The non-dispensing pharmacist in primary care

an interprofessional model to improve pharmaceutical care and patient safety

Vivianne Maria Sloeserwij

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De apotheker-farmacotherapeut in de huisartspraktijk

een interprofessioneel model om farmaceutische patiëntenzorg en patiëntveiligheid in de eerste lijn te verbeteren

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The non-dispensing pharmacist in primary care
PhD thesis, Utrecht University, the Netherlands

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(met een samenvatting in het Nederlands)

Proefschrift

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Copromotor: Dr. D.L.M. Zwart

Voor Laure en Willem

Above all, watch with glittering eyes the whole world around you.
Because the greatest secrets are always hidden in the most unlikely places.

Roald Dahl

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Chapter 1

General introduction

Medication can do harm – especially in elderly with multiple medications.[1,2] Many (general) practitioners will recognise one of the following situations:

- discharged from hospital, an old lady resumes taking her own antidiabetic medications. In addition, she continues taking the insulin medication as prescribed in hospital. This results in a hypoglycaemic event, for which she is urgently readmitted to hospital;
- through the years, an 84-year old man has collected about ten different medications – prescribed after a myocardial infarction, a cerebrovascular accident, and a non-resolving depression after the death of his wife. Visiting his general practitioner (GP) for some minor ailment, he casually asks, 'are all those medications really needed, doctor?'
- a 75-year old woman requests a home visit, because of increased dyspnoea. She is known with heart failure. Lately, she has contacted the practice frequently for knee pain, for which she was prescribed paracetamol. At the patient's home, the GP finds her highly dyspnoeic, with multiple strips of over-the-counter non-steroidal anti-inflammatory drugs (NSAIDs) on the bedside table.

These examples illustrate the (potential) harm that medication can do in the population at highest risk. Given the aging of the population, this population at risk is growing. Current pharmaceutical care is unable to adequately address the growing population's needs.[3–7] Hence, improvement is needed.

This thesis is about improving pharmaceutical care and patient safety in primary care.

Why starting improvements in primary care?

Primary care can be defined by three mutually connected core values: the care is *generalist, continuous* and *patient-oriented*.[8] We believe these characteristics are also important characteristics for improving safe and effective pharmaceutical care: pharmaceutical care requires an integral approach (for it often covers a range of medications), needs regular evaluation (because pharmaceutical needs can change with increasing age and new comorbidities) and demands a central role for the patient (after all, the patient is the one taking the pills, and his or her preferences and wishes should be considered).[9]

In addition to these core values, in some countries the GP as primary care provider is gatekeeper to hospital and specialist secondary care. This gatekeeping role gives GPs (compared to specialists in secondary care) a relatively complete overview of the patient's health, including medication use. This overview is important when aiming to improve pharmaceutical care. Finally, most medications (both newly started medications and repeat prescriptions) are prescribed in primary care, adding to the appropriateness of starting improvement there.

Barriers to improving current pharmaceutical care

Optimal pharmaceutical care should be performed by the following threesome, in close collaboration with one another: the GP, the pharmacist and the patient. However, it seems difficult to provide such triple-collaborated care in the current healthcare system. Several barriers have been identified hampering improvement of pharmaceutical care so far: pharmacists have no access to relevant patient records[3] and they lack clinical knowledge and communication skills to provide good pharmaceutical care[4,5]; collaboration between pharmacists and GPs is often suboptimal[6,7]; and both pharmacists and GPs lack sufficient time and reimbursement to provide the rather time-consuming pharmaceutical care[5].

A new model of pharmaceutical care is needed

These barriers might be overcome in a new model of pharmaceutical care provision, where pharmaceutical care is provided within the primary care practice by a fully integrated and additionally trained non-dispensing pharmacist, working closely together with the GP. For this interprofessional model, a *role-shift in the pharmacists' profession* is fundamental: instead of (mainly) *dispensing medication*, pharmacists in this new model *provide (solely) pharmaceutical care*. Their focus changes from 'the drugs' towards 'the patient that uses the drugs': drug-centred becomes patient-centred.

Several forms of this 'new pharmaceutical care model' with a clinical pharmacist working closely together with the GP in primary care teams have already been researched in Australia, Canada and the United Kingdom.[10–13] Recently, it has also been introduced in the Netherlands.[14] Although the models that were studied differ (slightly) from one another, overall results so far are promising: drug therapy problems are identified and successfully reduced[15,16], surrogate patient outcomes such as blood pressure and HbA1c improved[17], and patients' adherence to their medication regimen increased[15,18].

Besides promising results, these studies also provided some insight into the key elements that are essential conditions to make the new pharmaceutical care model work best: 1. **full integration** of the pharmacist in the primary care team, with close collaboration with the GP,[17,19] 2. **additional education** for the pharmacist to become a healthcare provider, by learning and developing communication and clinical skills[20,21] and 3. **shared responsibility** between the pharmacist and GP over the pharmaceutical care provided.[18,19]

Box 1. Characteristics of the non-dispensing pharmacist in primary care

For whom?	Patients at high risk of medication problems (being elderly with multiple medications), and patients with specific medication problems.
How are those patients reached?	Patients can be referred to the NDP by the GP, patients can make an appointment themselves, or the NDP can invite patients that might benefit from an intervention, based upon characteristics registered in the medical records (and eventually also based upon further discussion about this selection with the GP).
What kind of patient care does the NDP provide?	The NDP provides patient care both in patients with high-complex and low-complex medication problems. For patients with high-complex medication problems, the NDP does a clinical medication review, reconciliation after hospital discharge and/or performs consultations for specific medication-related questions. For these interventions, the NDP prepares by reading the medical records of the patient (checking medication records, medical history and eventual laboratory findings) and then discusses the current health status of the patient with the GP. Next, the NDP interviews the patient at the patient's home or at the general practice, paying specific attention to the patient's views, wishes and needs regarding their medications. Finally, the NDP combines the information from the medical records and the patient's interview, to identify potential drug therapy problems and to formulate suggestions for solutions. These problems and solutions are discussed with the GP and the patient. After mutual agreement, potential solutions are (gradually) executed by the NDP or the GP, in follow up home visits, consultations or telephone checks as required. All care provided by the NDP is recorded in the medical records, comparable to the medical notes from the GP and the practice nurse. For patients with low-complex medication problems, the NDP can be consulted by the GP to advise about the pharmaceutical care in a certain patient. For these consultations, the NDP again prepares by reading the medical records before discussing the current health status of the patient with the GP, but the NDP has no direct contact with the patient. The NDP provides the GP with advice about options for optimising the pharmaceutical care, and the GP discusses this with the patient and provides follow up if needed.
Does the NDP have other tasks?	The NDP is working in the primary care practice solely, and does not dispense medication (or do other work) in the community pharmacy. However, in the primary care practice he or she has additional tasks on a practice level (besides the tasks on the patient level as described above), as it has been recognised before that the model is working optimally when the NDP undertakes additional activities besides performing medication reviews alone.[17] So, the NDP provides quality improvement projects: for specific medication problems, all patients who potentially have these problems are identified and contacted, in order to improve pharmaceutical care on a practice-level. Also, the NDP provides education to the practice staff, such as GPs, practice nurses and practice assistants.

Introducing "the non-dispensing pharmacist (NDP) integrated in primary care teams"

This thesis evaluates the interprofessional model of integrated pharmaceutical care provision, as developed and implemented in the Pharmacotherapy Optimisation through Integration of a Non-dispensing pharmacist in primary care Teams (POINT) project.[14] In this model, pharmacists work in general practices instead of their original workplaces, the community pharmacies. In the general practice, the clinical, now non-dispensing pharmacist (NDP) is part of the primary care team. He or she works as a care provider. To start in this new role, the NDP needs additional education to develop clinical and communication skills, in order to be enabled to incorporate the patients' context, wishes and needs into an individualised pharmaceutical care plan. During the training program, these skills are further mastered while performing patient care, using the principle of workplace learning.[20] In **Box 1.** an overview of the care provided by the NDPs in the POINT project is given.

