeting after two months into the intervention. During the first sessions all expert teams were assisted by the researchers to help with the software package and available for questions. STRIPA was used to support the medication analyses. The training was deemed useful, especially to get acquainted with STRIPA and with the fellow expert team member. Most skills and knowledge were acquired during the course of the study. The expert teams all indicated that the STRIPA was a big support for the structured medication analysis. A barrier was that STRIPA was not supporting the drafting of PTPs.

- *Table 7.2 continues* -

- Table 7.2 continued -

Key intervention components	Data source[1]	Specific research questions	Outcomes
2.e GP consultation	I, III	What were strategies to support implementation of the intervention by the GPs and practice nurses? How were these strategies perceived by the GPs?	Intervention GPs were informed by the researchers during a kick-off meeting and received printed materials on the intervention. Practice nurses received a workbook with practical steps and the researchers assisted the practice nurses when needed and were available for questions via e-mail or phone. We tried to adapt the PTP forms to a format usable in the GP EMR but integration proved impossible to integrate the PTP. How the kick-off meeting printed materials and communication was perceived is unknown. GPs indicated that once they got used to the PTP evaluation forms they were easy and structured but some considered the non-compatibility with the GP IT system a barrier.
3. Moderating factors: quality of delivery			
3a. Patient selection	II	How was the quality of the patient selection and how was this evaluated by the GPs?	Quality of the patient selection is not relevant and not addressed.
3b. Patient involvement	IV	How was the quality of the patient involvement?	Implementation rate of DRPs modified on basis of patient input was significantly higher as compared to DRPs not modified on basis of patient input (respectively 60% and 46%, T-test $p < 0.001$).
3c. Preparation of medication analyses	II, III	How was the quality of the preparation of the CMRs and how was this evaluated by the expert team and GPs?	The quality of the preparation was good but occasionally medical or medication files were incomplete. The quality of the medical files differed between GP practices. As a consequence in these cases recommendations were less useful and it required more effort of the GP to conduct the patient consultation. However, GPs reported that in most cases incorrect data could be easily corrected and incorrectly proposed interventions were ignored or adjusted.

- Table 7.2 continues -

- Table 7.2 continued -

Key intervention components	Data source[1]	Specific research questions	Outcomes
3d. Medication analysis	III, IV, V	How was the reproducibility of the medication analysis? To what extent were DRPs and proposed interventions related to the STOPP and START criteria in the intervention patients? How was the quality of the medication analyses evaluated by the GPs?	PTP reproducibility between different expert teams was moderate. A mean [sd] of 1.5 [1.2] in the number of DRPs and 2.4 [1.4] deviations in type of DRPs was found per patient between two different expert teams. In total 33.1% of the DRPs was related to a STOPP criterion and 19% to a START criterion. For details see table 7.3. GPs considered PTPs of good quality and more elaborate than they were used to from other polypharmacy projects or community pharmacist initiatives.
3e. GP consultation	IX	How was the quality of the GP consultation according to the patient, in terms of understanding and asking questions?	82% indicated to understand everything or almost everything during the consultation. 75% indicated that they could ask all questions or almost all questions during the consultation.

-Table 7.2 continues -

- *Table 7.2 continued* -

Key intervention components	Data source[1]	Specific research questions	Outcomes
4. Moderating factors: context			
4. General	I, III, X	How did the organization of GP practices affect the implementation?	There were differences between GP practices in how easy the intervention was embedded into daily practice. Implementation went much smoother in GP practices in which a practice nurse was assigned to organize this type of interventions. Personnel changes during the course of the study were barriers for continuation of the intervention and good implementation.
		How did attention for polypharmacy in primary care and in society affect the implementation?	GPs in the intervention group found specific attention for polypharmacy, medication reviews and the primary care guideline encouraging and considered them important GP care topics.
		To what extent was the usual care in the control group implemented as planned? (possible contamination)?	The 11 control GP practices confirmed that no structured CMRs were conducted, except in a small student project. However, all practices were involved in an elderly care project with extra attention for pharmacotherapy but only a small number of their patients was involved.
		How were expert teams and GPs reimbursed?	No reimbursements were offered to patients. Expert teams were paid an hourly rate for their work in the medication analyses. GP practices were paid per patient included.

CMR=Clinical Medication Review; DRP=Drug Related Problem; EMR=Electronic Medical Record; GP=General Practitioner; IT= Information Technology; PTP=Pharmacotherapeutic Treatment Plan; START= Screening Tool to Alert doctors to Right Treatment; STOPP= Screening Tool of Older Person's Prescriptions; STRIPA= Systematic Tool to Reduce Inappropriate Prescribing Assistant

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VIII. GP EMR data
IX. Patient survey after 3 months
X. Short survey among GPs of control practices

Results

Outcomes per key intervention component for each dimension of the framework are shown in detail in table 7.1 and 7.2.

Adherence to the intervention

Patient selection was carried out according to the inclusion criteria. However, for this topic, we deviated from the study protocol, most practice nurses did not carry out patient selection and invitation themselves due to difficulties in using the newly-developed software application and due to time restraints. The Opti-Med researchers provided extensive support or carried out the patient completion themselves instead.

Also, the Opti-Med researchers collected most information (GP EMR data, medication overview from pharmacy and patient questionnaire) for the medication analyses instead of the practice nurses, due to time restraints.

Nineteen percent of all DRPs identified were based on the input from the patient questionnaire. The majority of these DRPs were related to medication knowledge or adherence to medication.

The expert teams carried out medication analyses for all but one of the 275 participants of the intervention group and for all 243 control patients. According to the expert team members, medication analyses were conducted in a highly structured manner, mainly due to use of the STRIPA tool. They also mentioned that the method and high number of medication analyses by fixed couples improved efficiency and collaboration. The expert team members and the GPs mentioned the 'external' nature of the team as an additional value, because of the fresh perspective of such a team allowing an independent 'objective' assessment.

In 90% (247/275) of the patients, GPs discussed the proposed changes in medication with their patients. 42% of the patients had their consultation within the planned first month after inclusion. The method of consultation was deliberately not specified by the researchers. Most GPs planned double consultation time and used a few minutes to prepare the consultations using the PTP.

Figure 7.3 gives an overview of the frequency, nature of DRPs and proposed changes in medication as well as their implementation rate, and

reasons for not implementing as proposed. Nearly 50% of all proposed medication changes were (partially) implemented (consented implementation).

'Addition of a drug' was significantly more often implemented than 'cessation of drug' (46.7% vs. 34.7% (t-test, p=0.002). The implementation rate of non-pharmacological recommendations (e.g. laboratory tests) was significantly higher than proposed changes in medication (69.2% vs 42.6% (t-test p<0.001). The most frequent reasons for non-implementation were: 'proposed change is based on incomplete medical or medication files', 'prescription originates from a medical specialist in secondary care' or 'the change in medication has been tried before by patient and/or prescriber'.

The total time spent by all healthcare providers for one patient was estimated at 94 minutes. This includes one minute for patient selection, 15 minutes for preparation, 22 minutes per expert team member for medication analysis and 34 minutes for GP consultation.

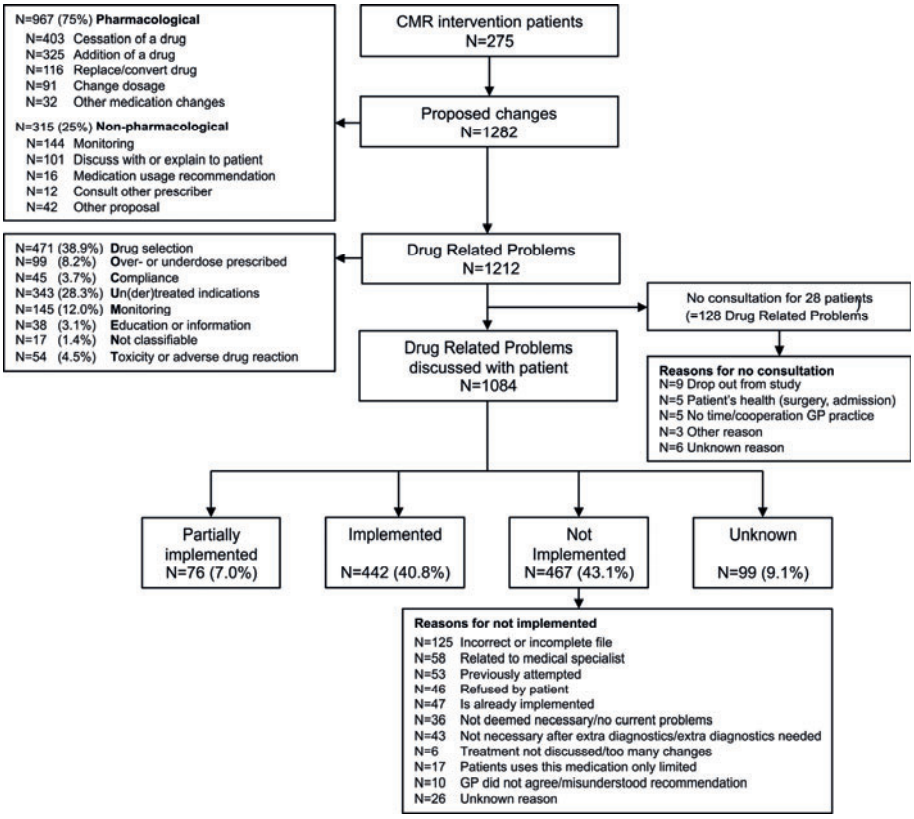

Figure 7.3 Frequency and nature of proposed changes and drug related problems

For 275 intervention patients, 1282 pharmaceutical and non-pharmaceutical changes were proposed by the external expert teams. Retrospectively, the researchers identified 1212 drug related problems with the DOCUMENT tool [21], out of these proposals.

