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Medication reviews by clinical pharmacists in older hospitalised patients

Implementation, performance and effects

THOMAS G. H. KEMPEN



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Abstract

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Background Inappropriate use of medications is a leading cause of avoidable harm in health care. Medication reviews by clinical pharmacists improve medication use, but evidence on hard clinical outcomes in older hospitalised patients is scarce and implementation in practice is challenging. The aim of this thesis was to study the implementation, performance and effects of medication reviews by clinical pharmacists in older hospitalised patients.

Methods A case study explored the factors involved in the implementation and sustainability of medication reviews by clinical pharmacists in Region Uppsala, Sweden. A pragmatic multicentre cluster-randomised crossover trial (MedBridge) was conducted to study the effects of hospital-based comprehensive medication reviews (CMRs) including post-discharge follow-ups on older patients' healthcare utilisation, compared with only hospital-based reviews and usual care. The primary outcome measure was the incidence of unplanned hospital visits within 12 months. A process evaluation was conducted alongside the trial, for which different methods were applied: semi-structured interviews with patients and healthcare professionals, intervention fidelity assessment and process outcomes assessment. A practical tool to identify medication-related hospital admissions, one of the trial's secondary outcomes, was developed and validated.

Results Multiple factors involved in the implementation and sustainability of medication reviews by clinical pharmacists were identified. Examples of facilitating factors were a national focus on quality of care for the elderly and clinical pharmacy education. In total, 2637 participants (median age 81 years) were included in the MedBridge trial. The primary outcome measure did not differ between the treatment groups. Analysis of the interviews with patients and healthcare professionals resulted in seven and six themes, respectively, that were related to the performance of the trial's interventions. A recurrent theme was the unclear role and responsibilities of the ward-based pharmacist. The intervention fidelity was high during hospital admission and lower surrounding discharge. In 77% of the intervention patients, at least one medication discrepancy or drug-related problem was solved. The developed tool, AT-HARM10, was deemed valid for use by pharmacy students to identify medication-related admissions in older patients.

Conclusions This thesis suggests that, despite a high percentage of patients with medication discrepancies or drug-related problems being solved, hospital-based CMRs with and without post-discharge follow-ups, as conducted in the MedBridge trial, do not decrease the incidence of unplanned hospital visits in older patients. Future research and clinical initiatives may benefit from addressing the factors related to the implementation and performance of medication reviews that were identified in this thesis.

Keywords: Medication review, medication reconciliation, multi-professional collaboration, hospital medicine, polypharmacy, inappropriate prescribing, drug-related problems, medication-related hospital admissions, pragmatic clinical trial, cluster analysis, randomised controlled trial, qualitative analysis, process evaluation, implementation science

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List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

- I **Kempen TGH**, Gillespie U, Färdborg M, McIntosh J, Mair A, Stewart D. (2019) A case study of the implementation and sustainability of medication reviews in older patients by clinical pharmacists. *Res Social Adm Pharm*, 15(11):1309-1316
- II **Kempen TGH**, Bertilsson M, Lindner KJ, Sulku J, Nielsen EI, Högborg A, Vikerfors T, Melhus H, Gillespie U. Medication Reviews Bridging Healthcare (MedBridge): Study protocol for a pragmatic cluster-randomised crossover trial. (2017) *Contemp Clin Trials*, 61:126-132
- III **Kempen TGH**, Kälve mark A, Gillespie U, Stewart D. (2020) Comprehensive medication reviews by ward-based pharmacists in Swedish hospitals: What does the patient have to say? *J Eval Clin Pract*, 26(1):149-157
- IV **Kempen TGH**, Kälve mark A, Sawires M, Stewart D, Gillespie U. (2020) Facilitators and barriers for performing comprehensive medication reviews and follow-up by multiprofessional teams in older hospitalised patients. *Eur J Clin Pharmacol*, 76(6):775-784
- V **Kempen TGH**, Cam H, Kälve mark A, Lindner KJ, Melhus H, Nielsen EI, Sulku J, Gillespie U. (2020) Intervention fidelity and process outcomes of medication reviews including post-discharge follow-up in older hospitalized patients: Process evaluation of the MedBridge trial. *J Clin Pharm Ther*, 2020 Mar 14.
- VI **Kempen TGH**, Bertilsson M, Hadziosmanovic N, Lindner KJ, Melhus H, Nielsen EI, Sulku J, Gillespie U. (2020) Effects of hospital-based comprehensive medication reviews including post-discharge follow-ups on older patients' healthcare utilisation (the MedBridge trial): pragmatic cluster-randomised crossover trial. *Under review*
- VII **Kempen TGH**, Hedström M, Olsson H, Johansson A, Ottosson S, Al-Sammak Y, Gillespie U. (2019) Assessment tool for hospital admissions related to medications: development and validation in older patients. *Int J Clin Pharm*, 41(1):198-206

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Papers not included in this thesis

The following papers were published during this doctoral project, but are not part of the thesis:

- **Kempen T**, Melhus H. (2018) A Trial of Blood-Pressure Reduction in Black Barbershops. [Letter to the editor] *N Engl J Med*, 379(2):199.
- McIntosh J, Alonso A, MacLure K, Stewart D, **Kempen T**, Mair A, Castel-Branco M, Codina C, Fernandez-Llimos F, Fleming G, Gennimata D, Gillespie U, Harrison C, Illario M, Junius-Walker U, Kampolis CF, Kardas P, Lewek P, Malva J, Menditto E, Scullin C, Wiese B; SIMPATHY Consortium. (2018) A case study of polypharmacy management in nine European countries: Implications for change management and implementation. *PLoS One*, 13(4):e0195232.
- Stewart D, Gibson-Smith K, MacLure K, Mair A, Alonso A, Codina C, Cittadini A, Fernandez-Llimos F, Fleming G, Gennimata D, Gillespie U, Harrison C, Junius-Walker U, Kardas P, **Kempen T**, Kinnear M, Lewek P, Malva J, McIntosh J, Scullin C, Wiese B. (2017) A modified Delphi study to determine the level of consensus across the European Union on the structures, processes and desired outcomes of the management of polypharmacy in older people. *PLoS One*, 12(11):e0188348.

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Abbreviations

AT-HARM10	Assessment Tool for identifying Hospital Admissions Related to Medications
CFIR	Consolidated Framework for Implementation Research
CI	Confidence interval
CMR	Comprehensive medication review
DRP	Drug-related problem
ED	Emergency department
EHR	Electronic health record
GP	General practitioner
IRR	Inter-rater reliability
ITT	Intention-to-treat
mITT	Modified intention-to-treat
MedBridge	Medication Reviews Bridging Healthcare
MRA	Medication-related hospital admission
MRC	UK Medical Research Council
NPT	Normalization Process Theory
RCT	Randomised controlled trial
RR	Risk ratio
SALAR	Swedish Association of Local Authorities and Regions; <i>Sveriges Kommuner och Regioner</i>
SIMPATY	Stimulating Innovation Management of Polypharmacy and Adherence in the Elderly
WHO	World Health Organization

Introduction

Inappropriate prescribing and use of medications in older patients

The world's population is ageing. The percentage of people aged 65 years or older is estimated to double from 8% in 2015 to 16% in 2050.¹ At the same time, morbidity patterns are shifting towards chronic diseases.² Older people are more likely to experience multimorbidity, defined as the coexistence of two or more chronic conditions in the same individual,³ and the management of multimorbidity has an increasing impact on health systems around the world.³ The use of medications in older patients is probably the most frequently used healthcare intervention in the world. Multimorbid patients are likely to be prescribed multiple medications, often referred to as polypharmacy.⁴ Different definitions of polypharmacy exist, but when defined as five or more medications daily, a recent literature review reported a prevalence between 26% and 65% in people aged 65 years or older in the USA, New Zealand and countries in Europe.⁵

Polypharmacy can be a rational response to managing multiple health conditions. However, single-disease evidence-based guidelines often do not consider issues of multimorbidity. In case of polypharmacy, this can lead to individual treatments becoming inappropriate and even harmful.⁵ This is especially a risk in older patients, because of age-related changes in body composition, physical and cognitive function.^{6,7} It has been estimated that 18 billion US dollars in global healthcare costs can be avoided annually by improving the management of polypharmacy in older patients.⁸ Inappropriate prescribing and use of medications in older patients are therefore recognised by the World Health Organization (WHO) as a key patient safety issue. In response, the WHO has initiated a global initiative aiming to reduce severe, avoidable medication-related harm by 50% in 2017–2022.⁹

Medication reviews

One of the proposed actions by the WHO is to perform medication reviews in patients who use multiple medications.¹⁰ The concept of a medication review can be interpreted in different ways, but it is often defined as a structured, critical examination of a patient's medications with the objective of reaching

an agreement with the patient about treatment, optimising the impact of medications and minimising medication-related harm.¹¹ Medication reconciliation, “the process of identifying an accurate list of a person's current medications and comparing them with the current list in use, recognising any discrepancies, and documenting any changes, thereby resulting in a complete list of medications”,¹¹ is usually the first or preceding step of a medication review.¹² Medication reviews can be undertaken in all care settings and range from paper-based reviews of patients’ medication lists by a single healthcare professional to more complex, multi-professional approaches with direct patient involvement and taking into account the patients’ underlying conditions and symptoms.¹³ These complex approaches are also referred to as advanced,¹² clinical¹⁴ or comprehensive¹³ medication reviews (CMRs).

In a medication review process, drug-related problems (DRPs), defined as “undesirable patient experiences involving medication therapy that actually or potentially interfere with a desired patient outcome”,¹⁵ are identified. DRPs concern all sorts of inappropriate medication prescribing and use, such as overtreatment, noncompliance, drug-drug interactions and adverse drug reactions. Finally, a medication review should conclude with a decision about the treatment, aiming to solve and prevent DRPs, including a plan for any necessary follow-up and monitoring.¹¹

Clinical pharmacists

Conducting medication reviews is generally one of the key tasks of clinical pharmacists who work either in primary or secondary care. Clinical pharmacy was first introduced in the USA in the 1960s.¹⁶ The American College of Clinical Pharmacy defines clinical pharmacy as “that area of pharmacy concerned with the science and practice of rational medication use” and states that clinical pharmacists work directly with other healthcare professionals and patients to ensure that prescribed medications contribute to the best possible outcomes for patients.¹⁷ Clinical pharmacists can carry out various activities, depending on the context in which they work, the patient population and their own specific competences. Besides performing medication reviews, examples of activities are: therapeutic drug monitoring, participation in ward rounds and cardiovascular risk management.¹⁸

Evidence on medication reviews

Medication reviews by clinical pharmacists are effective in improving surrogate endpoints, for example the number of DRPs, glycated haemoglobin (HbA1c) levels in patients with diabetes mellitus and cholesterol levels in patients with cardiovascular disease.^{19–22}

Evidence on clinically hard endpoints, such as hospital admissions, is less convincing. In 2005-2006, a randomised controlled trial (RCT) was conducted

on the effects of CMRs by clinical pharmacists in patients aged 80 years or older at two internal medicine wards at Uppsala University Hospital.²³ CMR reduced the incidence of all hospital visits (risk ratio (RR) 0.84, 95% confidence interval (CI) 0.72 to 0.99) during 12-month follow-up compared with usual care. Even emergency department (ED) visits (RR 0.53, 95% CI 0.37 to 0.75) and medication-related hospital admissions (MRAs; RR 0.20, 95% CI 0.10 to 0.41) were reduced. The intervention included a detailed medication treatment plan being sent to the patient's general practitioner (GP) upon discharge and a follow-up phone call two months after hospital discharge to ensure adequate home management of medications.

A 2016 Cochrane review investigated whether medication reviews in hospitalised patients lead to improvement in mortality and hospital visits compared with usual care.²⁴ Based on ten RCTs, including the one from Uppsala, the authors concluded that there was no evidence that medication reviews reduce mortality or hospital admissions, although ED visits may be reduced. In general, estimates were uncertain and follow-up within the included studies was short. The authors expressed a need for high-quality RCTs, with long follow-up and a cluster-randomised design to minimise contamination bias.²⁴

Medication-related hospital admissions

Mortality and healthcare use, e.g. hospital admissions, are generally considered relevant outcomes in systematic reviews of the effectiveness of medication reviews in hospitalised patients.^{24–26} Given the variety of different mechanisms that can lead to death or healthcare use, more specific outcomes are warranted. As medication reviews primarily target medication use and DRPs, the admissions that are directly being affected are MRAs. For this reason, MRAs have been listed as one of the key outcomes for studies addressing polypharmacy in older patients.²⁷ Unfortunately, there is no generally agreed and valid method to identify and measure MRAs.