The interprofessional model with the NDP integrated in primary care teams aims to prevent potential patient harm by medication, such as illustrated at the beginning of this introduction: the old lady with the hypoglycaemic event, the 84-year old man with unrevised polypharmacy and the woman with an exacerbation of heart failure triggered by over-the-counter bought NSAIDs.

Where does the interprofessional model of integrated pharmaceutical care stand now?

So far, the interprofessional model of integrated pharmaceutical care as described above seems a promising and a valuable addition to current primary care. In the Netherlands, we already know that five of the ten clinical NDPs who started during the POINT-study continued working after the intervention-period ended (now already 5 years). This suggests enthusiasm among the working field for this new care model and feasibility of the introduction in primary care.

A prior thesis[22] studied the model through the eyes of (non-dispensing) pharmacists. It addressed specific issues of the NDPs integrating in primary care practice and investigated how training added to their professional identity development, essential for the shift in the pharmacists' role.

Yet, before wide scale implementation of the model can be recommended, the effectiveness of the model needs to be demonstrated on direct clinical outcomes such as medication-related hospitalisations. In addition to the effect on direct clinical outcomes, the working mechanisms of this new care provider in primary care teams that explain its success need to be explored. Investigating the view of patients, as key participants in the model after all, and exploring the perspectives of GPs may provide more insight in acceptance and feasibility.

Objectives of this thesis

This thesis aims to provide insight in the potential additional value of the interprofessional model to primary care. Through the eyes of primary care practitioners, we aim to answer the questions *what is the effect* of the new model in increasing pharmaceutical safety in general practice, and *when, why and how* is the model effective – both compared to current models of pharmaceutical care.

Outline of this thesis

In this thesis, we first further introduce the interprofessional model of integrated pharmaceutical care and the way we researched its effect in *Chapter 2*. Here, we explicitly motivate our choices regarding the use of a non-randomised design.

Then, we aim to answer the first question about the effects of the new model on improving quality and safety of pharmaceutical care: does it work? We report effects on medication-related hospitalisations, as well as on healthcare costs, drug burden (*Chapter 3*) and prescription indicators (*Chapter 4*).

After measuring the effects of the interprofessional model, the second research question when, why and how it is effective, is addressed. Here, we explore the patients' perspectives (*Chapter 5)* and the GPs' perspectives (*Chapter 6*).

Finally, the main findings of this thesis and the practical implications are discussed in *Chapter 7*.

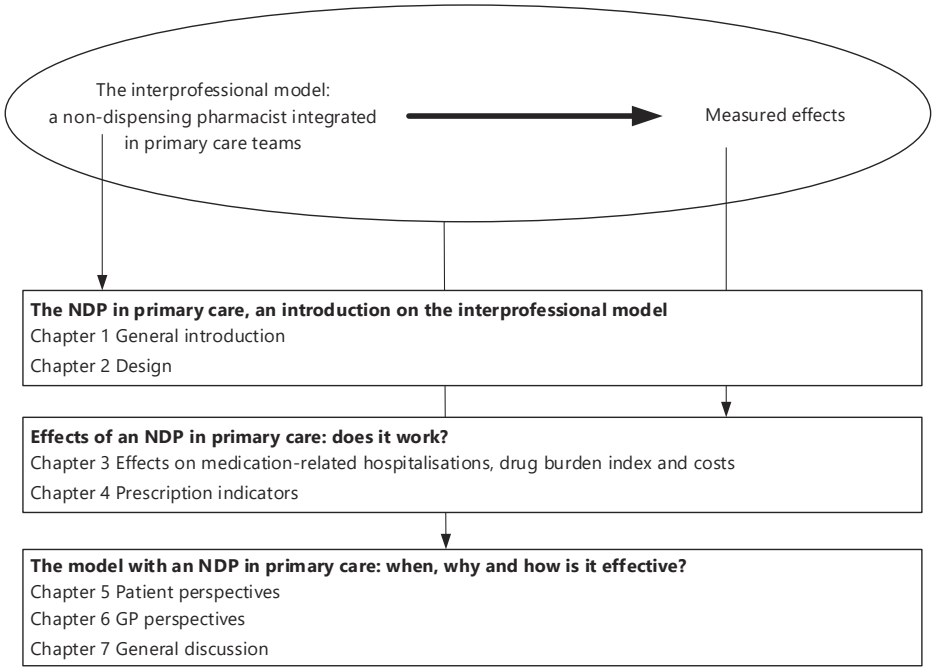

Figure 1. Outline of the thesis

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Chapter 2

Design of the POINT study: Pharmacotherapy Optimisation through Integration of a Non-dispensing pharmacist in a primary care Team (POINT)

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* Both authors contributed equally to this article

BMC Fam Pract. 2015; 16:76

ABSTRACT

Background: In the Netherlands, 5.6% of acute hospital admissions are medication-related. Almost half of these admissions are potentially preventable. Reviewing medication in patients at risk in primary care might prevent these hospital admissions. At present, implementation of medication reviews in primary care is suboptimal: pharmacists lack access to patient information, pharmacists are short of clinical knowledge and skills, and working processes of pharmacists (focus on dispensing) and general practitioners (focus on clinical practice) match poorly. Integration of the pharmacist in the primary health care team might improve pharmaceutical care outcomes.

The aim of this study is to evaluate the effect of integration of a non-dispensing pharmacist in general practice on the safety of pharmacotherapy in the Netherlands.

Methods: The POINT study is a non-randomised controlled intervention study with pre-post comparison in an integrated primary care setting. We compare three different models of pharmaceutical care provision in primary care: 1) a non-dispensing pharmacist as an integral member of a primary care team, 2) a pharmacist in a community pharmacy with a predefined training in performing medication reviews and 3) a pharmacist in a community pharmacy (care as usual). In all models, GPs remain accountable for individual medication prescription. In the first model, ten non-dispensing clinical pharmacists are posted in ten primary care practices (including 5 – 10 000 patients each) for a period of 15 months. These non-dispensing pharmacists perform patient consultations, including medication reviews, and share responsibility for the pharmaceutical care provided in the practice. The two other groups consist of ten primary care practices with collaborating pharmacists. The main outcome measurement is the number of medication-related hospital admissions during follow-up. Secondary outcome measurements are potential medication errors, drug burden index and costs. Parallel to this study, a qualitative study is conducted to evaluate the feasibility of introducing a NDP in general practice.

Discussion: As the POINT study is a large-scale intervention study, it should provide evidence as to whether integration of a non-dispensing clinical pharmacist in primary care will result in safer pharmacotherapy. The qualitative study also generates knowledge on the optimal implementation of this model in primary care. Results are expected in 2016.

Trial registration number: NTR4389, The Netherlands National Trial Register, 07-01-2014.

Keywords: Pharmacotherapy, Polypharmacy, Non-dispensing clinical pharmacist, General practice, Primary care, Hospitalisation

BACKGROUND

Adverse drug events account for 5,6% of acute hospital admissions in the Netherlands. Almost half of these admissions are potentially preventable.[1] Older age, polypharmacy, multimorbidity, impaired cognition and impaired renal function have been identified as risk factors for these preventable medication-related hospital admissions (HARMs).[1] Given the ageing of the population, the population at risk will grow in near future. Hence, new strategies are needed to improve the effectiveness and safety of pharmacotherapy in clinical practice and to prevent these hospital admissions.

As most of the pharmacotherapy is initiated in general practice, its quality may be primarily improved by structural reviewing patients' medication in primary care. So far, the results of studies on the effectiveness of medication reviews have been inconclusive: several studies reported a positive effect on the number of drug therapy problems,[2-7] but no effect on morbidity, mortality or quality of life was found.