Moderating factors

Participant responsiveness

Over half of the patients reported to have prepared themselves for the consultation with the GP by bringing or studying their own medication, preparing questions, or bringing someone to the consultation. Fourteen percent of the patients who had a consultation with the GP did not recall it. Of the patients who did recall the consultation, the majority considered it useful.

Strategies to facilitate implementation

Patient selection was facilitated by software specifically developed for the Opti-Med study. However, most practice nurses considered it difficult to use and time consuming. Collecting information from the GPs' EMRs and pharmacy records in preparation of the medication analyses was useful but time-consuming. The quality of the preparation for the medication analysis was deemed sufficient by the expert teams.

Training in performing CMRs was deemed useful by the expert team members. However, they indicated that most knowledge and skills were acquired when performing the medication analyses. The use of the STRIPA tool was found to greatly support and to highly structure the medication analysis. Some GPs indicated that the form with the PTP was not very user-friendly; however, after a few consultations, most GPs became familiar with it. Seventeen percent of the patients reported to have been assisted in completing the patient questionnaire.

Quality of delivery

The GPs considered the PTPs drafted by the expert teams of very good quality. The mean difference between the number of DRPs per patient identified by two expert teams was 1.5 (standard deviation (sd) 1.2) and the mean number of differences in type of DRPs was 2.4 (sd 1.4).

In total 33.1% of the DRPs identified were related to a STOPP criterion and 19% to a START criterion (table 7.3), but a considerable part of the identified DRPs could not be related to a STOPP or START criterion (e.g. practical medication problems, changes in dosage or evaluation of drug effect)

The majority of the patients indicated that they could ask (almost) all questions and understood (almost) everything during the consultation with the GP.

The implementation rate of proposed medication changes influenced by patient input was significantly higher as compared to the implementation rate of proposed changes not influenced by patient input (respectively 60% and 46%, $p < 0.001$).

Contextual factors

GPs considered the increased attention for polypharmacy, medication reviews, and the recently published Dutch multidisciplinary guideline on polypharmacy [7] encouraging and important for GP care. CMRs were not performed for patients in the control practices, therefore contamination was minimal.

The embedding of the Opti-Med intervention varied between GP practices. GPs and practice nurses reported less complaints and questions from patients when a practice nurse was specifically assigned to the organization of the intervention. GPs mentioned that personnel changes during the course of the study was a barrier for the continuity and implementation of the intervention.

Table 7.3 Prevalence of STOPP-START among intervention patients per DOCUMENT DRP type

DOCUMENT DRP type	Total	STOPP	START
	N (%)	***N (%)***	***N (%)***
Drug selection	471 (38.9)	372 (30.7)	17 (1.4)
Over or underdose prescribed	99 (8.2)	7 (0.6)	3 (0.2)
Compliance	45 (3.7)	3 (0.2)	1 (0.2)
Un(der)treated indications	343 (28.3)	1 (0.1)	212 (17.5)
Monitoring	145 (12.0)	0	0
Education or Information	38 (3.1)	0	0
Not classifiable	17 (1.4)	0	0
Toxicity or ADR	54 (4.5)	18 (1.5)	0
Total	1212 (100)	401 (33.1)	233 (19.2)

ADR=Adverse Drug Reaction; DRP=Drug Related Problem; START= Screening Tool to Alert doctors to Right Treatment; STOPP= Screening Tool of Older Person's Prescriptions

DRPs were identified by the expert team at baseline and classified by the researchers according to the validated DOCUMENT[21] classification system to categorize DRPs into 8 categories. Retrospectively, STOPP and START criteria were assigned to the DRPs.

Discussion

For all key intervention components the implementation fidelity was moderate to high. Almost all key intervention components were generally carried out as planned. However, for the elements patient selection and preparation of the CMR analyses the researchers were more involved than intended. Almost half of the proposed changes in medication were implemented, starting new medications seemed easier than stopping medications. Patient involvement may also be considered accomplished as planned, one fifth of the proposed medication changes was influenced by patient input.

Training of the expert teams, the use of the STRIPA tool and the structured PTP forms facilitated implementation of the intervention. Difficulties with patient selection due to non user-friendly software and incomplete medical and medication files used for the medication analyses appeared factors promoting non-adherence to the intervention. The reproducibility of the medication analyses between the expert teams was moderate. There were differences in the embedding of the intervention between GP practices. A designated and motivated practice nurse was an important contextual facilitating factor for adherence to the intervention.

To our knowledge, this is one of the first comprehensive process evaluations of a CMR intervention study. Other studies on CMRs did not included or only a limited process evaluation or a different method of CMR [23,24]. A comparison with previous studies is therefore difficult, however, some results can be compared.

The implementation rate of proposed medication changes of almost 50% is within the range found in other studies [25,26], higher implementation rates may be found when the patient's own pharmacist and GP are involved in the medication analysis and less non-relevant recommendations may be formulated. However, GPs did not experience the irrelevant recommendations as inefficient and time consuming and reported that this disadvantage often was outweighed by the advantage of the efficiency, objectivity and expertise of the external expert team.

The 94 minutes time spent is acceptable compared to other studies and estimations in guidelines [7,27]. Almost a quarter of the time is spent by the practice nurse instead of the GP and/or pharmacist, which is less costly.

However the time investment is still considerable, but may reduce over time. A previous study with Opti-Med data shows that the expert teams can improve the efficiency over time.[28]

The moderate reproducibility of the medication analyses between the expert teams could be partly explained by variations among experts. In a recent Dutch qualitative study on case vignettes with polypharmacy and multimorbidity, it was concluded that GPs varied in medication management strategies which resulted in differences in proposed medication changes [29].

Lessons learned for CMRs in a non-RCT setting

This process evaluation provides a better insight into the implementation fidelity of an innovative method for CMRs. Implementation fidelity was studied alongside a pragmatic cluster RCT, which does not resemble daily practice. E.g., the efforts and time investment of the researchers are applicable in daily practice.

As the selection of patients and preparation of the CMRs in this study was mainly performed by researchers there are still some barriers to overcome before these key intervention components can be successfully implemented in daily practice. Time, training and dedication of a practice assistant or practice nurse in the GP practice for CMRs are necessary.

The medication analyses being performed by external expert teams seems feasible, however reimbursement and organization of expert teams outside the scope of a research project will be necessary. Currently in The Netherlands GPs and pharmacists are reimbursed for conducting CMRs. A dedicated coordinator may be needed to organise the work of expert teams within e.g. an existing regional collaboration structure between GPs and/or pharmacists.

Reimbursements for the GPs and reminders by the researchers for GPs and patients may have increased the implementation rate of the GP consultations. Of the invited patients, almost 60 % did not reply or indicated that they did not want to participate. It might be that in daily practice, a part of this group may need a different approach with possibly more face-to-face contact to identify the actual medication intake, DRPs and preferences.

Identified barriers for implementation in daily practice, such as time restrains and incompleteness of medical files are commonly known from other pharmaceutical care studies or evaluation projects [8,24,30].

Limitations

Several limitations may have influenced the evaluation of the adherence to the intervention and moderating factors determining the implementation fidelity of the intervention.

First, the researchers who carried out the Opti-Med intervention were also involved in the process evaluation. We used a subjective rating to measure implementation fidelity, an objective rating is impossible in this type of process evaluations.

Second, as compared to the framework of Hasson the moderating factors 'comprehensiveness of the policy description' and 'recruitment' have not been included in the present evaluation. Comprehensiveness of the policy description was not assessed since the number of key components in the intervention is limited and it was not feasible to obtain an external assessment of the policy description with respect to the complex intervention. Recruitment is covered under the adherence dimension 'coverage'. Furthermore, not all dimensions of adherence and of the moderating factors have been assessed extensively. The assessment of the quality of delivery of the intervention for GP consultations and patient involvement was very limited. Video recordings of consultations might have provided more insight into the quality of delivery. The duration and topic list of the GP interview was limited. Finally, results from a patient survey gave us only limited insight into the patients' responsiveness and quality of delivery of the patient involvement, compared to e.g. qualitative patient interview data.

Conclusion

Overall, the implementation fidelity was moderate to high for all key intervention components of the CMR intervention. This means that almost all intervention key components were delivered as intended. The absence of its effectiveness with respect to enhancing quality of life cannot be explained by insufficient implementation fidelity. Nevertheless, this process evaluation provides insight into how this method of conducting CMRs can be implemented

in daily practice. Barriers on organizational level must be overcome; the availability of user-friendly software, easy exchange of medical and medication data, and coordination and management of the intervention within a larger collaboration between GPs and pharmacists are very important for successful implementation.

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Conflicts of interest

All authors declare that they have no conflict of interest.

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Supplementary Material I. Topic lists of semi-structured interviews with GPs and focusgroup with expert team

Topic guide semi-structured interviews GP (and practice nurse)

Objective: What are the experiences of the GPs with the Opti-Med medication review proposed interventions and consultations?

I. Evaluation medication review proposed interventions and consultations

- Could you tell me a little about how the Opti-Med intervention was organized and implemented in your GP practice?

- What were your expectations beforehand of medication reviews, especially the feasibility and usefulness for you and the patient?

- How were the consultations with the patients?
  Prompts:
  - *what went good and what went wrong;*
  - *which problems were handled in the consultations;*
  - *were there differences between the first consultations and later on?*

- Were the proposed interventions from the expert teams comprehensible?
  Prompts:
  - *did you always agree with the proposed intervention?*

- What were the most common reasons to not follow up a proposed intervention?