A frequently used method consists of an expert panel making an implicit assessment and reaching consensus, often based on information from the patient's electronic health record (EHR).^{28,29} Such an assessment is relatively expensive, as it involves the use of senior healthcare professionals and it can take a lot of time. Different tools to facilitate MRA assessment exist,^{30–34} but none of these are both validated and able to identify all types of DRPs that can cause hospital admissions. There is thus a need for a practical and quick tool that can be used to identify MRAs with limited expert involvement.

Implementation in clinical practice

More than ten years after the publication of the RCT at Uppsala University Hospital, the performance of medication reviews by clinical pharmacists has spread to more wards at the hospital, nursing homes and primary care centres in the region. However, most of the current medication reviews are not as extensively performed as the ones in the previous RCT. Especially parts of the medication review surrounding hospital discharge have been reduced due to a lack of time. In a recent RCT from Denmark, hospital-based medication reviews by clinical pharmacists, including motivational interviews with the patient and contact with primary healthcare providers upon and after discharge, reduced the incidence of readmissions and ED visits during 180 days follow-up compared with usual care (hazard ratio 0.77, 95% CI 0.64 to 0.93).³⁵ However, solely hospital-based CMRs were not effective compared with usual care (hazard ratio 0.94, 95% CI 0.79 to 1.13). Hence, the most effective part of the intervention in the previous RCT may not be carried out in current practice.

Healthcare interventions that seem successful in research can be challenging to implement in clinical practice.³⁶ CMRs by clinical pharmacists have spread heterogeneously throughout Sweden in the last decades. Region Uppsala, one of the 21 Swedish self-governing authorities responsible for health care at regional level, has one of the highest numbers of clinical pharmacists in the country. It is unclear what has led to this seemingly successful implementation. A better understanding of the different actions and factors involved may support the implementation and sustainment of medication reviews or similar initiatives in other settings, both in Sweden and other countries.

Implementation research

Implementation is the act or process of “carrying an intention into effect, which in health research can be policies, programmes, or individual practices (collectively called interventions)”.³⁷ Implementation research aims to understand what, why, and how interventions work in the real world and to investigate approaches to improve implementation.³⁷ Multiple theories, models and frameworks exist that can be applied implementation research, which can be divided into five categories as proposed by Nilsen:³⁸

- 1) Classical theories that originated and have been used in sociology, psychology and organisational science, e.g. social cognitive theory³⁹;
- 2) Theories that have been developed by implementation researchers, such as Normalization Process Theory (NPT, Box 1);
- 3) Process models specifying steps or stages of an implementation process, such as Kotter's 8-Step Process for Leading Change (Kotter, Box 1);

- 4) Determinant frameworks with factors that act as barriers to and enablers of implementation outcomes. One example is the Consolidated Framework for Implementation Research (CFIR, Box 1)⁴⁰;
- 5) Evaluation frameworks that can be used to assess successful implementation, such as RE-AIM⁴¹.

Box 1. Examples of theories, models and frameworks in implementation research which have been used in this doctoral research project.

Normalization Process Theory (NPT)

NPT is a sociological tool that consists of four domains describing the work that people do to implement and integrate a new practice: coherence, cognitive participation, collective action, and reflexive monitoring.⁴² NPT has been used to evaluate implementation in a variety of settings and complex interventions in health care.^{43–45}

Kotter's 8-Step Process for Leading Change (Kotter)

Kotter is a change management model that uses an eight-step approach: create a sense of urgency; build a guiding coalition; form a strategic vision; communicate the vision; enable action by removing barriers; generate short term wins; sustain acceleration; and institute change.⁴⁶ These steps do not necessarily have to be taken consecutively. Kotter has mostly been used to evaluate change in health care.^{47,48}

Consolidated Framework for Implementation Research (CFIR)

The CFIR is a framework based on existing theories, which consists of five domains, with each domain divided into several constructs: intervention characteristics; outer setting; inner setting; characteristics of individuals; and process.⁴⁰ CFIR has mostly been used to guide data analysis in implementation studies.⁴⁹

Evaluation of complex interventions in health care

Complex interventions, defined as interventions that contain multiple components which interact to produce change,⁵⁰ such as CMRs, are often evaluated through pragmatic trials. Pragmatic trials are generally designed to measure the effects of an intervention in the same context as in which it will be performed in practice, whereas explanatory trials are generally designed to measure the effects of an intervention in an ideal controlled context.⁵¹ Pragmatic RCTs can therefore be regarded as the “gold standard” methods for assessing real-world effectiveness of clinical interventions.⁵² There are, however, limits

to the questions that pragmatic trials can answer. Especially for complex interventions, it may be difficult to know why the intervention was effective (or not).

The UK Medical Research Council (MRC) therefore recommends conducting a process evaluation to understand the differences between expected and observed outcomes and to provide knowledge to support future implementation.⁵³ Process evaluation is complementary to the actual outcomes evaluation and can be conducted either before, during or after an RCT. The MRC has defined three core elements of process evaluation: implementation, mechanisms of impact and contextual factors (Figure 1).⁵³ Here, implementation is “the process through which interventions are delivered, and what is delivered in practice”;⁵³ mechanisms of impact are the intermediate processes through which interventions affect outcomes; and contextual factors are external to the intervention and the people directly involved.⁵³ Implementation theories, models and frameworks, mentioned in the previous paragraph, can be used in studies to investigate the three elements of process evaluation.

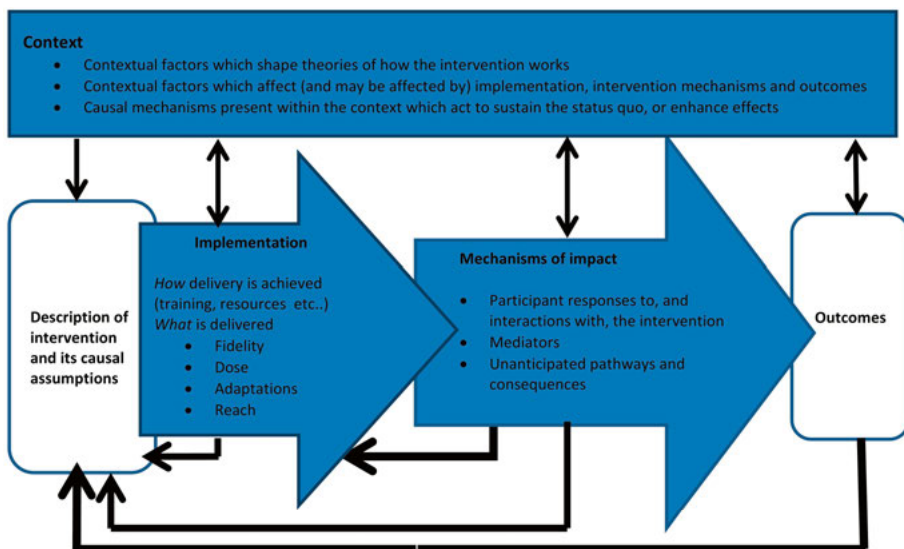


Figure 1. UK Medical Research Council framework for process evaluation by Moore et al.⁵³ (reused with permission): key functions and relationships amongst them. Blue boxes represent the three core elements of process evaluation.

Both quantitative and qualitative methods are used for process evaluation. Assessing clinical pharmacist notes in patients’ EHRs to measure intervention fidelity, i.e. the consistency of the performed interventions with the planned interventions,⁵⁴ can for example provide understanding of the implementation in trials of medication reviews. Examples of process outcomes are: discrepancies between the patient’s medication list in the EHR and the medication used

by the patient and DRPs.^{55,56} Assessment of the correction of these discrepancies, proposals to solve identified DRPs and the acceptance of these proposals, may provide understanding of the performance of medication reviews and their mechanisms of impact.

One of the most common qualitative method in health sciences is semi-structured interviewing. This method can inform all elements of process evaluation.^{53,57} Semi-structured interviews have some guiding questions to reiterate the focus or aim of the study, but not too many, to draw out spontaneous and relatively uninterrupted descriptions of the participants' experiences, views and thoughts.⁵⁷ These participants can be any kind of stakeholder, e.g. patients, physicians and pharmacists in trials of medication reviews.⁵³ Combined, quantitative and qualitative findings can provide rigorous support to understand a complex trial's results.

Aim of this thesis

The overall aim of this thesis was to study the implementation, performance and effects of medication reviews by clinical pharmacists in older hospitalised patients. The specific objectives were:

- To explore the events, actions and other factors that were involved in the implementation and sustainability of medication reviews in older patients by clinical pharmacists in Region Uppsala (Paper I);
- To describe the rationale and design of a pragmatic cluster-randomised crossover trial (MedBridge) to study the effects of hospital-initiated CMRs including post-discharge follow-ups on older patients' healthcare utilisation, compared with only hospital-based reviews and usual care (Paper II);
- To explore older patients' experiences with, and views on, hospital-initiated CMRs and follow-up telephone calls by ward-based clinical pharmacists within the MedBridge trial (Paper III);
- To explore the facilitators and barriers for performing CMRs and post-discharge follow-ups in older hospitalised patients from the healthcare professional perspective (Paper IV);
- To assess the intervention fidelity and process outcomes of CMRs and post-discharge follow-ups within the MedBridge trial (Paper V);
- To study the effects of hospital-initiated CMRs including post-discharge follow-ups on older patients' healthcare utilisation, compared with only hospital-based reviews and usual care (Paper VI);
- To develop and validate a practical tool to identify MRAs (Paper VII).

Methods

Paper I

Design and setting

This study used a case study design.⁵⁸ The unit of investigation was the process of implementation and sustainment of the performance of medication reviews by clinical pharmacists, with Kotter and NPT as underlying theories to support the investigation.^{42,46} The case study focussed on Region Uppsala, the regional authority with the responsibility for the provision of health care to the 380.000 inhabitants of Uppsala County. External factors were also part of the scope of this case study. Two national organisations were therefore included: the Swedish Association of Local Authorities and Regions (SALAR; *Sveriges Kommuner och Regioner* in Swedish) and the National Board of Health and Welfare (*Socialstyrelsen*), a government agency under the Ministry of Health and Social Affairs. The study included data up to 2015. It was part of a European Union co-funded project, Stimulating Innovation Management of Polypharmacy and Adherence in the Elderly (SIMPATY), which aimed to stimulate, promote and support innovation across the Europe Union in management of polypharmacy and treatment adherence in older patients.⁵⁹ Similar case studies were performed in seven other countries in Europe. Findings from the framework analysis across all cases have been reported elsewhere.⁶⁰

Data collection and analysis

Literature review

A literature review was performed by two researchers (TK and UG), from September to December 2015, to identify documents relevant to this case study. A guide with questions, drawn from Kotter and NPT, was used to structure the review process (Appendix A in Paper I). The MedLine database, Google search and Region Uppsala's intranet were used to collect peer-reviewed publications and 'grey' literature, such as policy documents and guidelines. Relevance of the publications and literature was determined through consensus by the two researchers.

Semi-structured interviews

Semi-structured interviews were held by the same researchers with different stakeholders. The sampling strategy was to recruit participants from different positions and institutions, including at least one policy maker, one manager responsible for implementation and one healthcare professional. The interview guide topics were based on Kotter and NPT: the rationale for the introduction of medication reviews, implementation strategies, integration into daily practice, evaluation, and plans for future developments (Appendix A in Paper I). Four interviews were held by in November and December 2015, which lasted for 50-80 minutes. The interviews were audio-recorded, transcribed and thematically analysed using a coding framework based on Kotter and NPT. A summary of the findings from the literature review and of the thematic analysis of the interviews were combined into one report.

Focus group

The content of the report was then discussed by a focus group in February 2016. Participant sampling and recruitment for the focus group followed the same process as for the interviews. Eight stakeholders, three of whom had been interviewed, were approached and agreed to participate. The focus group was run by the two researchers and lasted for 120 minutes, using a topic guide developed by the SIMPATHY project leaders (Appendix A in Paper I). It included questions on how the findings in the summary report matched with personal experience and knowledge, and if there were any points that had been missed or not emphasised enough.