Several difficulties hamper the implementation of medication reviews in primary care [8–10] and may have contributed to the inconclusiveness of these results. First of all, as community pharmacists get no or an insufficient fee for performing medication reviews, a financial incentive is lacking. However, this does not seem to be the only problem. Another important difficulty in the implementation is the lack of information: community pharmacists do not have access to routine patient records. Consequently, performing proper medication reviews is often impeded, as not all available information can be taken into account. Third, pharmacists lack clinical pharmacology knowledge and clinical reasoning skills, for pharmaceutical training and practice are historically drug product oriented instead of patient oriented. Community pharmacists' tasks mainly concern the organisation and monitoring of logistic processes (e.g. dispensing the right medication in the right dose to the right patient); community pharmacists perform little to no direct pharmaceutical patient care. As a result, pharmacists have sparse experience in clinical pharmacotherapy. Fourth, in the present system pharmacists and general practitioners (GPs) have different responsibilities, backgrounds and working processes, resulting in inadequate collaboration.[11] Fifth, the present way of practicing of both GPs and pharmacists is mainly reactive, while the pharmaceutical care process requires a proactive approach. Finally, there is a misfit between time-consuming nature of performing medication reviews and the current workload of both GPs and pharmacists.

Implementation of a non-dispensing pharmacist (NDP) in primary care teams might address these implementation problems and improve outcomes of pharmaceutical care. The NDP – as a healthcare team member – would have access to patient records and the required clinical information. The lack of clinical knowledge and skills of the pharmacist could be overcome by a training in clinical pharmacy. Collaboration with the GP is expected to improve, because the NDP is positioned into the clinical practice and is a full member of the primary care team, with the GP as head of the team. Furthermore, as the NDP's scope alters from drug product oriented to patient

oriented, the professional perspective will collide better with that of the GP.[12, 13] Finally, this change in scope relieves the NDP of his responsibility for the dispensing process, and enables the NDP to work fulltime on the improvement of pharmacotherapy.

This model of integrated pharmaceutical care has already been studied in Canada,[14, 15] Australia[16] and the United States of America.[17] It was found that the model has the potential to address many of the barriers to effective pharmaceutical care in the ways described above, thereby optimising medication use and hence leading to better healthcare outcomes.[14, 16] In Canada, physicians recognised many interprofessional benefits by working with a pharmacist directly integrated into their practice. Also, benefits of improved education were described.[14] The Australian study reported a significant reduction in medication-related problems after intervention by the pharmacists, and a significant improvement of adherence to the medication regimen.[16] In the USA, both GPs and patients perceived qualitative benefits from the pharmacotherapy consultations.[17]

However, the ultimate benefit of this model for patients, namely the prevention of HARMs, has not been demonstrated yet. Therefore, we designed the Pharmacotherapy Optimisation through Integration of a Non-dispensing pharmacist in a primary care Team (POINT) study, in which we assess, amongst others, the effect of a non-dispensing pharmacist on medication-related hospital admissions.

METHODS

Design

The POINT study is a non-randomised, controlled intervention study with pre-post comparison (see Table 1 for a time schedule of the POINT study).

Table 1 Time schedule of the POINT-study

Period	Dates
Pre intervention period (1 year)	1st of January 2013 – 31st of December 2013
Start-up period, prior to intervention period (3 months)	1st of March 2014 – 31st of May 2014
Intervention period (1 year)	1st of June 2014 – 31st of May 2015

Three different models of pharmaceutical care provision in primary care will be compared:

- *Group A (intervention group)*: a GP practice with a non-dispensing pharmacist based in the practice as an integral member of the primary healthcare team;

- *Group B (control group 1)*: 'upgraded' care as usual: a GP practice collaborating with a dispensing pharmacist based in a community pharmacy in the traditional way, with the pharmacist having had a predefined, certified additional training in reviewing medication,
- *Group C (control group 2)*: care as usual: a GP practice collaborating with a dispensing pharmacist based in a community pharmacy in the traditional way.

A flowchart of the study design is shown in Fig. 1. Concurrently, a qualitative implementation study is performed. The protocol was peer-reviewed by the funding organisation.

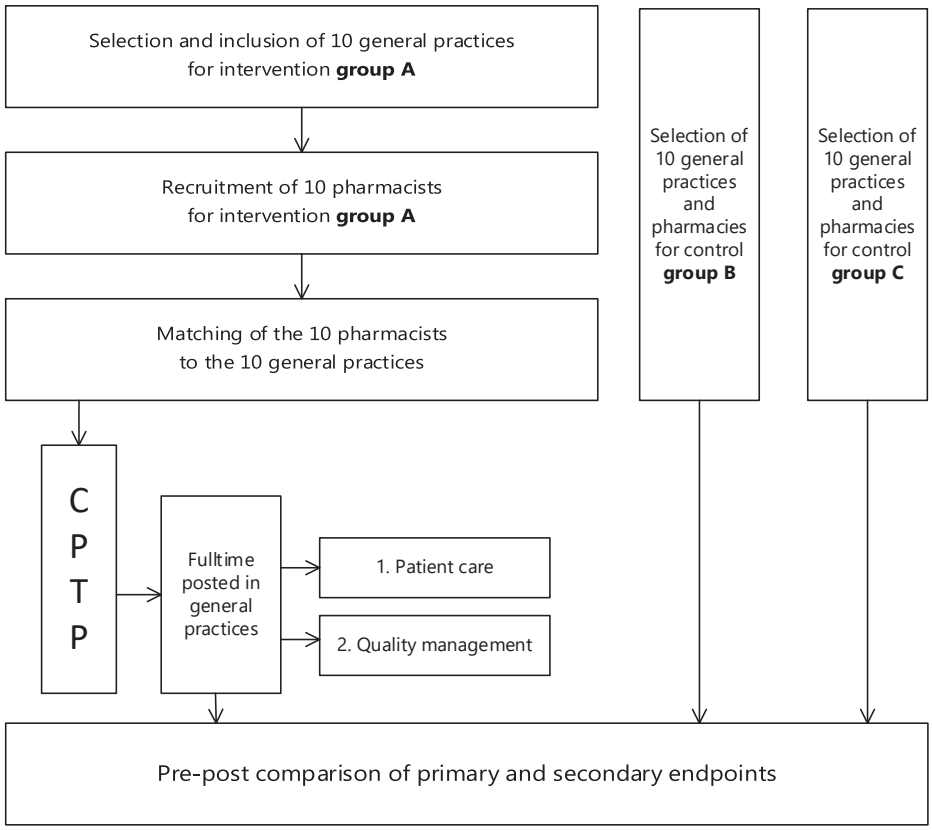

Fig. 1 Flowchart of the study design.

Abbreviations used: CPTP Clinical Pharmacy Training Program (newly developed for the intervention)

Setting

The project is implemented within primary care practices from the Julius General Practitioners Network (University Medical Centre Utrecht) and the Academic Network of General Practitioners (VU University Medical Centre Amsterdam). These networks consist of more than 200 collaborating general practices.

Group A: selecting GPs, non-dispensing pharmacists and matching both

General practices from the above mentioned networks are all pro-actively invited to participate in the POINT study. Ten general practices are selected, based on the following criteria: willingness of the GPs to participate in the project; willingness of the GPs to cooperate in the development and evaluation of the role of the NDP; minimum of 5000 registered patients; availability of an office for a NDP, with access to the GP information system; minimum of one practice nurse working on disease management programs for chronic conditions such as chronic obstructive pulmonary disease, diabetes, cardiovascular disease or mental health; healthcare centre accredited by the Dutch College of General Practitioners (NHG).[18] The research collaboration is formalised in a collaboration agreement.

Ten non-dispensing pharmacists are employed, using a structured application procedure. All participating pharmacists have a master degree in pharmacy (PharmD) and preferably have working experience in providing pharmaceutical care to individual patients. Furthermore, in the selection procedure communication and collaboration skills, as well as pharmacotherapy knowledge, empathy, self-reflection skills and innovative attitude are emphasized.

Subsequently, each NDP is posted in one of the ten selected primary care centres in Utrecht or Amsterdam regions. The NDPs work full time and exclusively in the general practices, for a period of 15 months. The introduction of such a new role in a healthcare practice is complicated and faces a variety of challenges.[14] For example, pharmacists need to be trained to fulfil their new tasks, both pharmacists and GPs have to collaborate closely and GPs have to explore the complementary role of the NDP. Therefore, the first three months are used as a start-up period before actually starting the intervention period.