- Could you tell me a little about the completeness of the medical and medication data on which the proposed interventions by the expert teams were based?

- In your opinion, what did you think of the external party, that did not know the patient, reviewed the medication?
  Prompts:
  - *expectations beforehand and opinion now?*
  - *pros and cons of not knowing the patient?*

- Could you tell me a little about the follow-up and monitoring of Opti-Med patients over time?

- Did you learn something about pharmacotherapy for elderly and did you implement these extra knowledge in practice?

- Did you contact medical specialist and/or pharmacists to consult on medication changes in the context of the Opti-Med study.

- Was the Opti-Med intervention indeed innovative for your GP practice?

- Can you mention other elements in the approach and execution of the Opti-Med medication reviews that contributed to high quality of efficient medication reviews or less qualitative or efficient medication reviews?
  Prompts:
  - *point of attention/improvement*
  - *Impact contextual factors (e.g. personnel changes)*

II. Target group

- In your opinion, is the current targeted patient group a useful group for medication reviews?
  Prompts:
  - *interesting/useful subgroups (polypharmacy, oldest old etc?*
- In this study patients with geriatric problems (instability, immobility, incontinence and impaired cognition) were the target group and a new angle for the medication reviews. In your opinion, were these geriatric problems dealt by means of the medication reviews?

III. Implementation in daily practice

- Do you think the Opti-Med method could be implemented in daily GP and pharmacy practice, and how?
  Prompts:
  - *feasibility/priority*
  - *organisation*
  - *role of practice nurses*
  - *cooperation*
  - *training/education*

Topic guide focusgroup discussion expert teams

Objective: What are the experiences of the expert team members with the Opti-Med medication review analyses?

I. Evaluation of the method of performing reviews; facilitators and barriers

- Could you tell me a little about using the structure of the medication analysis (STRIP)?
  Prompts:
  - *did you follow the individual steps of the STRIP guideline and helped that to improve quality and/or efficiency?*
  - *you start with assigning all medications to condition, then undertreatment, overtreatment etc?*

- Did you use the STOPP- and START criteria and/or Dutch GP guidelines (NHG).
  Prompts:
  - *this is mostly embedded in the STRIP-assistant, did you consult guidelines in addition?*

- Could you tell me a little about the knowledge you had before and after the training and the knowledge you derived from performing the medication reviews?
  Prompts:
  - *did you have sufficient knowledge and training to perform the medication reviews?*

- In your opinion, was the data complete provided to perform the medication reviews?
  Prompts:
  - *how often did it occur that essential information was missing to perform a good medication review, or possibly there was too much information?*
  - *in your opinion, were there possibly errors of data entry or in the original files from the GP or pharmacy.*

- How do you feel about the fact that you did not know the patient?
  - *cons and pros*

- What did you think of the cooperation and discussion between physician and pharmacist within the expert team?
  Prompts:
  - *what were you expectations beforehand, and how is this currently?*
  - *was there of was there no consensus?*
  - *complementary knowledge/skills/approach?*

- What did you think of drafting the pharmacotherapeutic treatment plan for the GP?

- What were important differences of Opti-Med compared to regular medication reviews (as far as your experiences reach)
  Prompts:
  - *structure*
  - *time-investment*
  - *quality*

- Can you mention other elements in the approach and execution of the Opti-Med medication reviews that contributed to high quality of efficient medication reviews or less qualitative or efficient medication reviews?
  Prompts:
  - *point of attention/improvement*

II. Target group

- In your opinion, is the current targeted patient group a useful group for medication reviews?
  Prompts:
  - *interesting/useful subgroups (polypharmacy, oldest old etc.?*

- To what extent could you take into account the geriatric problems with respect to medication changes or other proposed interventions?

III. Surplus value patient information

- According to you, what is the surplus value of the patient information to tailor the pharmacotherapeutic treatment plan?
  Prompts:
  - *what type of interventions were proposed?*

- Is this input comparable to information which you would derive from a face-to-face contact with the patient?

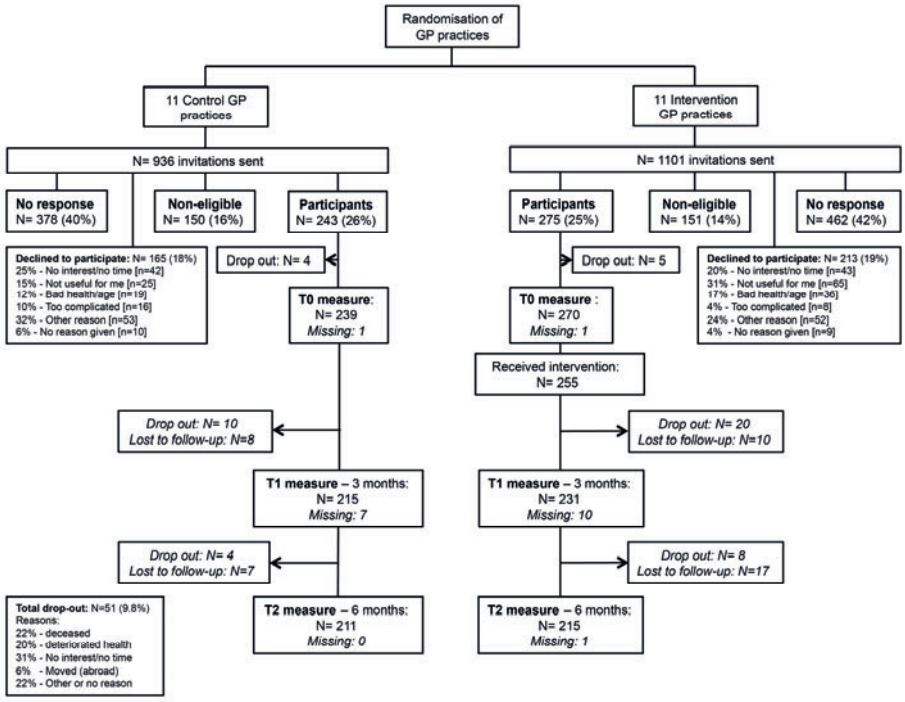
IV. Implementation in daily practice

- Do you think the Opti-Med method could be implemented in daily GP and pharmacy practice, and how? Especially the use and organization of external expert teams?
  Prompts:
  - *what form could we use for teams?*
  - *who has which responsibility*
  - *role of elderly care specialist*
  - *training/education*

V. Evaluation of STRIP-assistant

- To what extent does the use of the STRIP-assistant, contributed to high quality and efficient medication reviews? Do you have points for improvement for the STRIPA decision-support web application facilitating the pharmacotherapeutic analysis?

Supplementary Material II. Figure of study flow of Opti-Med participants



8

General discussion

Inappropriate medication use is a prevalent and challenging problem among older people. Clinical medication reviews (CMR) may reduce this inappropriateness and thereby may improve their quality of life (QoL).

There are several challenges and knowledge gaps within the field of CMRs: their effectiveness with respect to health outcomes, the best target group, patient participation and implementation in daily clinical practice. The present thesis aimed to gain more insight into these challenges and knowledge gaps by means of a variety of studies each designed to answer a different research question. The objective of this thesis was to gain more insight into patient participation in medication reviews and to investigate the effectiveness and feasibility of an optimized CMR intervention in older people with geriatric problems in general practice and second. This thesis was based on the following research questions:

1. What is known in the literature about ways of patients participation in the medication review process and its effects on the outcomes of a medication review?
2. Can patient participation in medication reviews be achieved via a questionnaire instead of an interview?
3. What is the (cost)-effectiveness of an optimized clinical medication review on quality of life and geriatric problems in comparison with usual care, in older patients with geriatric problems presented in general practice?
4. What is the implementation fidelity of optimized clinical medication reviews in the setting of general practice?

In this final chapter, we summarise the main findings and formulate answers to the research questions. Furthermore, we comment on the methodological aspects and reflect on the main findings of the studies in this thesis. Finally, the implications of our findings for future research and policy and clinical practice are discussed.

Main findings

Research question 1

> *What is known in the literature about ways of patients participation in the medication review process and its effects on the outcomes of a medication review?*

To answer this question we conducted a systematic literature review (**chapter 2)**. We systematically searched and reviewed the literature on the subjects of patient participation and medication reviews. In total, 37 studies with a variety of study designs met the inclusion criteria. In all studies, patient participation in medication reviews was limited to the level of information giving by the patient to the professional, mainly on actual drug use. The effects of patient participation were not frequently studied and poorly described. We found some evidence that involving patients in medication reviews might result in a better identification of drug related problems (DRP) as well as improved knowledge and patient satisfaction. However, no evidence on patients' health outcomes was found.

Research question 2

> *Can patient participation in medication reviews be achieved via a questionnaire instead of an interview?*

To answer this question we developed a patient questionnaire as preparation for a CMR and conducted an agreement study in 97 older community-dwelling patients (**chapter 3)**. In this study the agreement between patient information on actual medication use and occurrence of DRPs obtained with a questionnaire was compared with information obtained during an interview at home. Of all medications used, almost 90% was reported identically in the questionnaire and the interview. Agreement for the complete medication list was found for 45% of the patients. With respect to DRP level, agreement between questionnaire and interview amounted to 75%. The number of medications and DRPs reported in the interview was higher than in the

questionnaire. Agreement tended to be lower in vulnerable patients characterized by ≥4 chronic diseases, patients using ≥10 medications and those with a low health literacy. Taking the limitations into account, a questionnaire seems a suitable tool for medication reviews that may replace an interview for most patients.

