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
Chapter 8

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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.

General discussion
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

General discussion

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³
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 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.

General discussion

Box 8.1 Operationalisations of geriatric problems

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

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\textsuperscript{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\textsuperscript{9}, or outcome measures, e.g. a tool like the Drug Burden Index.\textsuperscript{10} Other approaches of CMRs and related initiatives in The Netherlands are a more intensive patient involvement using goal attainment scales\textsuperscript{11}, the integration of a non-dispensing pharmacist in a primary care team\textsuperscript{12} and implementation of the web application of the STRIP Assistant in primary care thereby also focusing on a less time consuming pharmacotherapeutic analysis.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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. 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-analysis⁷. 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. The first systematic reviews on metformin, beta-blockers, dipeptidyl peptidase 4 inhibitors (gliptins), vitamin K antagonists and new anticoagulants have been published recently. Ephor, the Dutch expert center for pharmacotherapy in older people, publishes evidence-based medication reports. 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. 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. 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 CRM 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 in 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.

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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 a 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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General discussion
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