Additional literature review and interviews

Based on the results of the focus group session, the literature review was updated and three additional interviews were conducted by at third researchers (MF). Interviews were performed in March 2018, but the participants were asked to focus on the period up to 2015 to be consistent with previous data collection. The interviews lasted for 20-40 minutes.

The focus group discussion and additional interviews were audio-recorded, transcribed and thematically analysed using the same method as with the first interviews. All three researchers were involved in the analysis. Presence of factors within Kotter's steps and NPT domains were categorised as facilitators, whereas a lack of absence of factors were categorised as barriers. Findings from the literature review were used to support the interpretation of these identified factors.

Paper II and VI

Study design

The Medication Reviews Bridging Healthcare (MedBridge) trial was a pragmatic, multicentre, three-treatment, cluster-randomised, crossover trial. The trial was performed and has been reported in accordance with the Helsinki Declaration⁶¹ and the applicable CONSORT extensions.⁶²⁻⁶⁴ The trial was registered at ClinicalTrials.gov under the identifier NCT02999412.

Setting and participants

The trial was conducted between February 2017 and October 2018 at four hospitals in Sweden: Uppsala University Hospital and the hospitals of Enköping, Gävle, and Västerås. Two wards per hospital were included and each ward acted as a cluster. The eight wards differed in terms of medical specialty: internal medicine (4), stroke and neurology (2), diabetes and nephrology (1), and geriatrics (1). The performance of medication reviews by pharmacists was either an established practice or pharmacists were introduced to this practice at each ward at least six months prior to the start of the trial. All pharmacists had followed post-graduate courses in clinical pharmacy.

All patients who were eligible for inclusion were asked for informed consent to participate. Inclusion criteria were age 65 years or older and admission to one of the participating wards for at least a full day on regular weekdays. Patients were excluded if they had received a medication review by a clinical pharmacist within the last 30 days, resided in another county than the hospital was located in, or were receiving palliative treatment.

Crossover and randomisation

Crossover and randomisation took place at cluster (ward) level. Each ward participated in the trial for six consecutive eight-week study periods, divided into two separate blocks of three study periods each (Figure 2). One of three treatments (intervention 1, 2, or control) was provided at the ward during each period, with permuted block randomisation ensuring that each treatment was performed within each block. The different treatments pertained to individual patients. Ward staff and participants were not blinded to treatment allocation. All patients eligible for inclusion received the treatment that was being performed at the ward at that time, regardless of their consent to participate in the trial. Individual patients could only be included in the trial once and any participant who was readmitted to one of the study wards also received the intervention being performed at that time.

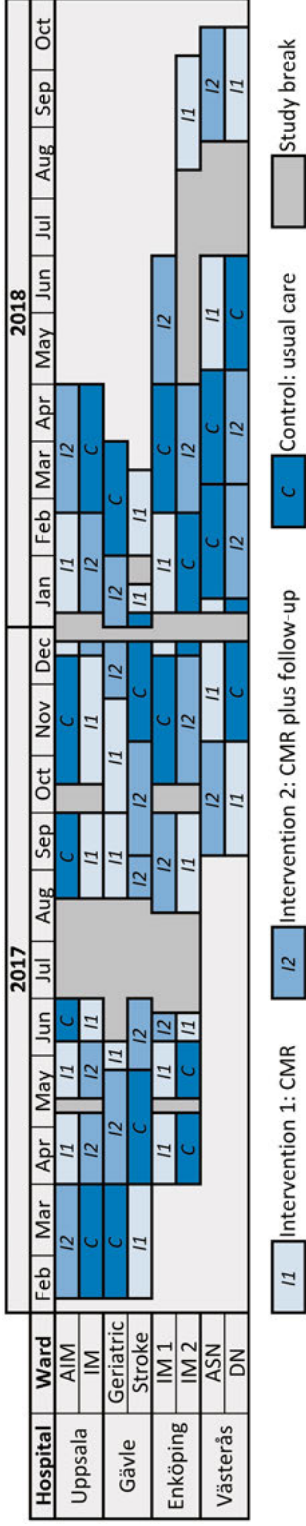


Figure 2. Cluster (ward) and period chart resulting from the block randomisation and as performed in the MedBridge trial (reused with permission, Paper VI). AIM = acute internal medicine; ASN = acute stroke and neurology; CMR = comprehensive medication review; DN = diabetes and nephrology; IM = internal medicine.

Interventions

Intervention 1, CMR, consisted of a medication reconciliation by a clinical pharmacist to ensure a correct list of medications. This was directly followed by a structured, critical examination of all the patient's medications in relation to the patient's conditions and symptoms, in collaboration with the ward physician, the nurse if appropriate, and the patient. A final medication reconciliation was performed by the pharmacist to ensure a correct list of medications upon discharge.

Intervention 2, hospital-based CMR including post-discharge follow-up (CMR plus follow-up), consisted of the same elements as intervention 1 with the following two additions: 1) a referral by the clinical pharmacist to the patient's GP with recommendations on actions to be taken after hospital discharge, if deemed necessary; and 2) two telephone calls to the patient by the pharmacist, 2–7 days and 1–2 months after discharge, to ensure that all the information about the patient's medication treatment had been understood correctly and to deal with any problems, concerns, or questions related thereto.

Control patients received usual hospital care. Some of the intervention components or related activities could be carried out by ward staff to a certain degree, but no pharmacist was involved at the ward.

Outcome measures and data collection

The primary outcome measure was the incidence of unplanned hospital visits within 12 months after index admission. An unplanned visit could be either a visit to the ED or an unplanned admission, not part of the patient's treatment plan, but resulting from an acute health problem. Secondary outcomes were all-cause unplanned hospital admissions and ED visits separately, unplanned medication-related admissions, GP visits, time to first unplanned hospital visit, all-cause mortality and costs of hospital-based care. The primary outcome was also measured in pre-specified subgroups based on characteristics at index admission (Supplementary file 1 in Paper VI).

Baseline and outcome data were extracted from the counties' EHR systems and healthcare registries. Unplanned hospital admissions were assessed by two final-year undergraduate pharmacy students, using a validated method to distinguish between unlikely and possible MRAs (AT-HARM10; Paper VII). Outcome data collection and assessments were blinded to treatment allocation.

Sample size and power calculation

The cluster-randomised crossover design would result in an approximately 1:1:1 ratio of trial participants in the three treatment groups. An incidence of two hospital visits per patient year was expected in the control group, based on a previous RCT and pilot study data. Power simulations were based on a

fixed effects Poisson regression with a between cluster variance of 0.5. The expected mean number of days at-risk per patient was 290 and on average seven hospital visits per 1000 patient-days were assumed in the control group. No compensation for withdrawals was accounted for in the sample size estimation. With these assumptions, 2310 study participants would have been needed to show a 10% reduction in hospital visits between CMR plus follow-up and control, with a power of approximately 83% ($\alpha = 5\%$).

Data analysis

Primary and secondary analyses were based on a modified intention-to-treat (mITT) population. The intention-to-treat (ITT) population was defined as: all patients who were eligible for inclusion in the trial. Patients who provided informed consent were considered part of the mITT population. Those who did not provide informed consent or withdrew before data collection were dropouts.

The differences in rates of visits and admissions between treatment groups were compared using log-linear models with Poisson variance function in the framework of generalised linear mixed models, with adjustments made for cluster and period effects. The number of out-of-hospital-days was used as offset and the number of unplanned hospital visits within 12 months before index admission as a patient-level covariate. Tukey's adjusted p values and 95% CIs were calculated to prevent multiple testing problems. Pre-specified subgroups were analysed with the same method as in the primary analysis. Multivariable models were used to test for interaction to evaluate statistically significant subgroup differences. Time to first unplanned hospital visit and mortality were analysed with nested frailty models, including gamma-distributed random effect. The non-parametric bootstrap method was used to compare costs of hospital-based care and estimate 95% CIs.

The planned sensitivity analysis (per-protocol) was not performed, because of a perceived high risk of bias in the as-treated analysis: multimorbid patients were more likely to have received the intervention. Instead, the ITT population was used for sensitivity analysis of the primary outcome measure (Supplementary file 2 in Paper VI).

A significance level of 0.05 (two-tailed) was used for all comparisons. All outcome analyses were performed using SAS software (SAS Institute Inc., Cary, USA) by statisticians who were blinded to treatment allocation until database closure.

Paper III-V

Study design and setting

Paper III, IV and V were part of a process evaluation of the MedBridge trial. The process evaluation was based on the UK MRC process evaluation framework⁵³ and consisted of four methods: patient interviews, healthcare professional interviews, intervention fidelity assessment and process outcomes assessment (Figure 3). These methods were chosen to investigate the three core elements of process evaluation, with some methods relating to more than one core element. Each method addressed different research questions (Table 1). For the two qualitative methods (Paper III and IV), an interpretive approach as proposed by Ritchie and Lewis⁶⁵ was taken: reality exists independently of individual subjective understanding, but it is only accessible to the researchers via the participants' interpretations.

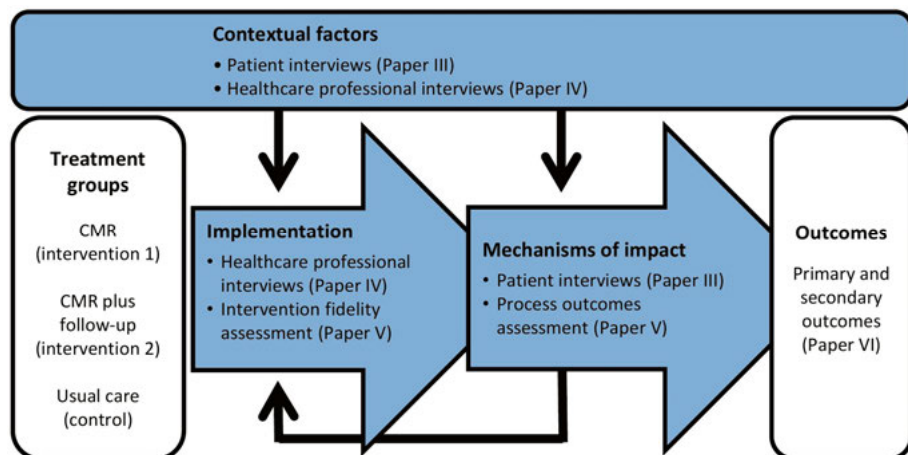


Figure 3. The three core elements of process evaluation (blue boxes) and relationships amongst them, and the four methods (bullet points) to investigate these elements within the MedBridge trial, based on the UK Medical Research Council process evaluation framework.⁵³ CMR = comprehensive medication review.

Table 1. *Methods, research questions and related core elements of process evaluation in the MedBridge trial.*

Methods	Research questions	Core element
Patient interviews (Paper III)	- What are the experiences with, and views on, the MedBridge trial interventions from the patient perspective?	Contextual factors and mechanisms of impact
Healthcare professional interviews (Paper IV)	- What are the facilitators and barriers for performing the MedBridge trial interventions from the healthcare professional perspective?	Contextual factors and implementation
Intervention fidelity assessment (Paper V)	- What percentage of patients in each treatment group received intervention components as defined in the trial protocol?	Implementation
Process outcomes assessment (Paper V)	<ul style="list-style-type: none"> - What number and types of discrepancies and DRPs were identified within the CMRs? - What number and types of recommendations were made by the pharmacists to solve DRPs? - What was the correction rate of discrepancies and implementation rate of recommendations within the CMRs? - What percentage of patients had at least one corrected discrepancy or implemented recommendation? 	Mechanisms of impact

CMRs = comprehensive medication reviews; DRPs = drug-related problems.

Participants and recruitment

Patient interviews

The potential participants in this study were participants within the MedBridge trial who had received one of the two interventions and were taking care of their own medication management in the ambulant setting, either with or without support by their next-of-kin. Purposive sampling⁶⁵ was used to ensure coverage across hospital wards and heterogeneity in terms of age, gender, intervention (CMR or CMR plus follow-up), clinical pharmacist involved, and the number (high or low) of medication-related problems identified during the CMR. The interview was planned one to four weeks after the patient's hospital discharge to minimise problems with recalling the experience.

Healthcare professional interviews

A purposive sampling approach⁶⁵ was used to recruit physicians and pharmacists that had been involved in the MedBridge trial at different hospitals, degrees of medical training and positions, and healthcare professionals who had either expressed scepticism or difficulties towards the interventions within the

trial. First, healthcare professionals were recruited and interviewed in Uppsala, followed by those in the other three hospitals.