Research question 3

> *What is the (cost)-effectiveness of an optimized clinical medication review on quality of life and geriatric problems in comparison with usual care, in older patients with geriatric problems presented in general practice?*

To answer this question we designed the Opti-Med intervention and conducted a cluster randomised controlled trial (RCT) among 22 general practices in 518 older patients who consulted their general practitioner for a geriatric problem (**chapter 4)**. The Opti-Med intervention was designed as an innovative intervention applying an optimally facilitated, prepared and structured problem-oriented CMR, with the specific objective to tackle the most important obstacles for large scale implementation of CMRs.

In **chapter 5**, results concerning the effectiveness of the Opti-Med intervention have been presented. No significant differences between the intervention and control group and over time were found for the primary outcome measures (quality of life [QoL] and geriatric problems), and for two secondary outcome measures medication satisfaction and adherence. The percentage of solved DRPs after six months was significantly different between the intervention and the control group. The Opti-Med intervention resulted in 22% more solved DRPs compared to usual care. However, the higher percentage of solved DRPs in the intervention group did not result in effects on the patients' health.

In **chapter 6**, the cost-effectiveness study of the Opti-Med intervention, which was performed alongside the Opti-Med effectiveness study, has been presented. Total societal costs in the intervention group were €684 higher than in the control group, but this difference was not statistically significant (95%CI -1142 ; 2387). Cost-effectiveness acceptability curves showed that for solved

DRPs, the probability of the intervention being cost-effective reached 0.95 at a WTP of €2100 per solved DRP. For all other outcomes (quality-adjusted life years (QALYs), quality of life and changes in geriatric problems), the probability was low at all willingness-to-pay (WTP) values (i.e. range 0.25; 0.49). Optimized CMRs were not considered cost-effective compared to usual care.

Research question 4

> *What is the implementation fidelity of optimized clinical medication reviews in the setting of general practice?*

To answer this question we conducted a quantitative and qualitative process evaluation alongside the Opti-Med effectiveness study according to the Conceptual Framework for Implementation Fidelity (**chapter 7)**. Adherence to the intervention and moderating factors for implementation fidelity were evaluated per key intervention component. Some elements, such as patient selection and preparation of the medication analyses were carried out by the researchers instead of the practice nurses. Cooperation between expert teams' members and the use of an online decision-support medication evaluation facilitated implementation. Barriers for implementation were time constraints in daily practice, software difficulties with patient selection and incompleteness of medical files. The total time investment of healthcare professionals for the Opti-Med intervention was 94 minutes per patient.

Overall, the implementation fidelity was moderate to high for all key intervention components. The absence of effectiveness of the intervention with respect to its primary outcomes could not be explained by insufficient implementation fidelity.

Methodological considerations

This paragraph addresses some methodological aspects of the studies described in the present thesis that should be considered when interpreting the studies' findings.

Measurement of the impact and level of patient participation in medication reviews

In the context of the systematic literature review (**chapter 2),** we discussed the difficulty to measure the impact of patient participation on the outcomes of CMRs. In most studies, an evaluation of the impact of patient participation on CMRs was not the primary focus of the study. Our conclusion that the impact of patient involvement has been described poorly therefore requires some nuance. Nevertheless, we can still conclude that only a few studies addressed this aspect. The process evaluation (**chapter 7**), comprised a comparison between proposed medication changes as a result of additional patient input (from the questionnaire) and proposed changes without patient input, but the impact of patient participation on the outcomes was not evaluated. The impact of patient participation in CMRs should preferably be assessed by means of a robust comparative study. In our trial, this would have required a third intervention arm. This option was considered at the start of the study, but rejected for budgetary reasons.

Apart from the input of patients via questionnaires in our trial, the level of actual patient participation in the CMRs was not assessed. The consultation with the GP to discuss CMR outcomes and decide upon changes in the medication regimen would have provided a good opportunity to fully assess the level of patient participation. Systematic observations of GP-patient interactions during these consultations (recorded on video) would have been the preferable method to assess the level of patient participation. Furthermore, patient preference on the level of involvement within a CMR was not assessed within this thesis, and may be a topic for future research.

This means that we do not have obtained insight in the exact level of patient participation for the CMRs conducted for this thesis and the effects of the patient's input is not assessed in a comparative study.

Design of the Opti-Med study

The Opti-Med study design included a cluster RCT carried out in 22 GP practices. The chosen design is a strength of this study, a multicenter cluster RCT with over 500 patients provides a high level of evidence and the study was conducted in daily general practice which strengthens its practical relevance. The advantage of a cluster RCT is that contamination within the same practice

is prevented and the implementation in daily practice of the intervention is easier. A disadvantage is that we needed more participants in order to obtain a sufficient study power.[1]

Several risks of biases may have been present within the Opti-Med study. Due to the nature of the intervention, it was impossible to blind participants, healthcare professionals and researchers for their study group allocation. This may have introduced performance and detection bias. We do not think that this affected the primary outcomes (QoL and geriatric problems), which were assessed by questionnaires. However, the assessment of DRPs by the expert teams and whether they were solved or not may have been subject to a detection bias leading to an overestimation of the number of DRPs identified and solved. Indeed, more DRPs were identified in the intervention group compared to the control group; we corrected for this difference in the analyses.

Cluster RCTs are known to be prone to bias.[2] Invitation and selection of patients was assisted by an IT tool in order to avoid selective inclusion. However, in the Opti-Med study, there were few differences in patient characteristics between the study groups. Patients in the usual care group had on average more chronic diseases whereas in the intervention group more DRPs were identified. We corrected for these baseline differences in the analyses.

For participating in an RCT providing informed consent and the completion of questionnaires are inevitable. A selection bias may have been introduced due to these requirements. People with low health literacy and lower socio economic status may be underrepresented because they may experience these requirements as an obstacle. We offered the option of assistance with the completion of the questionnaire by means of a visit by the nurse practitioner; this option was used only a few times. In the Opti-Med study, the participation rate was 30%, 48% of the patients did not respond and 22% declined. There were no differences in gender and age between participants and non-participants. The level of education was relatively high among participants, 31% indicated they had attended higher education. This percentage is representative for the population in the urban Amsterdam area where the study took place, but higher compared to the 17% found in the general Dutch population.[3] Unfortunately, other data on patient characteristics

of non-participants, such as education level and health literacy, were not available. Among the participants were more women and they used more medications compared to the persons who declined participation. There are reasons to believe that among the non-responders and decliners there are also patients who were not eligible.

On the other hand, it is possible that there is a group of more vulnerable people, i.e. those with a low health literacy who did not participate in the study. This group may need a different approach, such as an direct approach by the pharmacy assistant or practice nurse, for inviting them to participate. This would mean that the results probably cannot be extrapolated to more vulnerable older patients.

Outcome measures

Quality of life

In the Opti-Med study, EQ5D-3 and SF12 were used to measure QoL. These are validated instruments and often used, also in economic evaluations to calculate Quality-Adjusted Life Years (QALYs). These measures are not very discriminative and QoL is affected by multiple factors in the somatic, social, physiological and functional domains.[4] One can argue that these elements cannot be influenced by changes in the medication regime alone. We chose these generic measures for our primary outcome, because our study population was very heterogeneous and disease specific measures could therefore not be used. The EQ5D-3 is also the normative measure for economic evaluations. Moreover, maintaining or improving the QoL is among the most important goals for this target group. For future studies, it should be further explored whether more recent tools such as Adult Social Care Outcomes Toolkit (ASCOT) and ICEPOP Capability measure for Older people (ICECAP-O)[5,6] would be better alternatives for older people in pharmacological interventions; both tools are preference based measures for assessing QoL in older adults and assess a broader perspective than the traditional QoL life measures such as EQ5D and SF12 or SF36.

Geriatric problems

Geriatric problems were chosen as another primary outcome measure for the Opti-Med study with the aim to get more insight into QoL in a descriptive way. The operationalization of the outcome measure to assess the presence of geriatric problems was complex. We introduced two categories, resolved and improved geriatric problems, to distinguish between patients who experienced some improvement and patients for whom the geriatric problem was resolved.

This outcome measure has some limitations which should be taken into account when interpreting the results. Firstly, we did not use validated questionnaires or physical tests to measure all geriatric problems but used commonly used Visual Analogue Scales (VAS) to measure changes in geriatric problems. For pragmatic reasons, we did not assess the various problems with lengthy questionnaires or physical tests during home visits. Secondly, the use a of primary geriatric problem is a limitation (box 8.1) and may have left out some of the nuances of the multiple problems that characterizes this target group.

Moreover, the relationship between the geriatric problems and inappropriate medication use was not assessed. Inappropriate medication use may not always be related to the primary geriatric problem defined in this outcome measure. For instance, mobility was one of the most prevalent geriatric problems in our study population, and possibly one of the most difficult problems to influence with more appropriate medication use. In future studies, a more substantiated outcome measure for geriatric problems may be compelled and its relation to inappropriate medication use should be assessed.

The lack of a global and multidimensional outcome measure for the geriatric problems makes our conclusions on this outcome measure less confident.

Box 8.1 Operationalisations of geriatric problems

Definition primary geriatric problem based on decision rules:
1. Two or more falls in the previous 6 months
2. Highest VAS for the geriatric problems Dizziness, Mobility, Cognition problems or Incontinence. When equal VAS:
    1. Check with EMR for matching ICPC code for identification
    2. Dizziness>Mobility>Cognition problems>Incontinence
3. One fall in the previous 6 months
4. Fear of falling

The geriatric problem outcome measure was operationalised in two ways (dichotomous);
1. improvement versus worsening or stabilization of the primary geriatric problem
    - A difference after 6 months of two or more points on the VAS was considered as either an improvement or worsening.
    - For falls an improvement or worsening was absolutely more or less falls in the previous 6 months (T1 and T2 combined).