Group B and C: selecting GPs and collaborating pharmacists

For both group B and C, ten general practices and collaborating pharmacies are selected from the abovementioned networks as well. Criteria for participation are comparable to those concerning the size of the practices, described for group A. In addition, characteristics of patients of practices in groups B and C were matched as far as possible with group A, considering age distribution and socioeconomic status. Subsequently, practices and collaborating pharmacies are assigned to group B or C, depending upon whether the collaborating pharmacists have completed a certified training program on performing medication reviews in the Netherlands,[19, 20] or not, respectively. See Fig. 2.

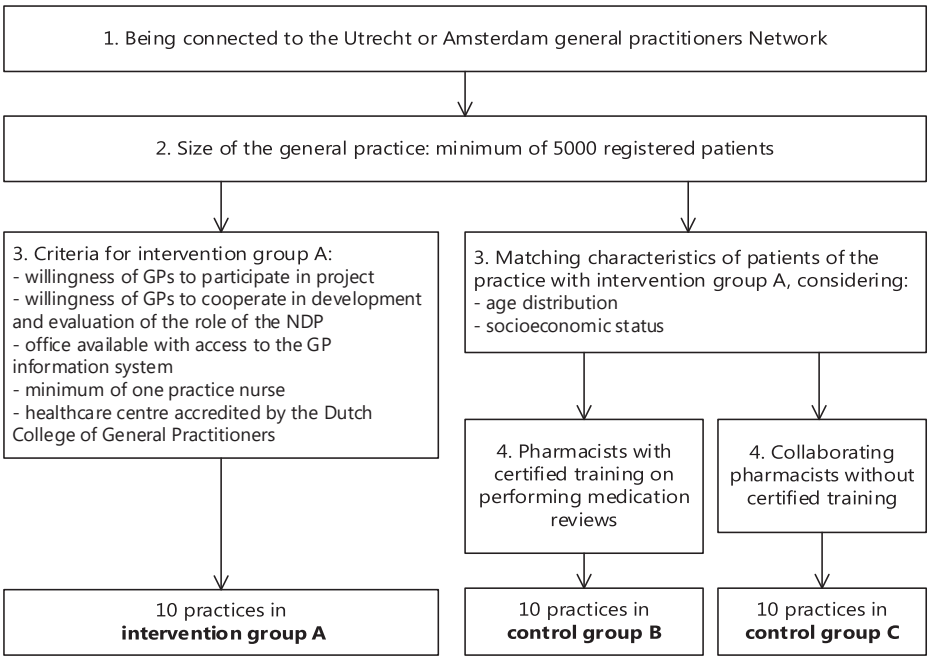

Fig. 2 Overview of the selection criteria for general practices for group A, B and C

Intervention

To improve the safety of pharmacotherapy within the general practice, the intervention in group A by the NDPs aims at two levels: individual patient consultation and quality management on an organisational level. Herewith, the NDPs are responsible for the medication management and pharmaceutical care provided in the general practice. The NDPs perform complementary work and do not take over tasks of the GP nor the community pharmacist.

Individual patient consultation

The patient care process consists of an assessment of the patient's drug-related needs, a care plan to meet the specific needs of the patient, and a follow-up evaluation to determine the impact of the decisions made and actions taken. In practice, the NDP provides pharmaceutical patient care for patients who are considered to be at risk of adverse drug events, such as HARMs. These patients, mostly of older age, with multimorbidity and polypharmacy (chronic use of five or more medicines),[1] are either

pro-actively invited by the NDP or referred by the GP to discuss and review their medication. Also, patients can make an appointment for a medication assessment at their own request. During the first consultation, which is preferably a home visit, the NDP will work on a therapeutic relationship and interviews the patient to gather information on the patient's experiences with and believes about medication, in order to assess his or her drug-related needs. Questions concern the goal of therapy for the patient, the current and past medication history, adherence to the medication regimen and patient reported medication issues. Afterwards, the NDP integrates the patient reported experiences and believes with the medical status to determine whether there are potential drug therapy problems. If necessary, the NDP provides recommendations for optimisation of pharmacotherapy to the GP: suggestions to stop, start or switch medication, to adjust dosages, or for actions to improve adherence. These recommendations result in a documented individual pharmaceutical care plan, as part of the patient's medical record. The implementation of recommendations is monitored by the NDP. Follow-up contacts can be conducted as a home visit, a practice visit or by telephone.

Furthermore, the NDP covers other aspects of pharmaceutical patient care, such as individual consultations for specific drug therapy problems or questions, and medication reconciliation in patients discharged from hospital.

All patient level interventions involve ongoing on-location collaboration with the healthcare team – being GP, practice nurses, assistants and the community pharmacists. The NDP is available at the GP practice and has daily formal and informal meetings with the GP in order to establish individual pharmaceutical care plans and to report on plans in progress. All members of the healthcare team can easily approach the NDP with questions about medication and patients' pharmacotherapy.

Quality management

The NDP aims to improve medication safety on an organisational level, through optimisation of processes within the practice around repeat prescribing, clinical care paths, administrative efficiencies and identification of common medication errors. The NDP is looking for possible optimisation options in medication regimens, such as monitoring renal function and electrolytes with indicated pharmacotherapy, tapering the chronic use of proton pump inhibitors, and optimising antibiotic prescribing. Hereby, the NDP organises targeted programs to improve the quality of pharmaceutical care in the practice. Also, the NDP provides education of patients and professionals involved.

Training program group A

To train the NDPs for their new role, a specialised Clinical Pharmacy Training Program (CPTP) is developed, based on workplace learning and the Canadian Medical Education Directions for Specialists (CanMEDS) Roles.[21] The CPTP started with a six-

day training workshop, an internship in a nursing home and assignments in practice. Plenary education days are gradually decreased and days in the general practice gradually increased, ending with full time practice work with weekly education days at the university. Key elements of the training are consultation and communication skills, clinical reasoning, clinical pharmacotherapy and being reflective in practice. NDPs are trained to use a patient centred approach in providing care, instead of a drug product centred approach. Barriers to implementation are discussed and ongoing support is provided through structural intervision sessions and a mentorship and buddy program.[22]

Outcomes and measurements

Primary outcome: medication-related hospital admissions (HARMs)

The primary outcome is the number of medication-related hospital admissions (HARMs) in the high-risk population. HARMs are defined as hospitalisations related to adverse drug events. To identify these medication-related hospital admissions, two pharmacists with clinical experience will independently assess each hospitalisation that occurred in the study population during follow-up, using discharge information combined with the medical and medication history. They will assess the causal relationship between the suspected medicine and the reason for hospitalisation, according to an adjusted version of the algorithm by Kramer et al.[23] In this version, three questions need to be answered (in contrast to six questions in the original algorithm): whether the reason for admission is known to be an adverse event of the suspected medicine, whether alternative causes can explain the relationship between the suspected medicine and the adverse event, and whether a plausible time relationship exists between the adverse event and the start of medication administration (or the occurrence of the medication error). On the basis of the answers, causality is classified as "possible", "probable", or "unlikely". Cases with an assessment of unlikely will be excluded.

Secondary outcomes

Potential medication errors The percentage of patients with potential medication errors will be measured.[24] These potential medication errors mainly concern prescription errors, such as under- and overprescribing and dosage errors. Other potential medication errors might be due to medication that is not or insufficiently effective, or to inadequate monitoring of the effects of the therapy. Also administration errors, such as non-adherence problems, will be measured as potential medication errors. A complete list of included potential medication errors can be found in Table 2.