Intervention fidelity assessment and process outcomes assessment

For intervention fidelity assessment, all MedBridge trial participants were included. For process outcomes assessment, at least one-third of all participants from each intervention period (either CMR or CMR plus follow-up) was randomised to be included using a random sequence generator.

Data collection

Patient interviews

A semi-structured discussion guide was used to guide the interviews (Appendix A in Paper III). The content of the discussion guide was based on the topics within the Picker Patient Experience Questionnaire,⁶⁶ the NHS Patient Experience Framework⁶⁷ and the intervention components of the MedBridge trial. Recruitment and interviewing took place between September 2017 and April 2018. The interviews were audio-recorded, transcribed verbatim by one researcher (AK) and checked for transcribing accuracy by the same researcher who performed the interviews (TK).

Healthcare professional interviews

A discussion guide was informed by the concepts of interprofessional collaboration by D'Amour et al.⁶⁸ The topics were: working processes, resources, competences, DRPs, intervention effects, and collaboration (Appendix 1a in Paper IV). The interviews in Uppsala were conducted by one researcher (MS) in March and April 2017 and lasted 15-40 minutes. For the additional interviews, the order of the topics in the discussion guide was changed and questions were added and reformulated (Appendix 1b in Paper IV). These interviews were held by another researcher (AK) between May and October 2018 and lasted 17-104 minutes. The interviews were audio-recorded and transcribed verbatim by the same researcher who performed the interviews and checked for transcribing accuracy by another researcher (TK).

Intervention fidelity assessment and process outcomes assessment

For intervention fidelity assessment, the trial participants' EHRs were retrospectively screened by research assistants to collect data on whether the patients had received intervention components. Any other intervention components performed without pharmacist involvement were considered usual care and were not included.

For process outcomes assessment, the pharmacists' notes in the patients' EHR were assessed to collect data on the number and types of identified medication discrepancies, DRPs and recommendations by the pharmacists. The

patient's medication list was assessed to categorise each discrepancy as *corrected* or *uncorrected*. DRPs were defined and classified using a modified system of that by Strand et al.¹⁵ (Appendix 1 in Paper V) and recommendations to solve DRPs were classified using a modified system of the French Society of Clinical Pharmacy⁶⁹ (Appendix 1 in Paper V). The patient's medication list and physicians' notes were then assessed to categorise each recommendation as *implemented* or *not-implemented*. Assessments were performed by final-year pharmacy students and a postgraduate clinical pharmacy student under the supervision of one researcher (TK).

Data analysis

Patient interviews

Data analysis followed a framework approach as proposed by Ritchie and Spencer.⁶⁵ The two researchers (TK and AK) discussed the coding framework being used and coded each interview independently with consensus reached by discussion.

Healthcare professional interviews

Thematic analysis was based on the framework approach by Ritchie and Spencer⁶⁵ with the CFIR⁴⁰ to structure the codes (Appendix 2 a-c in Paper IV). Two researchers (MS and TK) independently analysed and coded the interview transcripts from Uppsala and consensus was sought on conflicting results. A third researcher (UG) was available to decide in case no consensus was found. The three researchers then summarised and interpreted the data to create sub-themes, which were then categorised as either facilitators or barriers. For the interviews at the other three hospitals, two researchers (AK and TK) independently coded the interview transcripts followed by the same method as the interviews in Uppsala. Facilitators and barriers were then matched with those from the interviews in Uppsala and grouped into overarching main themes.

Intervention fidelity assessment and process outcomes assessment

Data were analysed with R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) using descriptive statistics. Correction rates of discrepancies and implementation rates of recommendations were calculated.

Paper VII

Development of the tool

First, a literature search was performed to find existing methods or tools to identify MRAs using the Medline database in February 2016. A preliminary version of the tool was based on the results of this search. We defined MRA as a hospital admission of which a DRP is either the main cause for admission or a significantly contributing cause for admission (i.e. without the DRP, the patient would not have been admitted). Elements from published tools and studies were listed to include all relevant categories of DRPs.^{15,30–32,70–78} The final tool consisted of ten “yes/no” questions and was called Assessment Tool for identifying Hospital Admissions Related to Medications (AT-HARM10). Questions 1-3 in the tool are used to identify admissions that are *unlikely* to be medication-related, whereas questions 4-10 are used to identify *possible* MRAs (Table 2). The assessment is finished when the answer is "yes" to any of the questions. If all the questions are answered "no", the assessment is indecisive and should be examined by an expert panel. Instructions for use, including examples, were developed for the tool (Appendix 1 in Paper VII).

Table 2. *The ten questions in the final version of the Assessment Tool for identifying Hospital Admissions Related to Medications (AT-HARM10; reused with permission, Paper VII).*

Question
Unlikely to be medication-related, if answered “yes”:
1. Was the admission caused by an infection or a previously undiagnosed disease (e.g. diabetes or heart failure) that is not medication-related?
2. Was the admission caused by progression of a previously diagnosed disease that is not medication-related?
3. Was the admission caused by physical trauma, substance intoxication, social circumstances or allergies that are not medication-related?
Possibly medication-related, if answered “yes”:
4. Is it hinted or stated in the medical record that the admission was medication-related (including non-compliance)?
5. Might (side) effects of the medications the patient was taking (prescribed or not prescribed) prior to hospitalisation have caused the admission (including over-treatment)?
6. Are there abnormal laboratory results or vital signs that could be medication-related and might have caused the admission?
7. Was there any drug-drug interaction or drug-disease interaction (i.e. a contraindication) that might have caused the admission?
8. Did the patient have any previously diagnosed untreated or sub-optimally treated (e.g. dose too low) indications that might have caused the admission?
9. Was the patient admitted because of a problem with the dosage form or pharmaceutical formulation (i.e. failure to receive the medication)?
10. Is the cause of the admission a response to cessation or withdrawal of medication therapy?

Validation

For content validity, meaning that all relevant aspects and no irrelevant aspects are included,⁷⁹ the preliminary version of the tool was assessed using a questionnaire about the tool's understandability, completeness and relevance. Seven clinical pharmacists answered the questionnaire and were encouraged to suggest modifications.

Fifteen clinical pharmacists applied the tool to a sample of hospital admissions to evaluate whether the data sources suggested to be used for the assessments were sufficient to apply the tool. The tool's user-friendliness was discussed and time spent on assessing the admissions was measured.

Seven final-year undergraduate and postgraduate pharmacy students were divided into four pairs to test the inter-rater reliability (IRR): the degree of consistency among the assessors when assessing the same set of samples.⁸⁰ Each assessor independently applied AT-HARM10 to 50 randomly selected admissions of patients aged 65 years or older, classifying them as either unlikely to be or possible MRAs. Pairs number 1+2 assessed one set of 50 admissions, and pairs number 3+4 assessed another set of 50 admissions. Each pair of assessors then discussed the admissions they disagreed on to reach consensus. Cohen's kappa within each couple and Fleiss' kappa between pairs were calculated to determine the IRR.

The sensitivity, specificity, positive predictive value and negative predictive value were calculated to measure the criterion-related validity, which is a measure of the validity of a tool by correlating the results with those from some other measure which has been used and accepted in the field.⁷⁹ In this study, the comparator was an expert panel of experienced clinicians which assessed the same 100 admissions as the four pairs of students.

Ethical considerations

All participants in the case study (Paper I) provided written informed consent prior to their participation. The Regional Ethical Review Board in Uppsala was consulted and the case study was exempted from ethical approval as it did not involve sensitive personal data according to the Swedish Personal Data Act (1998:204).

The MedBridge trial (Paper II-VII) received ethical approval from the Swedish Central Ethical Review Board (CEPN; registration number: Ö21-2016) and additional ethical approval from the Regional Ethical Review Board in Uppsala for the patient interviews (EPN Uppsala; registration number: 2016-251-1). Informed consent was obtained from all individual participants (or their next-of-kin) included in the trial and its process evaluation.

Results

Paper I

This study explored the events, actions and other factors that were involved in the implementation and sustainability of medication reviews in older patients by clinical pharmacists in Region Uppsala.

Six physicians, three clinical pharmacists and one nurse, all with different specialisations and positions within national and regional institutions, participated in the case study. Multiple facilitators and barriers were identified (Table 3). A summarised version of the findings are reported here with references to documents from the literature review and supported by illustrative quotes from either the initial interviews (I1-4), focus group (F2-9) or additional interviews (A8-10).

Table 3. *Events, actions and other factors involved in the implementation and sustainability of medication reviews by clinical pharmacists in Region Uppsala (reused with permission, Paper I).*

Kotter and NPT	Facilitators	Barriers
Create a sense of urgency	<ul style="list-style-type: none"> - Evidence on inappropriate polypharmacy - National focus on quality of care for the elderly 	
Build a guiding coalition, and cognitive participation (NPT)	<ul style="list-style-type: none"> - Multi-professional collaboration - Key individuals to drive change - Support from stakeholders 	<ul style="list-style-type: none"> - Lack of team setting in primary care - Scepticism towards physician-pharmacist collaboration
Develop a vision, communicate the vision, and coherence (NPT)	<ul style="list-style-type: none"> - National vision for quality of medication in older patients - Regional vision for pharmacists within healthcare - Local leadership and networking at national level - Public involvement 	<ul style="list-style-type: none"> - Lack of national plan for implementation of medication reviews - Unclear allocation of tasks and responsibilities - Lack of belief in the need for medication reviews
Enable action by removing barriers, and collective action (NPT)	<ul style="list-style-type: none"> - Education for healthcare professionals - Financial support and pay-for-performance - National legislation and guidance on medication reviews - Shared electronic medical records and prescribing tools 	<ul style="list-style-type: none"> - Lack of time and continuity in healthcare

Kotter and NPT	Facilitators	Barriers
Generate short-term wins, and reflexive monitoring (NPT)	<ul style="list-style-type: none"> - Periodical reports on quality indicators - Local evidence on the effects of medication reviews 	<ul style="list-style-type: none"> - Lack of national monitoring and evaluation
Sustain acceleration, and institute change	<ul style="list-style-type: none"> - From project funding to permanent positions - Continual monitoring and development plans 	<ul style="list-style-type: none"> - Focus shifting away from care for the elderly - Deregulation of the state's pharmacy monopoly

NPT = Normalization Process Theory.

Facilitators

After publications and attention in the USA, inappropriate polypharmacy was “*first acknowledged [as a problem] in Sweden in the 1980s.*”^(I1) In the 1990s, Swedish evidence became available,⁸¹⁻⁸³ which led to a national focus on care for the elderly. Socialstyrelsen, the National Board of Health and Welfare, published indicators for the quality of care and prescribing in the elderly in which the need for medication reviews was addressed.^{84,85}

In 1994-1995, Apoteket AB, the national Swedish community pharmacy chain (until 2009), and Socialstyrelsen conducted a large study on multi-professional medication reviews in nursing homes, which had positive results.⁸⁶ “*The multi-professional collaboration and certain key individuals in Uppsala were success factors for the development.*”^(F8) These key individuals ensured support from other stakeholders, such as the chairperson of the regional’s drug and therapeutics committee.

A national medication strategy, published in 2010, defined medication reviews as one of the prioritised activities,⁸⁷ which was used to drive change by local leaders as well. Public involvement also became important for support for medication reviews: “*There has been a great involvement of patients and pensioners, and this public engagement has definitely made a difference.*”^(F9)

In the 1990s and 2000s, Swedish pharmacists followed clinical pharmacy programmes and went on study visits in the UK, financed by the Swedish Pharmaceutical Society.⁸⁸ Based on examples from the UK, undergraduate and postgraduate courses in clinical pharmacy were developed at Uppsala University. Apoteket AB and Region Uppsala have financed clinical pharmacist positions since 2001. In 2007-2014, the Swedish government and SALAR carried out programmes and allocated large budgets to improve the quality of care for older people.^{89,90} In Region Uppsala, funding from this programme was used for medication reviews by clinical pharmacists.