2.'Resolved' geriatric problem: Absence of the geriatric problem versus the presence of the primary geriatric problem;
    - Resolved: Absence of the primary geriatric problem is defined as a VAS of two or less after 6 months or no falls in the previous 6 months
    - Unsolved: Presence of the primary geriatric problem is a VAS or three or more after 6 months or at least one fall.

Time horizon and duration of follow-up

In the evaluation of an intervention, the time horizon should be long enough to capture all effects and costs of this intervention. The follow-up period of patients participating in the Opti-Med study was six months. This may have been too short to identify long-term effects and costs. We hypothesized that effects of medication changes on QoL and geriatric problems would appear within six months. However, other possible effects of medication changes (e.g. the introduction of preventive medication) will only become apparent over a much longer period.

In addition, only 60% of the patients was informed on the results of the medication review within the planned 1,5 months. This means that for 40% of the patients, the time horizon was even shorter than 6 months.

We concluded that there were no effects on health outcomes and cost-effectiveness with the CMR intervention as compared to usual care on the short time. Possible effects on the longer term may be present, however we think this is not very likely.

Research within a Dutch academic GP network

The Opti-Med trial and the introductory questionnaire study were both conducted in GP practices participating in the Academic Network of General Practices of the VU University Medical Center. This is a network of GP practices

in Amsterdam and Haarlem, both urban areas in the west of The Netherlands. All GP practices contribute to a database that is used for research (e.g. patient selection) and feedback purposes. A part of the GP practices is also involved in education and research projects. Advantages of conducting research in such a network are the possibility to address research questions arising from daily practice and to involve GPs during the design of the study. Other advantages are easy recruitment of GP practices, the use of the database and logistics and motivated GPs who are familiar with participating in research projects. On the other hand, in contrast to these clear advantages there might be a disadvantage when it comes to the representativeness and external validity of the results of studies performed in an academic GP network compared to common GP practices. However, only a third of the participating practices were actively involved in education and research projects. This means that there may have been differences between practices. Another disadvantage of the academic research network is that all practices were located in an urban area, this also hampers the representativeness and external validity with regard to urbanization level. However, it is likely that in urban areas with higher density of GP practices and pharmacists, the use of expert teams for CMRs is probably more feasible and useful. A further disadvantage might be that patients as well as the GP practices already have participated in previous studies. This could have made certain patients somewhat reluctant to participate or GPs being already more knowledgeable on e.g. elderly care.

Finally, the already high quality of usual care in academic GP practices and non-affiliated general practices in The Netherlands in general may explain the lack of finding any effect of patient health outcomes of this CMR intervention. This also means that the intervention possibly cannot be extrapolated to all general practices in The Netherlands, at least in the more rural areas. In addition, the Opti-Med intervention also cannot be easily extrapolated to primary settings in other countries.

Reflection on main findings

Possible explanations for the absence of effectiveness and cost-effectiveness of the Opti-Med CMRs have been described in **chapter 5-7** and in the methodological considerations discussed in the previous paragraph. They range from the definition of the target group, the implementation fidelity, the selection of outcome measures to the duration of the follow-up period. Taking all these limitations into account, together with the evidence from other recent studies[7,8], the body of evidence for effectiveness of CMRs on health outcomes is thin. The study results presented in this thesis confirm this conclusion. In spite a moderate to good implementation fidelity, the Opti-Med CMRs were not effective for health outcomes and also not cost-effective as compared to usual care.

Despite the growing body of evidence not justifying the implementation of CMRs on a large scale in primary care, CMRs have become part of guidelines and have been widely implemented in pharmacy and general practice across developed countries. Ongoing studies on CMRs try to pinpoint and identify the elements for more successful results for CMRs. Examples thereof are the introduction of innovative selection criteria, e.g. medication use defined by using over 15 medicines[9], or outcome measures, e.g. a tool like the Drug Burden Index.[10] Other approaches of CMRs and related initiatives in The Netherlands are a more intensive patient involvement using goal attainment scales[11], the integration of a non-dispensing pharmacist in a primary care team[12] and implementation of the web application of the STRIP Assistant in primary care thereby also focusing on a less time consuming pharmacotherapeutic analysis.[13] Two large-scale European initiatives are currently designed and tested for their effectiveness on the endpoints hospital admission and mortality. PRIMA-eDS studies the effectiveness of an evidence-based electronic decision support (eDS) tool to aid physicians in reducing inappropriate prescribing with the aim to include 3,500 patients in a cluster-RCT.[14] The OPERAM study investigates the effects of the STRIP method including the STRIP-Assistant in multimorbid older people, with the aim to include 2,000 patients. [15]

In the Opti-Med study we aimed to optimize three key elements contributing to more efficient and effective CMRs; efficient involvement of

patients, a new target group with a problem-oriented approach and the efficient organization of CMRs. In this paragraph, we will reflect on these elements, also in the light of other recent research in the field of CMRs.

The involvement of patients in CMRs

The current Dutch polypharmacy guideline advises two important moments for patient involvement in a CMR.[16] The first moment is the patient assessment or history taking, with and in the presence of the patient and if necessary the informal caregiver. The second moment follows the medication analysis. Its aim is to discuss possible medication changes and provide counseling. In the present thesis we investigated whether an alternative and more efficient method for the first patient contact, i.e. the completion of a questionnaire as preparation for a CMR, was feasible and effective.

Patients should be involved in CMRs, notably because this is a part of the definition. Patient involvement should at least occur on the level of giving information regarding their actual medication use, presence of potential DRPs and their preferences, and at its conclusion with respect to the proposed changes from the medication review analysis. A higher level of involvement, e.g. in shared-decision making may be rather difficult to realize and very time-consuming. As yet active patient involvement in decision making is not common practice and is not frequently studied for its surplus or added value for the patient as emerged from the literature review (**chapter 2**). We concluded that completing a specifically designed questionnaire is an acceptable alternative to home visits or face-to-face interviews as preparation for CMRs. In the Opti-Med RCT we used a tailored questionnaire. In the process evaluation it appeared that one in five DRPs was identified via the questionnaire and the implementation rate of the proposed medication changes was also significantly higher for DRPs identified in this manner by the patient's input.

For complex patients, i.e. those using high numbers of medications by multiple prescribers or with other patient characteristics, such as high age or low health literacy, a questionnaire may be less suitable. However, when targeting large groups of patients and for conducting CMRs in an efficient way, the use of a questionnaire instead of a face-to-face interview seems useful. A step wise approach in which patients who are not able or willing to fill in the

questionnaire are contacted for an interview or a home visit might be appropriate.

Target group for CMRs; geriatric giants

Most CMRs within research settings and in primary care focus on polypharmacy patients and most CMRs are predominantly initiated by pharmacists. At the start of this study our hypothesis was that a problem-oriented approach for CMRs would result in effectiveness in terms of better QoL and a reduced burden due to geriatric problems. Eligible participants for the Opti-Med intervention were therefore selected on the basis that they presented a new geriatric problem to their GP instead of the number of medications. As fundament for these geriatric problems in this thesis, we chose to use the geriatric giants as described by Isaacs.[17]

Geriatric giants have multiple causation, chronic course and no simple cure in common.[17] This outlines the challenge of 'treating' or improving geriatric problems in the older population. In the present thesis it was assumed, but not investigated that there is an association between inappropriate drug use and the existence of geriatric problems. However, there are many studies showing an association between polypharmacy or the use of certain medication categories and geriatric problems or the so-called geriatric syndromes.[18-33]

The exact interplay of multimorbidity, polypharmacy, inappropriate drug use and geriatric problems is unclear. The question remains to what degree geriatric problems can be influenced or even prevented by medication reviews and subsequent medication changes. For falls, there is some evidence that they may be reduced by CMRs as shown in a recent meta-analysis[7]. For most other geriatric problems this relationship is less evident.

In the Opti-Med study, the problem-oriented approach in contrast to the presence of polypharmacy as inclusion criterion did not lead to positive effects on health outcomes. In future initiatives, a much more complex target group might be considered and investigated. Due to the chronic and multifactorial nature of geriatric problems the embedding of CMRs in a more integrated care program seems a logic choice. However, integrated care programs in frail community-dwelling elderly have also shown not to be very effective and are also very difficult to implement.[34-36]

Efficient organisation of CMRs

An important element of the Opti-Med study was to design an intervention that was optimally organized to improve the efficiency of CMRs and thereby facilitating the implementation of CMRs on a large scale in the general practice setting.

In the pilot phase GPs indicated that performing the pharmacotherapeutic analysis was very time consuming. They also considered to have insufficient pharmacotherapeutic knowledge to adequately perform CMRs. Therefore, the Opti-Med intervention introduced an important new element for optimization and improved efficiency; the use of an external expert team to perform the medication analysis. As described in chapter 6, the experiences with such a team were very positive. The expert teams indicated that the efficiency was explained by frequent analyses, a fixed team of a pharmacist and physician, and the use of the STRIPA web tool. Another study with Opti-Med data showed that the teams assisted by the STRIPA tool became more efficient over time.[37]

Thus, expert teams and STRIPA were successful means to improve the efficiency and organization of CMRs in general practice. However, as a result the researchers had a more prominent role in the selection of patients and preparation and coordination of the CMRs than foreseen (**chapter 7**). A well-coordinated organization and overview of the selection and invitation procedure, preparation of the medication review and communication between the expert team, the GP practice and the pharmacy is essential for further implementation in daily primary care. The Opti-Med intervention and the use of the STRIPA tool showed that the efficiency and time spent on CMRs can be improved. Further improvements should be found in IT solutions for patient selection and implementation of the CMR results, but also in training of dedicated coordinators within a practice. However, CMRs of high quality including patient participation and involvement of the patient's GP and pharmacist will remain an organizational challenge and therefore continue to be time consuming.