Table 2 Overview of outcomes, measurements and data sources

Outcomes	Measurement	Data sources
Primary outcome		
Frequency of HARMs	Number of HARMs	DL, MH, MED
Secondary outcomes		
Potential medication errors	% patients with:	
	- medication not indicated	MED/MR
	- underprescribing	MED/MR
	- dosing error (too low or too high)	MED/MR
	- therapeutic duplication medication	MED/MR
	- medication contra-indicated	MED/MR
	- drug-drug interactions	MED/MR
	- medication not effective	MED/MR
	- inadequately monitored therapy	MED/MR
	- administration errors (e.g. non-adherence)	MED/MR
Drug burden index	Drug burden of medications with sedative and/or anticholinergic effects	MR
Costs	Medication costs and healthcare-related costs	Database of insurance company

Drug burden index The drug burden index will be calculated for every patient. This drug burden index measures exposure to anticholinergic and sedative medication, and is associated with poorer physical and cognitive performance in older people.[25] Hence, the drug burden index can be seen as a proxy of drug therapy risk and medication safety.

Costs A cost analysis will be performed, based upon reimbursement data from databases of a Dutch major health insurance company. Direct medical costs, such as for medication, hospital care, specialist care, diagnostic tests and other healthcare-related costs will be included.

Data collection

Data of all patients in groups A, B and C are accessible through the routine health care databases of the Julius General Practitioners Network (Utrecht) and the Academic Network of General Practitioners (Amsterdam). After the intervention period (see Table 1), key data will be extracted anonymously from the electronic medical records in the general practices of both the pre- and post-intervention period, through standard procedures and existing algorithms. These data (see Table 2) are combined with reimbursement data from the major healthcare insurance company in the Utrecht and Amsterdam region, obtaining 40-55% of the reimbursement data of the region. No data will be obtained directly from patients.

Confounding factors

To be able to control for possible confounding, characteristics of the involved general practices and pharmacies in each group will be collected, using a questionnaire. Additional information will be gathered about pharmaceutical care provision, the medication review protocol used, the setting of the pharmacy and the general practice, the collaboration between the pharmacy and the general practice and agreements on pharmaceutical care provision.

Analyses and statistical method

All primary and secondary outcomes will be compared in pre-post analyses and between groups comparisons will be conducted. Descriptive statistics will be calculated for the baseline characteristics according to data of the overall population in group A, B and C, as well as for the high risk patients. The effect on the primary outcome will be tested with logistic multilevel analysis. The potential medication errors, drug burden index and costs will be tested with mixed effect models. Baseline characteristics can be integrated into the mixed effect models to control for confounding.

Sample size calculation

With an expected prevalence of 4,5% HARMs in 12 months within the high-risk population,[26] we expect an effect of 50% reduction of HARMs.[1] To show a statistically significant difference between the intervention group A and control group C, we include ten practices, with a total of 45.000 patients, in each group. As 6,4% of patients in an average GP practice are part of the high risk elderly population,[26] this means that in each arm at least 2850 high risk patients are included. This is based on an alpha of 0,05 and a power (1-beta) of 0,8.

Qualitative study

In order to assess the feasibility of introducing a NDP in general practice, parallel to the POINT study qualitative data hereon is systematically collected. Semi-structured interviews with participating GPs and NDPs are conducted, and their views are described. Patients who are seen by a NDP are asked about their perceptions and experiences, using anonymised questionnaires. Hereby, conditions that hinder or facilitate the introduction of a NDP in general practice in the Netherlands may be identified.

Privacy and informed consent/Ethical approval

Based on the Dutch law for patient data protection, this study was exempt of formal medical-ethical approval by the Medical Ethical Committee University Medical Centre Utrecht. (METC protocol number 13-432C).

DISCUSSION

The POINT study aims to improve safety of pharmacotherapy in primary care, by introducing a non-dispensing pharmacist as a member of the primary care team in the Netherlands. This intervention aims to improve pharmaceutical care at both patient level and organisational level. Therefore, it may be more effective than a singular intervention, such as current medication reviews. A comparison will be made with two existing models of pharmaceutical care provision in primary care. This comparison will demonstrate whether the introduction of the NDP is more effective in improving the quality and safety of pharmacotherapy than existing care models.

Several methodological challenges were faced during the design of the POINT study.

Choice for the design

Despite the fact that a randomised controlled trial is the preferred design to evaluate the effect of an intervention, we thoughtfully chose to use a non-randomised model. In our opinion, willingness of all participating parties to improve pharmaceutical patient care is a key condition for the implementation of this intervention to succeed. This has been recognised before, during the implementation of a pharmacist in primary care in Canada.[14] Therefore, general practices participating in the intervention group of this study are selected instead of randomly allocated to one of three research arms.

This selection, of course, has disadvantages. Once proven effective, the broad implementation of this new function might be challenging because of the high standards we set for participating practices in this study. In addition, selection of motivated general practices might mask the effect of the intervention. As these practices are motivated to improve pharmaceutical care, standard pharmaceutical care might

be better than average beforehand, leaving little room for improvement. By including pre-post analyses, we attempt to obviate this problem.

Composition of the intervention

The introduction of the NDP is considered a complex intervention. This is for intervening at different care levels, as well as for integrating a new professional into the primary work processes, which requires redistribution of tasks and responsibilities around pharmacotherapeutic care. Although the tasks of the NDP are predefined, the actual implementation in the individual GP practices cannot be protocolled: in order to increase the likelihood of a successful implementation of the intervention, the intervention has to be aligned to the needs of each participating centre. Consequently, the actual implementation of the intervention itself may be heterogeneous. This can blur quantitative measurements. Therefore, parallel to this study, we conduct a qualitative study as described earlier. With this study, we will list facilitators and barriers to the implementation process, in order to assess the feasibility of introducing a NDP in a complex healthcare setting in daily practice.

Development of the clinical pharmacy training program

The clinical pharmacy training program (CPTP) has been newly developed for the POINT study and has neither been validated nor accredited. As the CPTP is developed by experts in the field of education, based on the theoretical frameworks of Vermunt, Kolb and Merrienboer [27–29] and as it is embedded in the department of vocational training for general practice, it is expected to be an adequate postgraduate training for the NDPs. Within the context of the POINT intervention study, the program is evaluated and attuned on a structural basis.

Choice of the primary outcome measurement

In the context of 'primum non nocere' [30] the prime aim of this study is to improve the safety of pharmacotherapy. Therefore, we chose reduction of medication-related hospital admissions (HARMs), being a severe adverse drug event, as primary outcome. This choice is, however, challenging in several aspects.

First, the incidence of HARMs in primary care is low. Although 5.6% of acute hospital admissions are related to medication,[1] this accounts for only about 3.4 medication-related hospital admissions per GP on a yearly basis – which means around 12–16 HARMs per participating practice in this study. In addition, we do have a limited follow-up period of only one year. However, our sample size calculation is based upon the occurrence of HARMs in a large group, so we expect this problem to be adequately addressed. Last, measuring HARMs is challenging for quite detailed data have to be obtained in order to determine HARMs. Causality assessments in the POINT study will

be based upon information of discharge letters, which is limited information. However, using this amount of information to determine HARMs has been done before.[31] Also, we do have experience from previous studies[1, 26] and will use a validated method to identify the primary outcome parameter.

Availability of data for secondary outcome measurements

To correctly measure and analyse the secondary outcomes, the required data need to be properly documented in the GPs' information systems. Due to the heterogeneous study setting we are dependent on the diverse working methods of the participating healthcare providers. As this possible loss of information will show equally in each research arm, we expect this will not influence our study results.

The cost evaluation performed in this study will yield an insight in the direct medical costs of each model of pharmaceutical care provision in primary care. For this evaluation, a subgroup of patients will be analysed, as data of the insurance company will not be available for all patients. A full economic evaluation including a societal costs and economic modelling is outside the scope of this research project.

CONCLUSION

This study will provide information as to whether the integration of a non-dispensing pharmacist in primary care will improve medication safety compared to current care models.

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Effects of the NDP in primary care: does it work?

Chapter 3

Effects of non-dispensing pharmacists integrated in general practice on medication-related hospitalisations

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ABSTRACT

Aims: To evaluate the effect of non-dispensing pharmacists (NDPs) integrated in general practice on medication-related hospitalisations, drug burden index and costs in patients at high risk of medication problems (being 65 years or older and using five or more chronic medications).