In 2012, new national legislation stated that medication reviews had to be performed in patients aged 75 years or older with five or more medications in use.⁹¹ The introduction of shared EHRs within Region Uppsala, and the development of regional guidelines on medication treatment in older patients were other important facilitators.⁹²

Region Uppsala has integrated most indicators for the quality of care and medication prescribing in the elderly into annual pay-for-performance agreements with hospitals and primary care centres.⁹³ In 2009, the positive results from the RCT at Uppsala University Hospital were published.²³

Project funding of clinical pharmacists has been replaced by permanent positions in recent years. The quality indicators are still being used at regional level to keep monitoring the quality of prescribing, and plans exist to create more clinical pharmacist positions in primary care. *“The pharmacists have established themselves out there.”* (I9)

Barriers

Multi-professional collaboration was harder to establish within primary care, because *“you usually only have the general practitioner working alone”* (F7). There was also scepticism towards this kind of collaboration: *“Many physicians [...] were quite negative towards clinical pharmacists.”* (A10)

No national plan for the implementation of medication reviews existed. Another barrier was the unclear allocation of tasks and responsibilities concerning medication reviews: *“There were great differences among healthcare professionals on the view of how and by whom these [medication review] activities should be performed.”* (I2)

Lack of time and continuity have been barriers that still exist in health care. Medication reviews also need follow-up by the GP, but *“patients often lack a permanent physician, so the effect of the reviews gets lost.”* (A9)

The absence of formal monitoring or evaluation of the impact of the national medication strategy and legislation on medication reviews was identified as a barrier for implementation and sustainability.

In recent years, there has been less focus on improving medication use in older patients than before, *“due to the different political landscape”* (I2). It also became harder *“to steer questions concerning medications”* (A8) after deregulation of the state's pharmacy monopoly in 2009.

Paper III

This study explored older patients' experiences with, and views on, hospital-initiated CMRs and follow-up telephone calls by ward-based clinical pharmacists within the MedBridge trial.

In total, 15 interviews were conducted. Twelve interviews were held with patients, two with both the patient and next-of-kin and one with the next-of-kin only. The age of the patients ranged from 66 to 94 years and there was heterogeneity in other characteristics.

The seven key themes that emerged from the interviews are listed in Table 4, summarised below and supported by quotes (P1-14 for the patients; N6, N9 and N15 for the next-of-kin).

Table 4. *Key identified (sub)themes related to the patients' experiences with, and views on, the MedBridge trial interventions (reused with permission, Paper III).*

Theme
Feeling of being taken care of and heterogenous health effects <ul style="list-style-type: none"> - Patients have a feeling of being taken care of - Understanding of the need of CMRs - It is good to perform a CMR, but the health effects are unknown - Heterogeneous effects on medication treatment - Positive or no effect on treatment adherence
The pharmacist is competent*
Despite the unclear role of pharmacists, their involvement is appreciated <ul style="list-style-type: none"> - Unclear role of the pharmacist - Limited understanding of the CMR process - Positive view on pharmacist involvement in healthcare - The pharmacist is available - It is the physician's responsibility
Patients rely on healthcare professionals for decision-making <ul style="list-style-type: none"> - Limited role of patients in decision-making - Patients depend on healthcare professionals - Patients rather not take medication - Patients decide themselves
Importance of being informed, but receiving and retaining information is problematic <ul style="list-style-type: none"> - It is important to be informed about medication - Good quality of information from the pharmacist - Recalling information is problematic - Patients receive a lot of other information at the hospital - Other information sources can be very helpful
Time, location and other factors influencing the effectiveness of CMRs <ul style="list-style-type: none"> - Timing of the pharmacist contact can be essential - It is difficult to inform old and ill patients - The hospital ward is a suitable location - There is little time during discharge
Generic substitution is a problem*

*This key theme has no sub-themes. CMR = comprehensive medication review.

Feeling of being taken care of and heterogenous health effects

Patients mentioned “*a feeling of being taken care of*” (N6) and acknowledged the need for CMRs. For most patients, it was impossible to say whether the CMRs were effective, because they did not know the result of the CMR in relation to what was part of usual care. Some patients could be “*upset*” (P2) because of medication changes that they did not agree with. Other patients expressed “*feeling much better*” (P5) or having more control over their medications.

The pharmacist is competent

Experiences with, and views on, the pharmacists' competence were positive. Patients and next-of-kin thought that the pharmacist was "*knowledgeable*" (P14) and that they were listened to.

Despite the unclear role of pharmacists, their involvement is appreciated

It was unclear what the role of the pharmacist at the ward was, and patients had little understanding about CMRs: "*I sure did have questions, but [...] I did not really know what the conversation was about.*" (P7) Several patients became "*surprised*" (P12) or "*confused*" (P1), because they had "*never experienced [a pharmacist at the ward] before*" (P5). In general, multi-professional collaboration in health care was appreciated: "*You [the pharmacist] with your knowledge and the physicians with theirs can put your heads together and maybe come up with something better than the physician alone.*" (P4) Some patients seemed more indifferent towards a pharmacist being involved.

Patients rely on healthcare professionals for decision-making

Patients had little involvement in decision-making: "*The patient doesn't get involved, but I think it would be very useful to understand why you get this medication.*" (P13). There was a trust in healthcare professionals to "*do the right thing*" (P5). Some patients mentioned having discussed treatment options.

Importance of being informed, but receiving and retaining information is problematic

Patients expected to receive information about reasons for change and side effects of medications, which they generally had received through the performance of the CMRs and follow-up phone calls. However, information could sometimes be conflicting: "*It is quite interesting that one [family] doctor thinks you should take those [medications] and then you're here [at the hospital] and both a pharmacist and a doctor say 'No, she will not have these medications, that is unnecessary'.*" (P2) Problems with receiving and retaining information were expressed in all interviews. Some patients had "*forgotten everything.*" (P3)

Time, location and other factors influencing the effectiveness of CMRs

The timing of the contact between the patient and the pharmacist could be unsuitable: "*It was quite a short call, because me and my wife were just on our way out.*" (P4) Patients' age and health condition, e.g. patients being too ill to discuss medications, were mentioned as general factors influencing the performance of CMRs. Lack of time and hasty discharges from the ward were

barriers to adequately inform patients: “*We went home after lunch, but it was so messy, and we were in a hurry.*” (P7)

Generic substitution is a problem

Generic substitution of medications was often addressed as a problem for older patients with regard to the management of their medications and the risk of medication errors.

Paper IV

This study explored the facilitators and barriers for performing CMRs and post-discharge follow-ups in older hospitalised patients from the healthcare professional perspective.

Interviews were held with 16 physicians and 7 pharmacists. All hospitals, positions and other predefined characteristics were present among the participants, with clinical working experience ranging from a few weeks to more than 25 years.

In total, 21 facilitators and 25 barriers were identified across all CFIR domains and grouped into six main themes (Table 5). Frequent recurring factors and those interpreted as important by the researchers are summarised below and supported by quotes from the interviews (D1-16 for the physicians; P1-7 for the pharmacists).

Table 5. *Facilitators and barriers for performing comprehensive medication reviews and post-discharge follow-ups by ward-based pharmacists from the healthcare professionals’ perspective, grouped into six main themes (reused with permission, Paper IV).*

Facilitators	Barriers
CMRs and follow-up are needed, but not in all patients	
<ul style="list-style-type: none"> - Patients need and appreciate CMRs^{I,IV} - Awareness of legislation and guidelines on CMRs among HCPs^{II,IV} - Need for and willingness to take part in research among HCPs^{I,III,V} 	<ul style="list-style-type: none"> - Not all patients want, need or feasible for CMR^{I,III,V} - Pharmacist involvement not always necessary^I - Little knowledge about evidence, legislation and guidelines on CMRs among physicians^{I,II}
General belief in positive effects of CMRs and follow-up	
<ul style="list-style-type: none"> - HCPs belief in positive effects of CMRs^{I,IV} - Pharmacist's work is relevant and appreciated by physicians^{I,III,IV} - CMR more thorough with pharmacist involvement^{I,III,IV} - Positive attitude among pharmacists towards referrals and phone calls^{I,III,V} (<i>only derived from pharmacist interviews</i>) 	<ul style="list-style-type: none"> - Uncertainty among physicians about the long-term effects of CMRs^I (<i>only derived from physician interviews</i>) - Insufficient quality of and communication about post-discharge follow-up by primary care^{II,III} - Phone calls may disturb patients^{II} (<i>only derived from pharmacist interviews</i>)

Facilitators	Barriers
Lack of resources is an issue, although CMRs may save time	
<ul style="list-style-type: none"> - CMR or pharmacist may save time and costs^{I,III} - Availability of shared electronic medical record^{II,III} 	<ul style="list-style-type: none"> - Lack of time among HCPs^{I,III,V} - No time set for physician-pharmacist contact^{I,III,IV} - CMR takes time for both pharmacist and physician^{I,III} - Phone calls and check upon discharge for all patients is not time efficient^{I-V} (<i>only derived from pharmacist interviews</i>) - Electronic medical record is not complete, fully shared or user-friendly^{II,III}
Pharmacists' knowledge and skills are valuable, but they need more clinical competence	
<ul style="list-style-type: none"> - Knowledge about the interventions among HCPs^{I,IV,V} - Pharmacist is reliable and has broad pharmaceutical competence^{I,III,IV} - Physicians cannot know everything about medications^{IV} (<i>only derived from physician interviews</i>) - Positive change in physicians' attitude and knowledge^{III,IV} 	<ul style="list-style-type: none"> - Pharmacist lacks or needs more clinical competence^{I,III-V} - Lack of information or training about the interventions and working process among HCPs^{III-V} - Physicians' competence may decrease^{IV} (<i>only derived from physician interviews</i>)
Compatibility of CMRs with hospital practice is challenging, and roles and responsibilities of ward-based pharmacists are unclear	
<ul style="list-style-type: none"> - CMR or pharmacist is well-adapted to hospital practice^{I,III-V} - CMR or pharmacist does not interfere with existing work flow^{I,III,V} - Physician has main responsibility^{II} (<i>only derived from physician interviews</i>) 	<ul style="list-style-type: none"> - Hard to fit CMR in hospital practice^{I,III,IV} - Primary care or others responsible and suited for CMR^{I,III,IV} - Pharmacist is not fully integrated in the ward team^{III} - Unclear role of the pharmacist^{I-V} - Pharmacist is dependent on physician^{II-IV}
Personal contact at the ward is essential for physician-pharmacist collaboration	
<ul style="list-style-type: none"> - Positive experience by physicians with pharmacist collaboration^{III,IV} (<i>only derived from physician interviews</i>) - Presence of pharmacist at the ward and availability^{III} - Personal relationships between HCPs^{III} - Pharmacist participates in medical rounds or meetings^{I,III} - Pharmacist has support from other colleagues^{III} (<i>only derived from pharmacist interviews</i>) 	<ul style="list-style-type: none"> - Pharmacist is not always present at the ward^{III} - Limited contact between pharmacist and consultant physician^{III} - Physicians can feel criticised by the pharmacist^{III} (<i>only derived from physician interviews</i>) - Some physicians less inclined to listen to the pharmacist^{III,IV} - Pharmacist notes in electronic medical record not always appreciated^{I,III,V} - Frequent rotation of HCPs at the ward^{I,III}

Identified within the CFIR domains: ^IIntervention characteristics; ^{II}Outer setting; ^{III}Inner setting; ^{IV}Characteristics of individuals; ^VProcess.⁴⁰ CMR = comprehensive medication review; HCP = healthcare professional.

CMRs and follow-up are needed, but not in all patients

Physicians and pharmacists believed that CMRs were needed, but not in all patients: “You don’t need to go through all patients’ medication lists, but especially the older multimorbid patients with polypharmacy.” (D16) Some

physicians stated that a pharmacist may not always be needed as they can conduct CMRs themselves and that other medical specialists can be consulted instead: *“For example, if I’m uncertain about antibiotics [...] I talk to the infection specialist.”* (D14)

General belief in positive effects of CMRs and follow-up

CMRs and follow-up calls could reduce *“medication errors”* (D11), increase *“compliance”* (P2) and *“prevent readmissions”* (D3), but there seemed to be less confidence in long-term effects. Treatment proposals by pharmacists were *“most often relevant”* (D15) and the CMRs became of *“higher quality”* (D12) if pharmacists were involved. There were some doubts about the quality of follow-up in primary care: *“They [GPs] often accept our referrals, but then they are under much pressure in primary care and a follow-up visit may get forgotten, or it may take a long time until the next visit.”* (P1)

Lack of resources is an issue, although CMRs may save time

Lack of time was a barrier, but the performance of CMRs by pharmacists could be time-saving for physicians: *“Yes, it can take time [...] but I think it saves more time than what it takes, so it’s well-invested time.”* (D16) The cost-effectiveness of performing phone calls was questioned: *“I think that the way we’ve worked in the study, calling every patient, is a waste of time. I don’t think that we make the best use of our competence in that way.”* (P5) Shared EHRs was a major facilitator for communication, but the pharmacists’ notes could contain *“too much text”* (D13) and in-person discussion of treatment proposals was preferred.