Recommendations for future research

Target groups for CMRs

As mentioned above, one of the explanations for the lack of effectiveness in the Opti-Med study, as well as in many other studies, on health outcomes can be the patient group that is targeted group for a CMR. Future research should focus on identifying the best target group for CMRs in terms of positive health outcomes. The results of the present thesis do not give clear directions for what these best target groups might be. Subgroup analyses of polypharmacy patients or multimorbid patients did not yield distinctive results. A larger pool of data with a broader range of types of patients, such as an individual patient data meta-analysis may be suitable for further risk stratification.

Several previous studies (already 10 years ago) recommended bigger and longer RCTs to study the effectiveness of CMRs. However, before investing in new RCTs, the identification of the best target group is essential.

Future RCTs should incorporate the successful elements of the Opti-Med intervention as described in the present thesis such as electronic support tools for decision making and the use of expert teams.

Outcome measures

More sensitive and meaningful outcomes to assess the effects of CMRs on health outcomes are needed. At present a wide diversity of outcome measures, predominantly intermediate outcomes, is used in medication review and polypharmacy studies. In order to pool results, uniform outcome measures are needed. In this respect, Beuscart et al. describe that a core outcomes set to evaluate medication reviews should be developed, based on a systematic review from previous literature and qualitative research involving all stakeholders, including the patient.[38,39]

Lack of evidence in multimorbid oldest patients

Prescribing according to recommendations in clinical guidelines may lead to over- or misprescribing and increased risk of drug interactions, poor adherence and adverse drug effects.[40] Evidence-based medicine is the basis for evidence-based clinical guidelines. Applying this principle is a challenge in the case of both multimorbid and very old patients (or both) as they are both

underrepresented in most pharmacological studies and health care studies. This deficiency is mainly caused by the need for homogeneous patient samples and the single-disease focus in research and in the health care system. This practice is fairly incorrect, because these patients represent the target group that use the largest number of medications rather than single-disease middle-aged adults included in the majority of pharmacological trials. It is well known that older people respond differently to treatment in terms of effectiveness and adverse effects. Moreover, different treatment goals in terms of QoL and independence and important factors such as prognosis and life expectancy play an important role. Initiatives to improve the inclusion of older multimorbid patients in trials should therefore be encouraged and expanded. Within the European PRIMA-eDS study, there is the intention to develop a core set of systematic reviews on the current best evidence for the most appropriate drug treatment of the most common chronic diseases in older multimorbid patients.[41] The first systematic reviews on metformin, beta-blockers, dipeptidyl peptidase 4 inhibitors (gliptins), vitamin K antagonists and new anticoagulants have been published recently.[42-45] Ephor, the Dutch expert center for pharmacotherapy in older people, publishes evidence-based medication reports.[46] These are examples of evidence syntheses that may help to identify the most important knowledge gaps in treating multimorbid patients.

In addition to these initiatives, we recommend to design and conduct clinical trials that include and stratify older and multimorbid patients with the aim to gain more insight in the type of inappropriate medications which, notwithstanding all arguments against, are nevertheless often prescribed for this target group. This is not only necessary to draw up evidence-based guidelines tailored to this target group but also for e.g. assembling lists of explicit criteria for medication inappropriateness that can be used in the CMR process. At present, sufficient evidence on the inappropriateness of specific medicines or combinations of which use in multimorbid and very old people is still lacking.

Implications and recommendations for Dutch policy and clinical practice

In the Netherlands, the current implementation of CMRs as described in the polypharmacy guideline is focused on quantity instead of quality.[47] The Dutch Health Inspectorate (IGJ) and the Ministry of Health, Welfare and Sport (VWS), but also the elderly patient organization (KBO) are focusing on a broad target group and remuneration. This means that the number of CMRs that should be performed or that patients are entitled to should increase.[48-51] The combination of enforcement of the quantity of CMRs and the broad target group is likely to result in reviewing less complex patients instead of the most complex patients, who possibly benefit most from a CMR. This movement may lead to inefficiency, capacity problems and results in a degradation of the value of CMRs.

Evidence-based practice entails more than evidence from RCTs. Besides scientific evidence, other considerations such as professional experience, expert opinions, patient preferences, costs, and feasibility all have to be weighed before a recommendation is drawn up. All together this can give reasons to recommend or not recommend CMRs. A multidisciplinary group of all parties involved in CMRs should discuss these and other considerations before drafting recommendations. Based on this thesis, on the evidence and on the experience as a researcher in the field, I suggest to consider another path for CMRs in The Netherlands than enforcing the quantity of CMRs. Both the target group and the approach for CRMs are up for debate.

Investing in other (preventive) interventions or measures to decrease inappropriate prescribing and medication use, and in the end prevent medication related hospitalisations and deaths, seems also useful. We recommend the following measures next to or even instead of CMRs:

On a micro-level, patient and informal caregiver awareness for problems such as adherence and in general drug appropriateness at high age should be enhanced;

At the meso-level the communication and exchange of medical and medication information between pharmacists, prescribers (also between prescribers) and patients should be improved.

Multidisciplinary education and multidisciplinary guidelines adapted to the older population with multiple chronic morbidity and medications will contribute to this goal. For example, the elderly care physician could have a more prominent role within primary care.

In general, the aim should be to integrate care on appropriate medication use and prescribing in primary elderly care, for example elderly care by nurse practitioners (POH) or pharmacy employees. This means that a light version of a medication review might be an option, or at least medication reconciliation, that may fulfill the need of the patient and the prescribers and allows the pharmacist to monitor the medication lists and medication use on regular basis. A comprehensive CMR is only recommended for a very specific high risk group, which, however, still has to be defined.

At the macro-level healthcare insurers, the Ministry of Health, Welfare and Sport and the Health Inspectorate should focus on the quality of the pharmacotherapeutic care rather than increasing the quantity of mandatory medication reviews. The external financial incentive of the current system is contra productive.

Final reflection

There seems to be a mismatch in the evidence for the effectiveness on patient's health outcomes and the current practice to conduct mandatory CMRs in The Netherlands. With the current approach, a CMR has developed into an inefficient tool with a number needed to review for one person to achieve an appropriate medication list and no near future medication related harm that may be too high.

Based on the studies described in the present thesis and literature, de-implementation of CMR in The Netherlands is not recommended, that would be a waste of all the efforts and existing agreements and infrastructure and cooperation between GPs and pharmacists that have evolved since the introduction of the multidisciplinary polypharmacy guideline in 2012. However, further large scale implementation of CMRs with focus on quantity instead of quality should be reconsidered.

Before proceeding further a high-risk target group that benefits most from CMRs in terms of health outcomes should be identified. Probably, this should be a smaller group than the current criteria for eligible patients for CMRs. For this group, CMRs can be conducted according to the polypharmacy guideline, however updated with some new successful elements as suggested in this thesis including electronic decision making support tools and the use of expert teams, which desirably also include an elderly care physician. A 'light' version of medication reviews, at least medication reconciliation, may be the future for the emerging and highly prevalent problem of inappropriate medication use in the older population. This should be accompanied by a pro-active primary care structure focused on appropriate medication use on the basis of a genuinely better cooperation, improved communication and exchange of electronic information between the pharmacist, pharmacy employee, GP, nurse practitioner, medical specialist and the patient.

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Summary

In **chapter 1** (the general introduction) the subject of inappropriate prescribing, inappropriate medication use and clinical medication reviews (CMR) is introduced. A CMR is an intervention that aims to reduce inappropriate prescribing and medication use. Three important gaps in the literature for CMRs are introduced: the lack of clinical effectiveness, the best target group for CMRs and patient participation. The implementation of CMRs in primary care settings in The Netherlands and worldwide poses some important feasibility challenges.

Furthermore, the rationale and outline of the thesis was presented in this chapter, in which we aimed to answer the following research questions:

1. What is known in the literature about ways of patients participation in the medication review process and its effects on the outcomes of a medication review?
2. Can patient participation in medication reviews be achieved via a questionnaire instead of an interview?
3. What is the (cost)-effectiveness of an optimized clinical medication review on quality of life and geriatric problems in comparison with usual care, in older patients with geriatric problems presented in general practice?
4. What is the implementation fidelity of optimized clinical medication reviews in the setting of general practice?

Chapter 2 includes a systematic literature review to answer the first research question. We systematically searched and reviewed the literature on the subjects of patient participation and medication reviews. In total, 37 studies with a variety of study designs met the inclusion criteria. In all studies patient participation in medication reviews was limited to the level of information giving by the patient to the professional, mainly on actual drug use. The effects of patient participation were not frequently studied and poorly described. We found some evidence that involving patients in medication reviews might result in a better identification of drug related problems (DRPs) as well as improved knowledge and patient satisfaction. However, no evidence on patients' health outcomes was found.