Methods: This was a multicentre, non-randomised, controlled intervention study with pre-post comparison (2013 versus June 2014 to May 2015) in 25 general practices in the Netherlands, comparing NDP-led care (intervention) with two current pharmaceutical care models (*usual care* and *usual care plus*). In the intervention group, ten specially trained NDPs were employed in general practices to take integral responsibility for the pharmaceutical care. They provided a broad range of medication therapy management services both on patient level (e.g. clinical medication review) and practice level (e.g. quality improvement projects). In the control groups, pharmaceutical care was provided *as usual* by general practitioners and community pharmacists, or *as usual plus* when pharmacists were additionally trained in performing medication reviews.

Results: Overall, 822 medication-related hospitalisations were identified among 11 281 high-risk patients during the intervention period. After adjustment for clustering and potential confounders, the rate ratio of medication-related hospitalisations in the intervention group compared to *usual care* was 0.68 (95% CI: 0.57–0.82) and 1.05 (95% CI: 0.73–1.52) compared to *usual care plus*. No differences in drug burden index or costs were found.

Conclusions: In general practices with an integrated NDP, the rate of medication-related hospitalisations is lower compared to *usual care*. No differences with *usual care plus* were found.

Trial registration number NTR-4389, The Netherlands National Trial Register.

Keywords general practice, medication safety, medication-related hospitalisation, non-dispending pharmacist, primary care

INTRODUCTION

With the aging of the population the number of patients with comorbidities and polypharmacy increases.[1] These elderly patients are especially prone to unsafe and ineffective pharmacotherapy, leading to adverse events and hospitalisations. In the Netherlands, 10.4% of acute hospitalisations in elderly patients in 2013 were related to medication and almost half of these hospitalisations were potentially preventable.[2]

Pharmacists can have an important contribution to safe and effective pharmacotherapy, but at present they cannot optimally fulfil this role. Several barriers are identified: pharmacists often do not have access to patient medical records and generally, they are insufficiently trained in clinical knowledge and consultation skills. Also, collaborative working relationships between pharmacists and general practitioners (GPs) are often suboptimal, despite working in the same geographical area. The workload of both GPs and pharmacists also contributes to a lack of focus on improving the quality of pharmaceutical care.[3,4] Full integration of a clinical *non-dispensing pharmacist (NDP)* in the primary care team could help to overcome these barriers.

Internationally, the role of pharmacists is developing from mainly dispensing medication towards providing pharmaceutical care in a clinical context.[5] In this new role, the clinical pharmacist takes overall responsibility for the patient's pharmacotherapy in close collaboration with the treating physician.[6] This new model of pharmaceutical care provision includes different pharmacist-led services, such as performing clinical medication reviews, conducting quality improvement projects, holding individual consultations for specific drug therapy problems and educating team members in pharmacotherapy.

Pharmacist-led services provided in general practice are demonstrated to reduce the number of drug therapy problems and improve intermediate outcomes, such as blood pressure, cholesterol and blood glucose.[7] So far, evidence on the effectiveness in terms of clinical outcomes such as morbidity or mortality is lacking. We conducted the POINT-study [8] (Pharmacotherapy Optimisation through Integration of a Non-dispensing pharmacist in a primary care Team), to assess the effect of integration of an NDP in general practice on medication-related hospitalisations. As secondary outcomes, we assessed the effect on drug burden index (DBI) and costs.

METHODS

A multicentre, nonrandomised, pragmatic, controlled intervention study with pre-post comparison was conducted between January 2013 and June 2015, comparing pharmaceutical care by an NDP as integral member of the primary care team (intervention group) with 2 current models of pharmaceutical care (control groups). For a detailed description of the study design, see the study protocol.[8]

Setting

This study was conducted in general practice in the Netherlands. Participating practices were affiliated to 1 of 3 research networks: Julius General Practitioners Network (University Medical Centre Utrecht), healthcare network Almere (Zorggroep Almere) and the Registration Network of General Practitioners Associated with Leiden University (RNUH-LEO).[9–11]

Participating practices

For the intervention group, we included practices that were explicitly willing to host an NDP. These practices had to meet the following additional criteria: availability of a consultation room for the NDP; access to the GPs' electronic medical records; a minimum of 5000 registered patients; at least one practice nurse working on chronic disease management programs.

For the control groups, we included practices that matched the characteristics of practices in the intervention group as much as possible with regard to practice size, degree of urbanisation, socioeconomic status and patients' age distribution.

The intervention group: NDP-led care

Ten NDPs (all PharmD) were embedded in 10 general practices in the intervention group, on a full-time basis. Concurrently, they participated in a newly developed 15-months Clinical Pharmacy Training Program based on interprofessional workplace learning.[12]

The NDPs were given integral responsibility for the pharmaceutical care in the practice, with a main focus on *high-risk patients*: patients aged 65 years or older and using 5 or more chronic medications.[13] At the patient level, the NDPs performed clinical medication reviews for patients with polypharmacy, medication reconciliations for patients discharged from the hospital and individual patient consultations for patients with specific drug therapy problems. Patients were either invited by the NDPs, referred by the GPs or could consult on their own request. At the practice level, the NDPs organised quality improvement projects to systematically identify and treat patients at risk of medication errors, and educated GPs and staff members on pharmacotherapy.

In addition to these predefined fixed tasks, the NDPs' responsibilities could be tailored to the specific needs of the practices. During the Clinical Pharmacy Training Program, alignment to the predefined tasks was evaluated and discussed regularly to increase fidelity of the intervention. No modifications to the original predefined tasks were made.

The control groups: usual care and usual care plus

The *usual care* group consisted of general practices where pharmaceutical care was provided in the traditional way, i.e. in collaboration with community pharmacists. In the *usual care plus* group, pharmaceutical care was provided in collaboration with community pharmacists who had completed a nationally accredited training program in performing medication reviews.[14,15]

Data collection

Data were collected between 2013 and 2015. The period between 1 January 2013 and 31 December 2013 served as baseline period (pre).[8] The intervention period started on 1 June 2014 and ended on 31 May 2015 (post). Three months prior to the intervention period, NDPs already started working in the practices. These months were considered necessary for the NDPs to learn basic clinical skills and to establish their position in the practice[16;] no data were collected in these months. For outcome measurements we only included high-risk patients.

Patient characteristics, such as patients' medical history, medication records and laboratory results, were extracted anonymously from the GPs' electronic medical records. The number of chronic conditions was based on a standardised morbidity index list[17] and a national prevalence list[18] of chronic diseases and multimorbidity. Data on acute, unplanned hospitalisations in above described periods were collected by research assistants. They visited participating practices to collect anonymised discharge letters of acute hospitalisations. Data from the GPs' electronic medical records were used for the analyses of medication-related hospitalisations and drug burden index. For the cost-analyses, anonymised healthcare cost reimbursement data from the major health insurance company[19] were used.

Primary outcome

The primary outcome was the number of medication-related hospitalisations in high-risk patients. If patients had multiple medication-related hospitalisations, all hospitalisations were included. Only acute hospitalisations were included, as planned hospitalisations are rarely related to medication.[20]

Assessment of hospitalisations

We performed a case-by-case assessment of all acute admissions, based on a modified version of the algorithm by Kramer *et al.*[21], to identify medication-related hospitalisations. We applied the following procedure, in which all assessors were blinded for the corresponding study groups:

STEP 1. a medical doctor or a senior medical Master student determined whether the reason(s) for admission could be related to a known side-effect of the used

medication. Side-effects with an incidence of at least 1% according to Dutch standard reference sources[22–24] and side-effects explicitly described in the discharge letter were included for further assessment.

STEP 2. An expert duo, consisting of a medical doctor (J.P., V.S.) and a clinical pharmacist (A.H., P.H., S.H., M.B.) assessed whether the hospitalisations selected in step 1 were *possibly* or *unlikely* to be medication related. For this assessment, 2 elements were taken into account: first, whether alternative causes (other than the suspected medication), such as a pre-existing clinical condition, explained the reason for admission; second, the time relationship between the potential side effect and the start of medication administration. Admissions that were beyond the scope of the NDPs were excluded, such as admissions in patients treated for malignancies, post-transplantation, patients on renal dialysis and psychiatric admissions.