Pharmacists’ knowledge and skills are valuable, but they need more clinical competence

Pharmacists had *“broad pharmaceutical competence”* (D15) that was *“complementary”* (D9) to the physicians’ competence. Their clinical skills could however be improved: *“For example, to change antihypertensive medication because of one high blood pressure measurement. Just because the patient is acutely ill today, does not mean that this treatment needs to be changed in the long term.”* (D14) Most physicians were uninformed about the CMR process and pharmacists expressed a lack of training and instructions on how to conduct monitoring and follow-up: *“It feels like we developed some kind of ad hoc method.”* (P5)

Compatibility of CMRs with hospital practice is challenging, and roles and responsibilities of ward-based pharmacists are unclear

Adapting and fitting the CMRs into the existing workflow was challenging at wards where pharmacists had recently been introduced. Some physicians wanted to focus on the cause of admission only and thought that *“primary*

care may be better suited” (D9) for performing CMRs. The role and responsibilities of the pharmacist were generally not clearly defined and pharmacists thought that their dependency on physicians hindered efficiency in the CMR process.

Personal contact at the ward is essential for physician-pharmacist collaboration

Collaboration with the pharmacists and their presence at medical ward rounds was valued: *“I have been on medical rounds in which the pharmacists did not participate, but came later, and that did not work so well.”* (D3) Frequent staff rotations and pharmacists not always being present at the ward were mentioned as barriers to building personal relationships. Some physicians were more sceptical and less inclined to listen to the pharmacist, but this seemed to improve over time. Junior doctors sometimes became *“a messenger between the pharmacist and consultant physician”* (D10), increasing the risk of miscommunication.

Paper V

This study assessed the intervention fidelity and process outcomes of CMRs and post-discharge follow-ups within the MedBridge trial.

Intervention fidelity assessment

Medication reconciliation upon admission and CMR during hospital stay were conducted in 94% to 98% of the CMR and CMR plus follow-up patients (Table 6). Medication reconciliation upon discharge was less often conducted (40% and 51% in CMR and CMR plus follow-up patients, respectively). Medication referrals were sent to the GP in 6% (n=47) of the CMR plus follow-up patients. The first and second follow-up phone call were performed in 81% (n=664) and 59% (n=482) of the CMR plus follow-up patients, respectively. The percentage of control patients receiving at least one unintended intervention component was 15% (n=132).

Table 6. *Intervention fidelity of intervention components per treatment group in the MedBridge trial (n=2637; reused with permission, Paper V).*

Intervention components	CMR (n=922)	CMR plus follow-up (n=823)	Control (n=892)
Medication reconciliation upon admission, n (%)	893 (97%)	810 (98%)	115 (13%)
CMR during hospital stay, n (%)	862 (94%)	796 (97%)	14 (2%)
Medication reconciliation upon discharge, n (%)	370 (40%)	418 (51%)	29 (3%)
Medication referral by pharmacist to GP, n (%)	9 (1%)	47 (6%)	1 (0%)
First follow-up call, n (%)	1 (0%)	664 (81%)	1 (0%)
Action in response to the first follow-up call, n (%)		389 (59%*)	
Second follow-up call	1 (0%)	482 (59%)	1 (0%)
Action in response to the second follow-up call, n (%)		269 (56%*)	

*Percentage of the number of phone calls. CMR = comprehensive medication review; GP = general practitioner.

Process outcomes assessment

A random sample of 37% (652/1745) of all CMR and CMR plus follow-up patients were included in the process outcomes assessment. Their baseline characteristics (on average 81 years old, 9.5 medications in use and 53% female) were similar to the total population.

The mean number of identified medication discrepancies per CMR was 1.1 (range 0 to 12) and 79% (589/747) of these discrepancies were corrected (Table 7). The mean number of identified DRPs was 2.0 per CMR, followed by 2.1 recommendations of which 73% (1006/1380) were implemented. In 77% (500/652) of the CMRs, at least one discrepancy or recommendation was corrected or implemented.

The most frequent DRP was *medication without indication* (18%, n=233; Figure 4). *Stop medication* was the most frequent proposed (21%, n=293; Figure 5) and implemented recommendation. The implementation rate for each type of recommendation ranged between 62% to 80% (except for *information to patient* which was considered implemented in all cases).

Table 7. *Process outcome results of a random sample of comprehensive medication reviews (n=652) within the MedBridge trial (reused with permission, Paper V).*

Discrepancies, mean ± SD (range)	1.1 ± 1.8 (0-12)
Patients with ≥ 1 discrepancy, n (%)	327 (50%)
Correction rate, proportion (%)	589/747 (79%)
DRPs, mean number ± SD (range)	2.0 ± 1.9 (0-14)
Patients with ≥ 1 DRP, n (%)	494 (76%)
Recommendations, mean number ± SD (range)	2.1 ± 2.1 (0-14)
Implementation rate, proportion (%)	1006/1380 (73%)
Patients with ≥ 1 discrepancy or DRP, n (%)	555 (85%)
Patients with ≥ 1 corrected discrepancy or implemented recommendation, n (%)	500 (77%)

DRP = drug-related problem; SD = standard deviation.

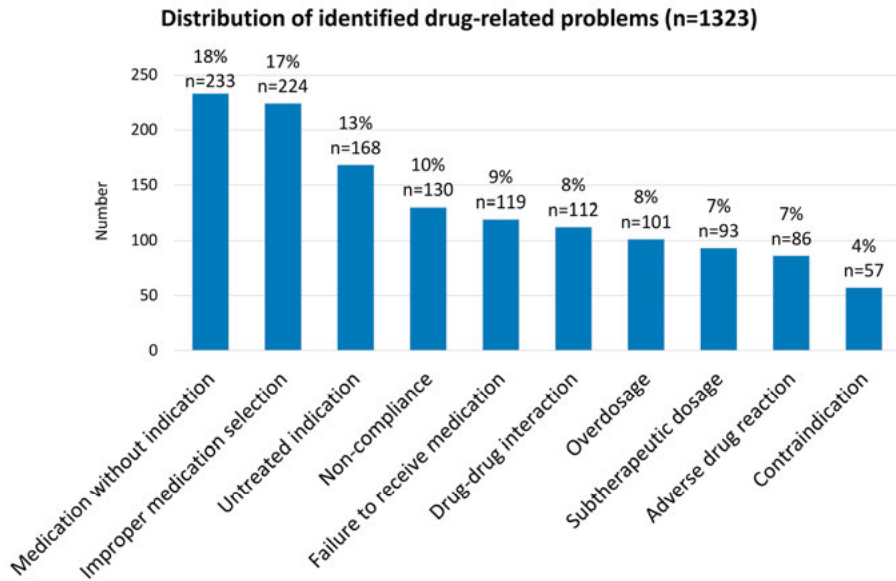


Figure 4. Distribution of types of identified drug-related problems (n=1323) within the comprehensive medication reviews (n=652; reused with permission, Paper V).

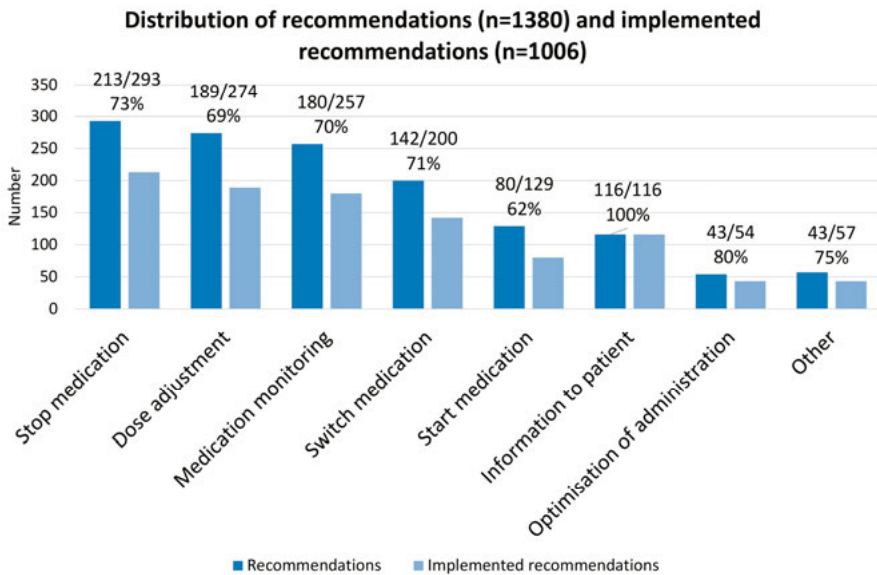


Figure 5. Distribution of recommendations by the pharmacists (n=1380) and implemented recommendations (n=1006) within the comprehensive medication reviews (n=652; reused with permission, Paper V).

Paper VI

This study investigated the effects of hospital-initiated CMRs including post-discharge follow-ups on older patients' healthcare utilisation, compared with only hospital-based reviews and usual care.

In total, 6059 patients were admitted and screened for eligibility during the study periods. Of the 2993 eligible patients, 2644 (88%) provided informed consent to participate in the trial. Seven participants withdrew their consent during follow-up, resulting in 2637 participants (CMR 924, CMR plus follow-up 825, usual care 895) included in the mITT analysis. Participants in each treatment group were similar in terms of baseline characteristics. The median age was 81 years (interquartile range 74 to 87), an average of 9 medications (interquartile range 5 to 13) was prescribed, and 51% (n = 1355) were female.

Primary outcome

The primary outcome did not differ in the intervention groups compared with usual care: 1.74 unplanned hospital visits per person-year for CMR (adjusted RR 1.04, 95% CI 0.89 to 1.22), 1.95 for CMR plus follow-up (adjusted RR 1.15, 95% CI 0.98 to 1.34) and 1.63 for usual care patients (Table 8).

Table 8. *Primary and secondary outcomes (incidences) after 12 months for each treatment group, and comparisons between intervention groups and control group.*

Outcome	Treatment group, crude rate			Adjusted rate ratio* (95% CI†)	
	CMR (n = 922)	CMR plus follow-up (n = 823)	Usual care (n = 892)	CMR vs. usual care	CMR plus fol- low-up vs. usual care
Unplanned hospital visits (primary)	1.74	1.95	1.63	1.04 (0.89 to 1.22)	1.15 (0.98 to 1.34)
ED visits	0.84	0.97	0.71	1.16 (0.94 to 1.44)	1.29 (1.05 to 1.59)
Unplanned hospital admissions	0.89	0.98	0.91	0.95 (0.80 to 1.12)	1.04 (0.88 to 1.24)
Unplanned medication-related admissions	0.29	0.36	0.32	0.89 (0.69 to 1.16)	1.12 (0.87 to 1.45)
GP visits	4.43	4.02	4.25	1.04 (0.91 to 1.19)	0.99 (0.86 to 1.15)

*Estimates adjusted for cluster (ward) as random effect, study period as fixed effect, and unplanned hospital visits in 12 months prior to inclusion as patient-level covariate. †Tukey's adjusted 95% CIs for multiple comparisons. CMR = comprehensive medication review; ED = emergency department; GP = general practitioner.

Secondary outcomes

The incidence of ED visits within 12 months was increased in the CMR plus follow-up group (0.97 visits per person-year; adjusted RR 1.29, 95% CI 1.05 to 1.59) compared with usual care (Table 8). This difference was also present after 3 months (adjusted RR 1.39, 95% CI 1.04 to 1.85) and 6 months (adjusted RR 1.27, 95% CI 1.00 to 1.62) compared with usual care (Supplementary file 3 in Paper VI). No differences were seen in any of the other secondary outcome measures (Table 9 and Supplementary file 3 in Paper VI).