In **chapter 3**, we described the development of a patient questionnaire as preparation for a CMR and an agreement study in 97 older community-dwelling patients to answer the second research question. In this study the agreement between patient information on actual medication use and occurrence of DRPs obtained with a questionnaire was compared with information obtained during an interview at home. Of all medications used, almost 90% was reported identically in the questionnaire and the interview. However, agreement for the complete medication list was only found for 45% of the patients. With respect to DRP level, agreement between questionnaire and interview amounted to 75%. The number of medications and DRPs reported in the interview was higher than in the questionnaire. Agreement tended to be lower in vulnerable patients characterized by ≥4 chronic diseases, patients using ≥10 medications and those with a low health literacy. Taking the limitations into account, a questionnaire seems a suitable tool for medication reviews that may replace an interview for most patients.

In **chapter 4**, we describe the design of the Opti-Med intervention, a cluster randomised controlled trial (RCT). The aim was to include 500 patients, 250 in each arm from 20 general practices. The Opti-Med intervention was designed as an innovative intervention applying an optimally facilitated, prepared and structured problem-oriented CMR, with the specific objective to tackle the most important obstacles for large scale implementation of CMRs.

In **chapter 5,** the results concerning the effectiveness of the Opti-Med intervention have been presented to answer the third research question. In total, 518 older patients from 22 general practices who consulted their general practitioner for a geriatric problem were included. No significant differences between the intervention and control group and over time were found for the primary outcome measures (quality of life and geriatric problems), and for two secondary outcome measures: medication satisfaction and adherence. The percentage of solved DRPs after six months was significantly different between the intervention and the control group. The Opti-Med intervention resulted in 22% more solved DRPs compared to usual care. However, the higher percentage of solved DRPs in the intervention group did not result in effects on the patients' health.

In **chapter 6**, the cost-effectiveness study of the Opti-Med intervention, which was performed alongside the Opti-Med effectiveness study, has been presented, to answer the third research question. Total societal costs in the intervention group were €684 higher than in the control group, but this difference was not statistically significant (95% CI -1142 ; 2387). Cost-effectiveness acceptability curves showed that for solved DRPs, the probability of the intervention being cost-effective reached 0.95 at a WTP of €2100 per solved DRP. For all other outcomes (quality-adjusted life years (QALYs), quality of life and changes in geriatric problems), the probability was low at all willingness-to-pay (WTP) values (i.e. range 0.25 ; 0.49). Optimized CMRs were not considered cost-effective compared to usual care.

In **chapter 7,** we described a quantitative and qualitative process evaluation alongside the Opti-Med effectiveness study according to the Conceptual Framework for Implementation Fidelity, to answer the last research question. Adherence to the intervention and moderating factors for implementation fidelity were evaluated per key intervention component. Some elements, such as patient selection and preparation of the medication analyses were carried out by the researchers instead of the practice nurses. Cooperation between expert teams' members (physician and pharmacist) and the use of an online decision-support medication evaluation tool facilitated implementation. Barriers for implementation were time constraints in daily practice, software difficulties with patient selection and incompleteness of medical files. The total time investment of healthcare professionals for the Opti-Med intervention was on average 94 minutes per patient.
Overall, the implementation fidelity was moderate to high for all key intervention components. The absence of effectiveness of the intervention with respect to its primary outcomes could not be explained by insufficient implementation fidelity.

In **chapter 8** (general discussion) I reflect on all the findings in the light of the current evidence and clinical practice. The most important methodological considerations and possible explanations for the absence of effectiveness and cost-effectiveness are discussed. They range from the definition of the target group, the implementation fidelity, the selection of outcome measures to the

duration of the follow-up period. In spite of a moderate to good implementation fidelity, the Opti-Med CMRs were not effective for health outcomes and also not cost-effective as compared to usual care. There seems to be a mismatch in the evidence for the effectiveness on patient's health outcomes and the current practice to conduct mandatory CMRs in The Netherlands as well as in many other developed countries. With the current approach, a CMR has developed into an inefficient tool. First, before proceeding further a high-risk target group that benefits most from CMRs in terms of health outcomes should be identified.

Samenvatting

Samenvatting

In **hoofdstuk 1** (algemene introductie) van dit proefschrift worden de onderwerpen ongepast voorschrijfgedrag, ongepast medicatiegebruik en medicatiebeoordelingen geïntroduceerd.

Een medicatiebeoordeling is een interventie met als doel het verminderen van ongepast voorschrijven en ongepast medicatiegebruik. De drie belangrijke kennislacunes in de wetenschappelijke literatuur voor medicatiebeoordelingen worden geïntroduceerd: het gebrek aan klinische effectiviteit, de optimale doelgroep voor medicatiebeoordelingen en de mate van patiëntenparticipatie. Een belangrijke uitdaging voor de haalbaarheid van een dergelijke interventie is de implementatie van medicatiebeoordelingen in de eerstelijnszorg in Nederland en wereldwijd.

In dit hoofdstuk is tevens de rationale en opzet van dit proefschrift gepresenteerd, met de volgende onderzoeksvragen:

1. Wat is er bekend in de literatuur over methoden van patiëntenparticipatie in het proces van een medicatiebeoordeling en wat zijn de effecten van patiëntenparticipatie op de uitkomsten van een medicatiebeoordeling?
2. Kan patiëntenparticipatie in medicatiebeoordelingen worden bereikt met behulp van een vragenlijst in plaats van een interview?
3. Wat is de (kosten)-effectiviteit van een geoptimaliseerde medicatiebeoordeling, bij oudere patiënten die zich met geriatrische problemen hebben gepresenteerd bij de huisarts, op kwaliteit van leven en de mate van geriatrische problemen vergeleken met reguliere zorg?
4. Wat is de implementatiegraad van een geoptimaliseerde medicatiebeoordeling-interventie in de setting van de huisartspraktijk?

In **hoofdstuk 2** wordt de eerste onderzoekvraag beantwoord met behulp van een systematische literatuur review. Er is systematisch gezocht in de wetenschappelijke literatuur, waarbij als selectiecriteria medicatiebeoordelingen en patiëntenparticipatie zijn aangehouden. In totaal, voldeden 37 studies met diverse onderzoeksopzetten aan de inclusiecriteria. In

alle studies was patiëntenparticipatie gerealiseerd op het niveau van informatie geven door de patiënt aan de professional, met name over actueel medicatiegebruik. De effecten van patiëntenparticipatie waren niet frequent onderzocht en slecht beschreven. Het lijkt waarschijnlijk dat het actief betrekken van patiënten bij een medicatiebeoordeling resulteert in betere identificatie van medicijn gerelateerde problemen (MRP), betere kennis van medicijnen en patiënttevredenheid. Echter, er werd geen bewijs gevonden over effecten van patiëntenparticipatie op gezondheidsuitkomsten voor patiënten.

In **hoofdstuk 3** wordt de tweede onderzoeksvraag beantwoord. De ontwikkeling van een patiënt- vragenlijst is beschreven, als voorbereiding voor een medicatiebeoordeling. In een studie bij 97 thuiswonende oudere patiënten werd patiëntinformatie over actueel medicijngebruik en MRPs verkregen via een vragenlijst en vergeleken met informatie verkregen via een interview bij de patiënten thuis.

90% van alle gebruikte medicatie was identiek gerapporteerd in de vragenlijst en het interview. Echter, bij slechts 45% van de patiënten was de gehele medicatielijst identiek voor beide methodes. De overeenstemming tussen de vragenlijst en interview op het niveau van MRPs bedroeg 75%. Het aantal gerapporteerde medicijnen en MRPs was hoger in het interview dan in de vragenlijst. De overeenstemming tussen beide methodes leek lager bij kwetsbaardere patiënten, gekarakteriseerd als patiënten die vier of meer chronische ziektes hebben, patiënten die tien of meer medicijnen gebruiken of patiënten met lagere gezondheidsvaardigheden.

Rekening houdend met de beperkingen van dit onderzoek, lijkt een vragenlijst een geschikt instrument voor medicatiebeoordelingen waarbij interviews vervangen kunnen worden bij de meerderheid van de patiënten.

In **hoofdstuk 4** wordt de opzet en organisatie van de Opti-Med studie beschreven, een cluster gerandomiseerde studie. Het doel was om 500 patiënten te includeren, 250 in groep, geworven uit 20 huisartspraktijken. De Opti-Med interventie werd ontworpen als een innovatieve interventie waarbij een geoptimaliseerde, goed voorbereide, gestructureerde en probleem-georiënteerde medicatiebeoordeling werd toegepast. Een specifiek doel van

Opti-Med was om de grootste obstakels voor implementatie op grote schaal van medicatiebeoordelingen aan te pakken.

In **hoofdstuk 5** zijn de resultaten ten aanzien van de effectiviteit van de Opti-Med interventie gepresenteerd om de derde onderzoeksvraag te beantwoorden. In totaal, werden 518 oudere patiënten uit 22 huisartspraktijken geïncludeerd. Alle patiënten hadden recent hun huisarts geconsulteerd voor een geriatrisch probleem.

Er werden geen significante verschillen gevonden tussen de interventie- en de controlegroep en over tijd voor de primaire uitkomsten (kwaliteit van leven en geriatrische problemen) en voor de twee secundaire uitkomstmaten (medicatie tevredenheid en therapietrouw). Het percentage opgeloste MRPs zes maanden na de interventie verschilde significant tussen de interventie- en controle groep. De Opti-Med interventie resulteerde in 22% meer opgeloste MRPs vergeleken met patiënten die reguliere zorg ontvingen. Echter, dit hogere percentage van opgeloste MRPs in de interventiegroep resulteerde niet in een positief effect op de gezondheid of kwaliteit van leven van de patiënten.