STEP 3. Results of step 1 and 2 were compared. In case of disagreement, consensus meetings with an experienced GP (D.Z., N.d.W.) and/or clinical pharmacist (A.L.) were arranged. Differences were resolved in discussion.

STEP 4. Of all cases excluded in step 1, a random 10% sample was double checked by a medical doctor (V.S.) and a clinical pharmacist (A.H.). In case of disagreement about the exclusion, the case was reassessed. According to a preset protocol, all excluded cases would be reassessed in case the percentage of disagreement exceeded 10%.

Secondary outcomes

DBI

The DBI[25] measures a patient's total exposure to anticholinergic and sedative medications, taking medication dosage into account: $DBI = \sum(\frac{D}{D+\delta})$, with D being the daily medication dose and δ being the minimum recommended daily dose, we used those stated in Dutch reference sources.[22] We calculated the DBIs at the start and at the end of the intervention period for each high-risk patient. A reduction in DBI of at least 0.5 was considered clinically relevant, as this is the average effect of stopping 1 anticholinergic or sedative drug.[26]

Costs

We calculated direct primary and secondary healthcare costs and total medication costs, in both the pre and the post period for each high-risk patient, using cost reimbursement data of the major health insurance company. We compared intervention practices with *usual care* practices, as in *usual care plus* practices too few patients were insured with this company.

Sample size

We assumed the annual incidence rate of medication-related hospitalisations in the high-risk population to be 4.5.[27] We expected a 50% reduction of medication-related

hospitalisations.[28] To demonstrate a statistically significant difference between the intervention and control groups, at least 2850 high-risk patients needed to be present in each study group. As the high-risk population comprises 6.4% of an average general practice in the Netherlands, 45 000 patients were needed for each study group.[27] Assuming an average practice size of 5000 patients, we aimed to include 10 practices per study group. This was based on a 2-sided alpha of 0.05 and a power (1 – β) of 0.8.[8]

Data analysis

The primary outcome, the number of medication-related hospitalisations in high-risk patients (count data), was analysed with a Poisson mixed model to compare the intervention and control groups, with adjusted rate ratios. The model included a random intercept to adjust for clustering at practice level and a residual (i.e. generalised estimating equations type) covariance matrix to account for patients that were included in both the baseline and intervention period. The intervention effect was assessed with the interaction between study group and study period. We adjusted for patients' age, sex, number of chronically used medications and number of comorbidities (medications and comorbidities as measured in the corresponding study period). On practice level, we adjusted for the degree of urbanisation and socioeconomic status.

In a sensitivity analysis, we excluded those types of medication-related hospitalisations that were previously not used in research of medication-related hospitalisations (fever/infection/inflammation) because of an unclear or weak association between medication and hospitalisation.

The secondary outcome DBI was analysed with a linear mixed model to compare treatment-effects between the intervention and both control groups. A subanalysis was performed excluding patients with a DBI-score of 0 at baseline. Costs were split into direct primary healthcare costs, direct secondary healthcare costs and medication costs, and analysed with linear mixed models on log-transformed data to compare the intervention and *usual care* group. All models included elements comparable but somewhat different to the primary outcome model; for details please see Appendix 1.

All analyses were performed using both SAS software Version 9.4 for Windows and IBM SPSS Statistics for Windows Version 23.0 (Armonk, NY).

Ethical considerations

The Medical Ethical Committee of the University Medical Center Utrecht waived formal medical-ethical assessment (METC protocol number 13-432C).

RESULTS

Study practices

Ten NDPs were embedded in 10 general practices in the intervention group. One NDP was unable to finish the training program and was withdrawn from the study. This resulted in 9 intervention practices with an embedded NDP. For the *usual care* and *usual care plus* groups, we approached approximately 125 general practices and included 10 and 6 participating practices, respectively.

The practices in the 3 study arms did not differ in multidisciplinary composition, professional accreditation status, GP training site or urbanisation level (Table 1).

The mean proportion of high-risk patients per practice was highest in the *usual care plus* group: 7.4% compared to 5.6 and 6.4% in the intervention and *usual care* groups. The mean socioeconomic status of patients was higher in the intervention practices (0.9) than in the control practices (0.6; Table 1)

The median number of medication reviews at baseline in the intervention group was 8 per 100 high-risk patients, compared to 15 in the *usual care* group and 3 in the *usual care plus* group. These medication reviews were conducted by community pharmacists and/or GPs, and were part of care as usual.[13] No information on the quality of medication reviews was available. Almost all practices had a high standard of quality of pharmacotherapy audit meetings.[31,32]

Patients

A total of 11 928 high-risk patients was included in the analysis. Of 647 patients (5.4%) only pre period data were available, as they were deregistered from the participating practices because of death (55%), moving (9%), or for unknown reason (36%). Of 317 patients who newly registered in the practices during the post period, no pre period data were available (Figure 1). The number of patients who were deregistered or newly registered was not equally distributed between the study groups. In the intervention, *usual care* and *usual care plus* groups, 3.9%, 5.1% and 7.3% of patients were deregistered, and 1.8%, 3.9% and 2.1% of patients were newly registered, respectively.

Differences in age and gender distribution between the 3 study groups were insignificant. The proportion of patients aged 85 years or older was 13% in the intervention group and 16% in both control groups (Table 1). The median number of chronically used medications was 6 in all study groups and the median number of registered comorbidities was 4 in both the intervention and *usual care* group and 5 in the *usual care plus* group.

Table 1: Practice and patient characteristics at baseline

		INTERVENTION group (9 practices)	USUAL CARE group (10 practices)	USUAL CARE PLUS group (6 practices)
PRACTICE	Practice size			
	Patients ≥18 years, *median (IQR)*	8,669 (4,765 - 10,689)	5,973 (5,371 - 6,646)	6,907 (4,474 - 13,981)
	High-risk patients, *median (IQR)*	427 (312 - 587)	344 (271 - 501)	523 (285 - 1,087)
	Setting and organisation			
	Degree of urbanisation[a], *mean ± SD (range)*	1.8±1.1 (1-4)	2.1±0.7 (1-3)	2.2±0.8 (1-3)
	Socioeconomic status[b], *mean ± SD (range)*	0.9± 1.0 (-1.2-2.2)	0.6± 0.9 (-2.1-1.7)	0.6± 0.5 (0-1.2)
	Health care centre, *n (%)*	7 (78)	7 (70)	3 (50)
	GP training practice, *n (%)*	8 (89)	7 (70)	4 (67)
	Indoor pharmacy, *n (%)*	6 (67)	6 (60)	4 (67)
	Collaborating pharmacies, *mean± SD (range)*	1 ± 1 (1-4)	2 ± 1 (1-4)	2 ± 2 (1-5)
PATIENT	High-risk patients, *n*	3,879	3,941	3,791
	Male sex, *n (%)*	1,703 (44)	1,756 (45)	1,693 (45)
	Age, *mean ± SD*	75 ± 8	75 ± 8	75 ± 8
	Patients <75 years, *n (%)*	2,069 (53)	1,901 (48)	1,893 (50)
	Patients 75-85 years, *n (%)*	1,318 (34)	1,414 (36)	1,296 (34)
	Patients ≥85 years, *n (%)*	492 (13)	626 (16)	602 (16)
	Chronic medications, *median (IQR)*	6 (5 – 7)	6 (5 – 8)	6 (5 – 8)
	Comorbidities[c], *median (IQR)*	4 (3 – 6)	4 (3 – 6)	5 (3 – 7)

SD Standard Deviation; GP General Practitioner; IQR Inter Quartile Range.