Table 9. *Secondary outcomes (frailty models and costs analysis) after 12 months for each treatment group, and comparisons between intervention groups and control group.*

	CMR (n = 922)	CMR plus follow-up (n = 823)	Usual care (n = 892)	Adjusted hazard ratio* (95% CI)	
				CMR vs. usual care	CMR plus fol- low-up vs. usual care
Time to first un- planned hospital visit, mean days (SD)	203.2 (151.5)	201.8 (150.8)	208.1 (148.9)	1.03 (0.91 to 1.16)	1.05 (0.93 to 1.19)
All-cause mortal- ity, n (%)	234 (25.4)	209 (25.4)	227 (25.4)	0.98 (0.81 to 1.18)	0.95 (0.79 to 1.15)
	CMR (n = 922)	CMR plus follow-up (n = 823)	Usual care (n = 892)	Difference of mean (95% CI‡)	
				CMR vs. usual care	CMR plus fol- low-up vs. usual care
Costs of hospital- based care§, mean SEK (SD)	79 910 (152 240)	88 750 (168 620)	88 040 (164 180)	-8 130 (-22 800 to 6390)	490 (-15 300 to 16 210)

*Estimates adjusted for cluster (ward) as random effect, study period as fixed effect, and unplanned hospital visits in 12 months prior to inclusion as patient-level covariate. ‡Based on 100 000 bootstrap estimates. §Including intervention costs: 571 SEK for CMR and 1031 SEK for CMR plus follow-up. CMR = comprehensive medication review; SD = standard deviation.

Subgroup analyses

CMR plus follow-up increased the incidence of unplanned hospital visits within 12 months in patients with more than one unplanned hospital visit in the 12 months prior to inclusion (adjusted RR 1.56, 95% CI 1.20 to 2.05; interaction test $p < 0.01$) and in patients with congestive heart failure (adjusted RR 1.36, 95% CI 1.04 to 1.77; interaction test $p = 0.36$) or diabetes mellitus (adjusted RR 1.34, 95% CI 1.02 to 1.75; interaction test $p = 0.22$), compared with usual care (Supplementary file 4 in Paper VI). There were no differences in the primary outcome between CMR and usual care in any of the pre-defined subgroups (Supplementary file 4 in Paper VI).

Paper VII

In this study, AT-HARM10 was developed and validated as a tool to identify MRAs.

The AT-HARM10 question most often used for the assessments was question 1 (148/400), followed by questions 8 (75/400) and 4 (68/400). All the questions were used at least twice and in none of the assessments an expert panel was needed. AT-HARM10 was considered sufficiently relevant and user-friendly. The time used for assessment was on average 5.7 (range 2.5 to 14) minutes per admission.

The strength of agreement within each pair of assessors was moderate to substantial (Cohen's kappa 0.45 to 0.75). The strength of agreement between all pairs was moderate (Fleiss' kappa 0.58 and 0.46).

The expert panel reached consensus for all 100 assessments, which resulted in 50% (n=50) being classified as *unlikely* to be and 50% (n=50) as *possibly* an MRA (Table 10). Pairs 1+3 and 2+4 assigned 52% and 42%, respectively, to be *unlikely*, and 48% and 58%, respectively, to be *possibly* an MRA. The sensitivity was 70% and 86%. The specificity was 70% and 74%. The positive predictive value was 73% and 74%, and the negative predictive value was 71% and 83% (Table 10).

Table 10. *Criterion-related validity of the Assessment Tool for identifying Hospital Admissions Related to Medications (AT-HARM10; adapted and reused with permission, Paper VII).*

		Expert panel		Total pairs	Sens.	Spec.	PPV	NPV
		unlikely	possibly					
Pair 1+3	unlikely	37	15	52 (52%)	70%	74%	73%	71%
	possibly	13	35	48 (48%)				
Pair 2+4	unlikely	35	7	42 (42%)	86%	70%	74%	83%
	possibly	15	33	58 (58%)				
Total expert panel		50 (50%)	50 (50%)					

Sens. = sensitivity; Spec. = specificity; PPV = positive predictive value; NPV = negative predictive value.

Discussion

Main findings

With a variety of study designs, participants and data sources, this thesis identified multiple themes and factors related to the implementation, performance and effects of medication reviews by clinical pharmacists in older hospitalised patients (Paper I and III-IV). This thesis also found that the intervention fidelity in the MedBridge trial was high during hospital admission and lower upon and after discharge, and at least one medication discrepancy or drug-related problem was solved in three out of four patients (Paper V). In the MedBridge trial, hospital-based CMRs with and without post-discharge follow-ups in older hospitalised patients did not decrease the incidence of unplanned hospital visits within 12 months compared with usual care (Paper VI). Finally, a practical tool to identify medication-related hospital admissions (AT-HARM10) was developed and its validation resulted in a moderate to substantial IRR and a moderate to high criterion-related validity (Paper VII).

Factors related to the implementation and performance of medication reviews (Paper I and III-IV)

In our case study, factors involved in the implementation and sustainability of medication reviews by clinical pharmacists were identified across all Kotter's principles and NPT domains (Paper I). Factors were also identified at all different levels of the healthcare system: from efforts by the national government to improve the care for older patients to key individual healthcare professionals to drive change at local level. Semi-structured interviews with physicians and pharmacists in the MedBridge trial resulted in multiple facilitators and barriers being identified across all five CFIR domains (Paper IV). These findings confirm the complexity of factors necessary for successful implementation, even if a formal change management or implementation process is not being used.^{40,94}

The results from all three qualitative studies seem consistent with those from qualitative research on medication reviews by ward-based pharmacists in other countries and regions.⁹⁵⁻¹⁰² Patients and healthcare professionals think that pharmacists are reliable and have complementary expertise,^{95-97,100} medication reviews are perceived to contribute to patient care and safety,^{97,98} and

multi-professional collaboration with pharmacists being present at the ward is being valued.^{97,99} Availability of time and resources, including shared EHRs, was deemed essential, as mentioned in other studies.^{100–102} Theories on implementation and interprofessional collaboration emphasise the importance of all of these factors.^{40,103}

Trust in healthcare professionals, being listened to and getting information are important elements for positive patient experience,^{67,104} which seem to have been present in the MedBridge trial (Paper III). Shared decision-making, another key element of patient experience,^{67,104} should be part of the medication review process.^{11,105} Patients in our study expressed a limited role in decision-making and not all patients wanted to be involved (Paper III). Many patients prefer to rely on healthcare professionals rather than having an active role in their treatment.^{106,107} High age, hospital context and acute illness, all present in the MedBridge trial, decrease the willingness to be involved.^{108,109} Physicians and pharmacists in our trial also questioned whether hospital wards are the best places to conduct CMRs (Paper IV). Despite limited involvement during hospital admission, it was important for patients to be well-informed upon discharge (Paper III). Recalling information was problematic for all interviewed patients. Information should be tailored to the individual patient and provided in such a way that they can regain an active role in the management of their medications after discharge.^{104,110} Although the MedBridge protocol allowed for patient specific tailoring by the pharmacist, the CMRs did not necessarily involve contact with the patient upon discharge and the pharmacists were not trained in shared decision-making.

A common perceived barrier across our three qualitative studies and those by others was uncertainty and unclarity about the roles and responsibilities of the clinical pharmacist.^{95–97,100,101} This seemed to be both a barrier to patient contact and to collaboration between physicians and pharmacists (Paper III–IV). Healthcare professionals need to understand their tasks and responsibilities.⁴² Current Swedish legislation is unclear about the role of pharmacists in medication reviews and states that it is solely the physician's responsibility.⁹¹ Findings in this thesis show that some physicians at hospital wards do not consider medication reviews to be their responsibility (Paper IV). Physicians in primary care may on the other hand not feel responsible for the patient's total medical treatment either.¹¹¹ Clinical pharmacists are probably more motivated to take this responsibility. Professional boundaries may shift by the introduction of new roles in health care.¹¹² In response, established professions may react by holding on to these boundaries, which may result in scepticism towards multi-professional collaboration¹¹³ as identified by the case study and healthcare professional interviews (Paper I and IV). Changing professional roles requires changing the system at all levels.¹¹² Our studies and previous research indicate that scepticism among physicians may decrease after the ac-

tual introduction of pharmacists (Paper I and V).¹¹⁴ However, not only individual and local reforms are necessary, but also the reframing of the pharmacy profession at higher levels of the healthcare system.

Pharmacists mentioned being dependent on physicians to make changes to patients' medication treatment (Paper IV). Little to no dependency on pharmacists was identified among physicians, whereas interdependency is an important element of collaboration.¹¹⁵ Unlike in the UK, New Zealand and North-America, pharmacists in Sweden do not have the right to prescribe. Providing this right may be an opportunity to improve collaboration and optimise the CMR process.¹¹⁶ To be able to take this responsibility, pharmacists need appropriate education and training. The healthcare professional interviews in this thesis identified a need for more clinical competence (Paper IV), which is an acknowledged improvement area for pharmacy education worldwide.^{117,118} Consistent with previous research,⁹⁷⁻¹⁰⁰ other barriers related to teamwork and collaboration were frequent staff rotations and pharmacists not always being present at the ward (Paper IV). Having pharmacists to structurally participate in medical ward rounds may be more efficient.¹¹⁹

Intervention fidelity and process outcomes (Paper V)

The intervention fidelity in the MedBridge trial was high for medication reconciliation upon admission and CMR during hospital stay, but lower for intervention components upon and after discharge. This lower fidelity may have resulted from the barriers identified in the qualitative parts of the process evaluation (Paper III-IV) and may have negatively affected the trial's outcomes. A lack of patient involvement at discharge and inappropriate follow-up on treatment changes may lead to new DRPs, with medication-related harm as a possible consequence.^{120,121}

On average one discrepancy and two DRPs were identified per CMR. Two to three problems in total per patient is frequently reported in studies investigating the effects of medication reviews on process outcomes, although the results can vary substantially between studies.¹²²⁻¹²⁴ Medications were stopped more than twice as often as started, which confirms previous findings that medication reviews decrease the average number of medications.¹⁹ The acceptance of recommendations in our trial seems relatively high and similar to studies in which communication between physicians and pharmacists is mainly face-to-face instead of written.^{122,123,125} Other factors present in the MedBridge trial and associated with a high implementation rate are patient interviews as part of the medication reconciliation and accessibility to the patients' EHR (Paper III-IV).^{125,126}

Effects on healthcare utilisation (Paper VI)

The lack of an effect on healthcare utilisation in the MedBridge trial is in line with findings of several previous RCTs on medication reviews and post-discharge interventions in hospitalised patients, with inconclusive results on hard clinical endpoints.^{24,127} Medication reconciliation, medication review, and post-discharge interventions performed in isolation generally seem ineffective,^{19,127,128} in contrast to similar interventions that are an integrated part of multi-faceted care programmes or existing care processes.^{26,129,130} As suggested by our process evaluation, the CMRs were not fully integrated in the daily workflow of the ward team and the post-discharge interventions were not successfully performed in collaboration with the physicians responsible for discharge and treatment follow-up (Paper III-IV). In addition, creating a clearly defined pharmaceutical care plan, which is deemed indispensable by different medication review guidelines,¹³¹ was not part of the CMR process in the MedBridge trial.

The results of this trial conflict with those of the previous trial at Uppsala University Hospital in 2005–2006, in which hospital visits were reduced by 16% and ED visits by 47%.²³ After that trial, medication reconciliation and medication review have become part of Swedish healthcare legislation and are recommended for patients aged 75 years or older and taking five or more medications. In the past years, physicians and nurses have been educated on these topics through national programmes and by clinical pharmacists at a local level.^{81,90} This may have positively affected usual hospital care, providing a possible explanation for a lack of the effects that were shown in the previous trial. The 29% increase in ED visits in CMR plus follow-up patients is harder to explain. Patients may have responded to the follow-up calls by becoming more vigilant in detecting any worsening of their disease symptoms, pushing them in the direction of seeking acute care.¹³² The clinical relevance of the increase in ED visits is questionable, as it did not seem to lead to more hospital admissions or increased costs of hospital-based care.

In a recent trial in Denmark, hospital-based medication review including post-discharge follow-up by pharmacists who had received a three-day training in motivational interviewing reduced the risk of readmissions in older patients.³⁵ Patient empowerment and shared decision-making, as with motivational interviewing, are important factors in discharge interventions to reduce readmissions.¹³³ As previously discussed, there seems to have been a lack of these factors in our trial (Paper III).