In **hoofdstuk 6** is een kosteneffectiviteitsstudie gepresenteerd, die werd uitgevoerd naast de Opti-Med effectiviteitsstudie om eveneens de derde onderzoeksvraag te beantwoorden.

De totale maatschappelijke kosten waren €684 hoger in de interventiegroep vergeleken met de controlegroep, dit verschil was echter niet statistisch significant (95% BI -1142 ; 2387). De kosteneffectiviteit-acceptabiliteit curves lieten zien dat voor opgeloste MRPs, de waarschijnlijkheid reikte tot 0,95 voor de interventie om kosteneffectief te zijn bij een betalingsbereidheid van €2100 per opgeloste MRP. Voor alle andere uitkomstmaten (quality-adjusted life years (QALYs, aan kwaliteit aangepaste levensjaren), kwaliteit van leven en verandering in geriatrische problemen) was de waarschijnlijkheid om kosten-effectief te zijn laag bij alle onderzochte *willingness to pay* waarden (range 0,25 tot 0,49). Geoptimaliseerde medicatiebeoordelingen werden niet kosteneffectief bevonden vergeleken met reguliere zorg.

In **hoofdstuk 7** is een kwantitatieve en kwalitatieve proces-evaluatie beschreven die werd uitgevoerd naast de Opti-Med effectiviteitsstudie om de laatste onderzoekvraag te beantwoorden. Het *Conceptual Framework for Implementation Fidelity* werd aangehouden voor deze studie.

Om de implementatiegraad te kunnen meten is nagegaan of de belangrijkste interventie componenten zijn uitgevoerd zoals beoogd, inclusief factoren die de implementiegraad konden beïnvloeden. Sommige componenten, zoals patiëntselectie en voorbereiding van de medicatie-analyses werden uitgevoerd door de onderzoekers in plaats van de praktijkondersteuners in de huisartspraktijk. De samenwerking tussen de expert-team leden ((huis)arts en apotheker) en het gebruik van een online beslissingsondersteunend instrument voor de beoordeling van medicatie waren facilitators voor implementatie. Barrières voor de implementatie waren tijdgebrek in de dagelijkse praktijk, problemen met de software voor de patiënten-selectie en incomplete medische dossiers. De totale tijdsinvestering van zorg-professionals voor de Opti-Med interventie was gemiddeld 94 minuten per patiënt.

Concluderend, de implementatiegraad was matig tot hoog voor alle belangrijke interventie componenten. De afwezigheid van de effectiviteit van de interventie kon niet worden verklaard door een onvoldoende hoge implementatiegraad.

In **hoofdstuk 8** (algemene discussie) is gereflecteerd op alle bevindingen in het licht van het huidige bewijs uit de literatuur en overwegingen uit de klinische praktijk.

De belangrijkste methodologische overwegingen en mogelijke verklaringen voor de afwezigheid van effectiviteit en kosteneffectiviteit van de Opti-Med interventie zijn bediscussieerd. Deze variëren van de definitie van de doelgroep, de implementatiegraad, de selectie van de uitkomstmaten tot aan de follow-up duur.

Ondanks de matige tot hoge implementatiegraad waren de Opti-Med medicatiebeoordelingen niet effectief wat betreft klinische uitkomsten en ook niet kosteneffectief vergeleken met de reguliere zorg. Er lijkt een wanverhouding te bestaan tussen het bewijs voor de effectiviteit van medicatiebeoordelingen op klinische uitkomsten en de huidige praktijk waarbij

medicatiebeoordelingen steeds meer dienen te worden uitgevoerd in Nederland en veel andere landen. Door deze aanpak heeft een medicatiebeoordeling zich ontwikkeld tot een inefficiënt instrument. Voordat we verder gaan met deze aanpak, zal eerst de hoog-risico groep die daadwerkelijk profiteert van een medicatiebeoordeling beter moeten worden geïdentificeerd.

Dankwoord

Dankwoord

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List of publications

List of publications

Willeboordse F, Hugtenburg JG, Schellevis FG, Elders PJ.
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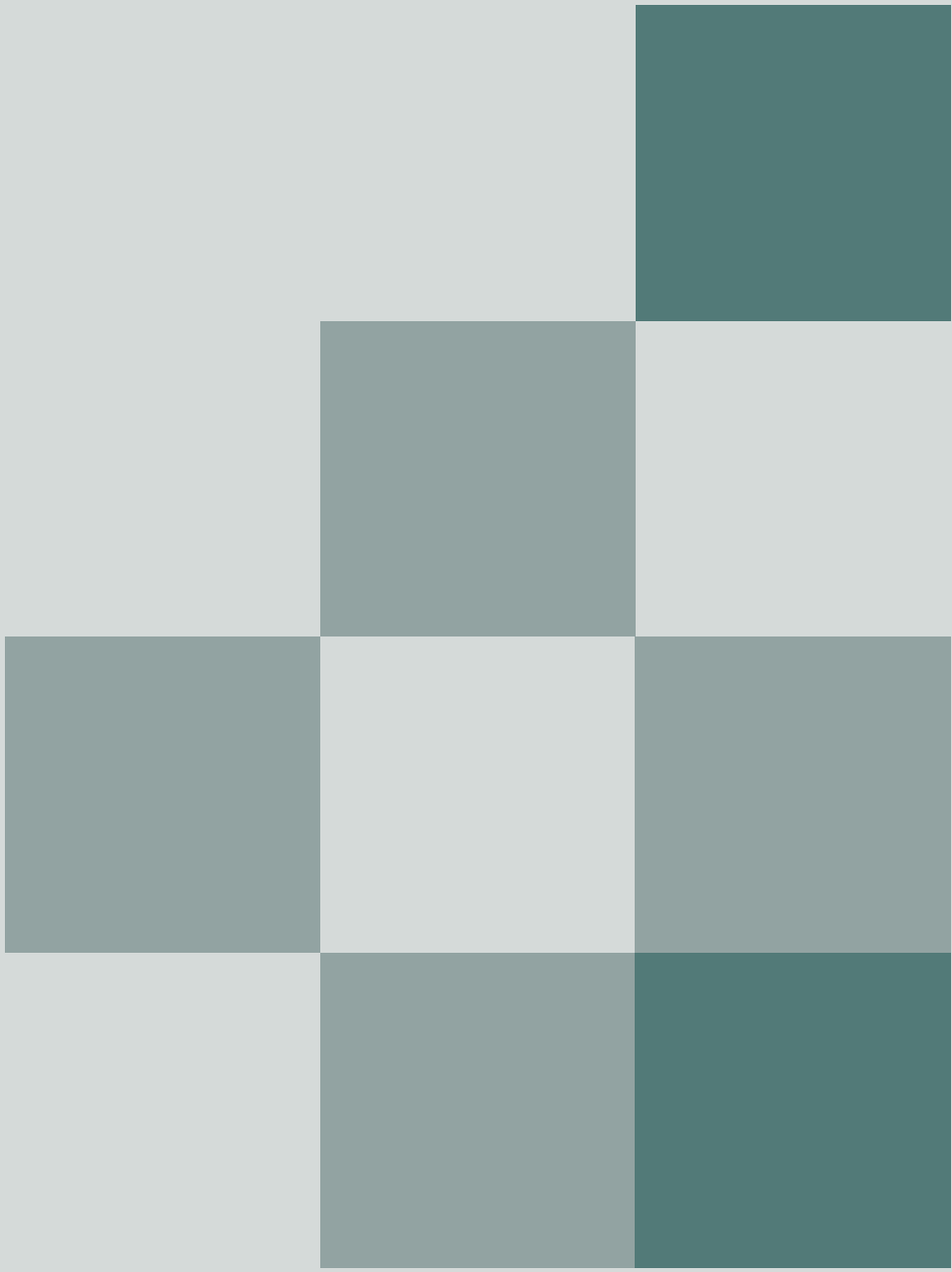
About the author

Floor Willeboordse was born on 17th of May 1985 in Oosterhout and lived her entire childhood in Dongen. After graduating from Sint Oelbert Gymnasium in 2003, she moved to Wageningen and started her Bachelor study Nutrition and Health at Wageningen University. After graduation, she continued her Master of Science Nutrition and Health, with a specialisation in Nutrition in Health and Disease at Wageningen University. During her Master of Science, she conducted two internships, first in Indonesia on the relationship between nutritional status and mild acute respiratory infections in low socio-economic urban areas in Jakarta and a second internship on predictors for energy and protein requirements in undernourished hospital patients. She graduated at Wageningen University in 2009 as a Master of Science. After her graduation she started as junior researcher at Pallas Health Research and Consultancy in Rotterdam and was involved in several public health and healthcare research projects.

Floor started her PhD research in 2012 on optimising medication reviews in primary care as described in this thesis. This research project was a collaboration between the Amsterdam Public Health research institute (formerly EMGO+ institute for Health and Care Research), at the Department of General Practice and Elderly Care Medicine of the VU University Medical Centre, and the NIVEL, Netherlands Institute for Health Services Research. She was amongst others involved in the organisation of science meetings for the researchers in the field of geriatrics and the organization of the PhD candidates meetings both at the Department of General Practice and Elderly Care Medicine of the VU University Medical Centre. She was also a member of the Netherlands School of Primary Care Research (CaRe) education committee. During her research period she followed several epidemiological and statistical courses at EPIDM, VU Medical Center, with the aim to register for Epidemiologist B.

Currently, Floor is working at the Knowledge Institute of the Dutch Association of Medical Specialists, Utrecht, as advisor, mainly working on evidence based medical guidelines for medical specialists.

Floor lives in Utrecht and is married to Bas van de Waterbeemd and has two daughters Iris (2) and Hannah (2).



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