The interventions in the MedBridge trial may not have been sufficiently targeted at a specific patient population. Almost all patients aged 65 years or older were included, regardless of their needs, reason for admission, condition, or medication use. Physicians and pharmacists mentioned that CMRs and post-discharge follow-ups have been conducted in patients for whom these

interventions did not seem feasible or needed (Paper IV) and 23% of the patients did not seem to benefit from the CMR in terms of problems solved (Paper V). Different tools to identify hospitalised patients at risk for DRPs exist, which could have been used to prioritise patients.^{134,135} Medication reviews and similar pharmacist interventions can improve clinical outcomes in patients with cardiovascular disease, diabetes mellitus type 2, chronic obstructive pulmonary disease, and dementia and/or cognitive impairment.^{21,22,136} In our trial, CMR was not effective in patients with previously diagnosed chronic obstructive pulmonary disease, and CMR plus follow-up even increased unplanned hospital visits in patients with congestive heart failure and diabetes mellitus. However, neither our interventions nor our outcome measures were developed to specifically address these conditions.

Assessment of MRAs (Paper VII)

AT-HARM10 was successfully tested for a broad range of standard validation parameters.^{79,80} The IRR had Cohen's kappa values ranging from 0.45 to 0.75 and Fleiss' kappa values of 0.46 and 0.58. The assessments took on average six minutes (range 2 to 14 minutes). All assessments were performed by pharmacy students and no expert panel was needed. A recently published method by Thevelin et al. (2018)³⁴ had similar IRR (Cohen's kappa 0.33 to 0.86; Fleiss' kappa 0.41). The assessment in their study took on average considerably more time (23 ± 6 minutes) and involved the use of an expert panel,³⁴ which makes it less suitable for studies with a large number of admissions to assess.

The percentage of MRAs identified with AT-HARM10 seems higher than in similar studies. Almost half of all admissions during the validation study and 35% (831/2391) during the MedBridge trial were considered possibly medication-related, whereas a recent systematic review of 19 studies examining MRAs reported a median of 21% (interquartile range 14% to 23%).²⁸ This difference may be explained by an older study population in our trial, the fact that all types of DRPs are included in the AT-HARM10 assessments and that the degree of certainty was not assessed, i.e. only those unlikely to be medication-related were excluded.

Methodological considerations

Different strengths of the studies in this thesis ensure rigour and trustworthiness of its findings, but a number of limitations need to be addressed. First, some limitations relate to the qualitative studies. Most researchers involved in the three qualitative studies in this thesis had a professional background in pharmacy, which may have impacted confirmability (Paper I and III-IV).¹³⁷

This was mitigated by involving other professions in data generation, triangulation and analysis, providing more variety of perspectives. Data saturation¹³⁸ was not formally assessed in the case study and healthcare professional interviews, hence relevant data could have been missed (Paper I and IV). A high number of patients were excluded from the interviews, because they did not manage their own medications or did not remember the contact with the pharmacist (Paper III). This limits the credibility of the findings, but it also addresses the unclear role of the pharmacist and problems with retaining information.

Second, all results of the intervention fidelity and process outcomes assessments were based on the interpretation of written notes in the EHR system (Paper V). Misinterpretation of written information may have affected the quality of the results. This was mitigated by encouraging pharmacists to record their findings as part of their daily practice. Moreover, established methods were used to classify discrepancies and DRPs.

Third, the cluster-randomised design of the MedBridge trial did not allow for patient recruitment before randomisation (Paper VI). This risk of selection bias was mitigated by screening all patients admitted to the study wards for eligibility and asking all eligible patients about participation. In the end, only 12% of the eligible patients were not included in the main analysis, indicating a low risk for a systematic between-group imbalance. A risk of contamination bias existed as well. Unintended intervention components were received by 15% (n = 132) of the control patients during index admission (Paper V). However, only 2% (n = 14) of the control patients received a CMR, indicating a low risk of contamination bias due to CMRs. The lower intervention fidelity upon and after discharge (Paper V) may limit the internal validity of the MedBridge trial, but it also reflects its pragmatic nature. As most barriers identified within our process evaluation seem common in other hospital settings in Sweden and abroad, the trial's intervention fidelity may have a high degree of representability. Perhaps, knowledge derived from the case study could have been used to design and implement the interventions in the MedBridge trial and increase fidelity, but no formal relation between these studies existed at that moment.

Furthermore, the outcome measures of the MedBridge trial may not fully reflect the effects of its interventions. Despite 77% of the CMRs resulting in at least one discrepancy or problem being resolved (Paper V), the incidence of unplanned hospital visits did not decrease (Paper VI). Patient-reported outcomes, such as health-related quality of life, might have been more suitable for capturing effects of these treatment changes. However, subjective measurement tools, like patient-reported outcomes, may introduce bias in trials where ward staff and study participants cannot be blinded to treatment allocation.¹³⁹ The clinical relevance of the solved discrepancies and DRPs was not assessed. Hence, it is unclear to what extent the lack of effects on healthcare utilisation in the MedBridge trial was driven by clinically irrelevant treatment

changes or by issues related to monitoring and follow-up or patient involvement.

Finally, a systematic review of the literature was not performed in the development process of AT-HARM10 (Paper VII). Relevant studies may therefore have been missed. However, a recent systematic review did not find other methods.³⁴ AT-HARM10 does not assess the preventability of MRAs. This may limit the tool's applicability, but we deliberately chose to keep the tool simple and straightforward.

Conclusions

- Multiple factors across the full range of change management and implementation principles were involved in the implementation and sustainability of medication reviews in older patients by clinical pharmacists in Region Uppsala (Paper I);
- Older patients generally have positive experiences with, and views on, CMRs and follow-up telephone calls by ward-based clinical pharmacists. However, some factors, like the unclear role of the ward-based pharmacist and problems with receiving and retaining information, may negatively impact the effects of these interventions (Paper III);
- From the healthcare professional perspective, multiple facilitators and barriers for performing CMRs and post-discharge follow-up in older hospitalised patients exist across a variety of themes (Paper IV);
- The intervention fidelity within the MedBridge trial was high for CMRs during hospital stay and lower for intervention components upon and after discharge. CMRs resulted in a high percentage of patients with changes to their medication treatment (Paper V);
- CMRs including post-discharge follow-ups in older hospitalised patients, as conducted and studied in the MedBridge trial, do not decrease the incidence of unplanned hospital visits compared with either hospital-based reviews alone or usual care (Paper VI);
- AT-HARM10 has been developed as a practical tool to identify MRAs and the tool is valid for use in older patients by final-year undergraduate and postgraduate pharmacy students (Paper VII).

Implications for research and practice

This thesis identified multiple factors to consider in future research and practice to successfully implement and perform medication reviews or similar interventions by clinical pharmacists in older hospitalised patients. Findings from the MedBridge trial do not support the performance of hospital-based CMRs as conducted in the trial. Other RCTs with similar interventions aimed to improve older hospitalised patients' health outcomes are currently being conducted and results are awaited.^{140–143} Meanwhile, this thesis opens up the opportunity to reflect upon how to improve medication use in older hospitalised patients and sustain these improvements after hospital discharge. In addition, it is important to acknowledge that it is still unclear whether improvements in what is considered appropriate prescribing and use of medications actually lead to positive effects on clinically relevant and/or relevant patient-reported outcomes.^{144,145} Future initiatives aimed at optimising medication use in older patients should therefore be subjected to RCTs including process evaluations and with clinically and patient-relevant outcome measures.

Before such trials are started, this thesis suggests that a structured approach using change management or implementation theory is needed to inform intervention development and study design and planning. Within such an approach, future initiatives could utilise the perceived need for and potential benefits of medication reviews, other stakeholders' trust in the competence of clinical pharmacists and the positive views towards multi-professional collaboration. Interventions should be tailored to the patients' individual needs and preferences and should be adapted to fit hospital practice. Perhaps, with regards to medication review activities beyond medication reconciliation, the focus should be solely on medications related to the cause of admission, and when treatment changes are made, adequate follow-up procedures must be in place. CMRs, where every prescribed medication and diagnosis are scrutinised, may be better suited for the outpatient setting.^{146–148} Appropriate allocation of time and resources is important, but just adding a pharmacist to the ward team is not sufficient. Roles and responsibilities of the pharmacist within the team and the patient (or next-of-kin) should be clearly defined and jointly decided upon. Appropriate clinical training and education for pharmacists should then be aligned with these roles and responsibilities.

The MedBridge trial exemplifies that a cluster design instead of a traditional RCT may still lead to contamination bias. Large RCTs of medication reviews in multi-professional teams or similar complex interventions may not

be possible to conduct without contamination. As it takes time before such interventions are successfully conducted in practice, any potential control group will subsequently be contaminated throughout this process.¹⁴⁹ In some settings, like in Region Uppsala, researchers should perhaps have to accept the fact that clinical pharmacists have become part of usual care and design their studies in accordance with it.

Lastly, AT-HARM10 is a valuable addition to existing research methods to identify MRAs in older patients and distinguishes itself by the limited resources needed for its use. The tool's validity in patients younger than 65 years and in settings in other countries is currently unknown. To confirm the results presented in this thesis, AT-HARM10 would benefit from further validation performed in other patient populations.

Summary

Inappropriate prescribing and use of medications are major causes of avoidable healthcare-related harm around the world. Medication reviews by a ward team including a clinical pharmacist have been introduced as an intervention in older hospitalised patients to optimise treatment outcomes and reduce harm. However, evidence on clinically relevant outcomes in secondary care is scarce, and implementation of these interventions in daily practice is challenging. The main aim of this thesis was therefore to study the implementation, performance and effects of medication reviews by clinical pharmacists in older hospitalised patients.

A case study explored the factors involved in the implementation and sustainability of medication reviews in older patients by clinical pharmacists in Region Uppsala, Sweden (Paper I). Multiple factors were identified through literature review, interviews and a focus group with different stakeholders. Examples of facilitating factors were a national focus on care for the elderly, clinical pharmacy education and evidence at local level. Barriers were, for example, a lack of time and continuity, and unclear tasks and responsibilities of the pharmacists.

A pragmatic cluster-randomised crossover trial (MedBridge) was designed (Paper II) and conducted (Paper VI) to study the effects of hospital-based comprehensive medication reviews (CMRs) including post-discharge follow-ups on older patients' healthcare utilisation, compared with only hospital-based reviews and usual care. The trial was conducted at eight wards with multi-professional teams at four hospitals in Sweden in 2017-2018. Patients aged 65 years or older, admitted to one of the wards, were included in one of three treatment groups: 1, CMR; 2, CMR plus post-discharge follow-up; 3, usual hospital care. In total, 2637 participants were included in the main analysis of the MedBridge trial. The participants were 81 years old on average and the median number of prescribed medications was 9. The primary outcome measure, the incidence of unplanned hospital visits within 12 months, did not differ between the intervention groups and usual care (Paper VI).

A process evaluation was conducted alongside the MedBridge trial to support an understanding of how the interventions were implemented and performed and which factors may have affected the trial's results. Interviews with patients and next-of-kin were conducted to explore their experiences with, and views on, the interventions in the trial (Paper III). Analysis of these interviews

resulted in seven key themes. In general, the experiences and views were positive, but some factors, like problems with receiving and retaining information, could have negatively impacted the effectiveness of the interventions in the MedBridge trial. Interviews with physicians and pharmacists were conducted to explore the facilitators and barriers for performing the trial's interventions (Paper IV). Multiple facilitators and barriers were identified and then grouped in six main themes. Examples of themes were: CMRs and follow-ups are needed, but not in all patients; roles and responsibilities are unclear; and personal contact at the ward is essential for physician-pharmacist collaboration. Finally, the intervention fidelity and process outcomes within the MedBridge trial were assessed (Paper V). In the CMR and CMR plus post-discharge follow-up groups, the intervention fidelity was 94% to 98% during hospital admission, and 40% to 81% upon and after discharge. On average, one medication discrepancy and two drug-related problems per patient were identified as process outcomes of the CMRs. In 77% of the patients, at least one medication discrepancy or drug-related problem was solved.

A practical tool to identify medication-related hospital admissions (AT-HARM10), one of the MedBridge trial's secondary outcomes, was developed and validated (Paper VII). The tool was deemed valid for use to identify medication-related hospital admissions in older patients by final-year undergraduate and postgraduate pharmacy students.

This thesis suggests that, despite a high percentage of patients with medication discrepancies and drug-related problems being solved, hospital-based CMRs with and without post-discharge follow-ups, as conducted in the MedBridge trial, do not decrease the incidence of unplanned hospital visits in older patients. Future research and clinical initiatives may benefit from a systematic approach addressing the factors related to the implementation and performance of medication reviews that were identified in this thesis. For trials measuring medication-related hospital admissions, AT-HARM10 can be used as assessment tool.

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