[a] Using a five point scale of degree of urbanisation (1=highly urbanised area, 5=rural area).[29]

[b] Data from Dutch Social and Cultural Planning Office, using status scores of zip code area of the general practice (a higher score represents a higher status).[30]

[c] Using the UK Quality and Outcomes Framework and overview of chronic diseases developed by the Dutch National Institute for Health and Environment.[17,18]

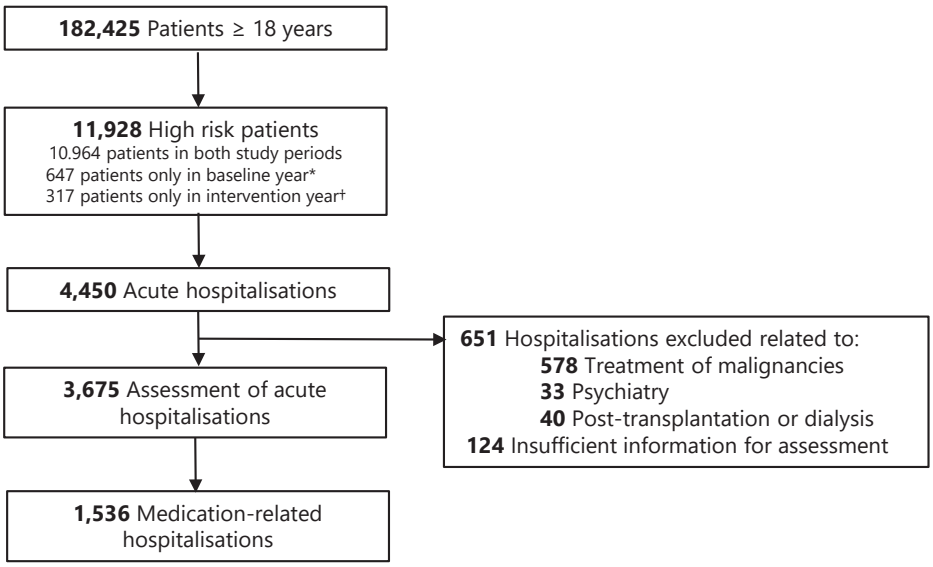

Figure 1: Flowchart of medication-related hospitalisations in the total study population in both study periods

* Deregistered high-risk patients in general practice during pre-period

† Newly registered high-risk patients in the general practice after pre-period

Primary outcome: medication-related hospitalisations

In the intervention period, we identified a total of 822 medication-related hospitalisations among 11 281 high-risk patients in the 3 study groups (Table 2). The adjusted mean rate of medication-related hospitalisations was 4.4 per 100 high-risk patients per year in the intervention group, 6.4 in the *usual care* group and 4.2 in the *usual care plus* group (Table 3). The adjusted rate ratio for medication-related hospitalisations in the intervention group compared to *usual care* was 0.68 (95% CI [CI] 0.57–0.82) and compared to *usual care plus* 1.05 (0.73–1.52) (Table 3). Of the patients with a medication-related hospitalisation, 5% had >1 medication-related hospitalisation.

Table 2: Unadjusted numbers of medication-related hospitalisations in high-risk patients

Study group	**INTERVENTION**		**USUAL CARE**		**USUAL CARE PLUS**	
Study period	**PRE**	**POST**	**PRE**	**POST**	**PRE**	**POST**
High-risk population, *n*	3,879	3,798	3,941	3,894	3,791	3,589
Acute hospitalisations, *n (%)*	542 (14.0)	584 (15.4)	691 (17.5)	841 (21.6)	517 (13.6)	500 (13.9)
Medication-related hospitalisations, *n (%)*	213 (5.5)	230 (6.1)	297 (7.5)	355 (9.1)	204 (5.4)	237 (6.6)
Patients with medication-related hospitalisations, *n (%)*	172 (4.4)	187 (4.9)	236 (6.0)	289 (7.4)	166 (4.4)	199 (5.5)

Table 3: Adjusted rates and rate ratios of medication-related hospitalisations in high-risk patients, per study group[a]

Adjusted rate, n medication-related hospitalisations per 100 high-risk patients per year		**Rate ratio** (95% CI)	
	POST		
Intervention group	4.4	Intervention group	
Usual care group	6.4	*vs. usual care* group:	0.68 (0.57 – 0.82)
Usual care plus group	4.2	*vs. usual care plus* group:	1.05 (0.73 – 1.52)

[a] Adjusted at patient level for age, gender, number of chronic medications and comorbidities as measured in the corresponding study period; at practice level for the degree of urbanisation and socioeconomic status; and adjusted for clustering, using a Poisson mixed-model. These adjustments resulted in estimates for an average patient in the total database.

Table 4: Reason for medication-related hospitalisation and associated medications, including both pre and post periods

Reason for admissiona	*n* (%)	Most associated medications (n)b
Fever/infection/inflammation (e.g. pneumonia, urinary tract infection)	394 (23)	Corticosteroids (377), immunosuppressive drugs (23), sympathicomimetics (19), opiates (10), diuretics (8), antibiotics (7), antimuscarinics (7), antiepileptics (7), statins (7), benzodiazepines (7)
Dizziness/collapse/hypotension/syncope[c]	352 (21)	Beta blockers (152), benzodiazepines (98), ACE-inhibitors (96), diuretics (81), angiotensin II receptor blockers (62), antidepressants (54), opiates (53), nitrates (51), calcium channel blockers (47)
Bleeding (non-gastro intestinal) (e.g. haematuria, epistaxis, anaemia)	162 (10)	Vitamin K antagonists (102), antiplatelets (74), heparins (10)
Gastrointestinal complication/bleeding (e.g. ulcer, gastritis, melena)	139 (8)	Antiplatelets (87), vitamin K antagonists (71), NSAIDs (12)
Congestive heart failure	122 (7)	Beta blockers (53), calcium channel blockers (36), diuretics (32), corticosteroids (13), ACE-inhibitors (7), NSAIDs (4)
Arrhythmia (e.g. bradycardia, atrial fibrillation)	82 (5)	Beta blockers (40), antiarrhythmics (32), antidepressants (7), ACE-inhibitors (7)
Renal insufficiency/electrolyte imbalance (e.g. hypokalaemia, hyponatremia)	85 (5)	Diuretics (59), ACE-inhibitors (21), proton pump inhibitors (9), angiotensin II receptor blockers (9), NSAIDs (7)
Nausea/vomiting/diarrhoea/gastroenteritis	57 (3)	Proton pump inhibitors (15), opiates (14), antibiotics (13), corticosteroids (8), laxatives (7)
Ileus/constipation	44 (3)	Opiates (22), calcium channel blockers (20), beta blockers (13), antidepressants (8), proton pump inhibitors (8)
Chest pain	42 (2)	ACE-inhibitors (25), beta blockers (7), antiplatelets (5), alpha blockers (4)
Confusion/drowsiness/delirium	32 (2)	Opiates (13), dopaminergics (12), benzodiazepines (9), antidepressants (7), antiepileptics (4), antipsychotics (4)
Hypoglycaemia or hyperglycaemia	30 (2)	Insulin (21), oral antihyperglycemics (12)
Other (e.g. cardiovascular events, dehydration, intoxications)	146 (9)	Diuretics (34), corticosteroids (28), dopaminergics (14), antiplatelets (14), ACE-inhibitors (12), vitamin K antagonists (11), opiates (9), beta blockers (8), digoxin (7), NSAIDs (6), antiepileptics (6), antidepressants (6), calcium channel blockers (6)

ACE angiotensin-converting enzyme; GI gastro intestinal; NSAID non-steroidal anti-inflammatory drug.

[a] In one medication-related hospitalisation (total n=1536) more than one cause could be identified (total n=1687).

[b] One medication-related hospitalisation (total n=1536) could be associated with more than one medication (total n= 2750).

[c] Also includes patients with a fracture following collapse.

The types of medication-related hospitalisations and associated medications are reported in Table 4. Most frequent hospitalisations were those related to infections, falls and bleeding. Most medication-related hospitalisations were associated with a single medication, but those related to falls and constipation were often associated with a combination of medications.

The sensitivity analysis excluding medication-related hospitalisations related to infections, showed similar adjusted rate ratios of the intervention compared to *usual care* and *usual care plus*: 0.70 (95% CI 0.55–0.89) and 0.97 (95% CI 0.68–1.39), respectively.

Secondary outcomes

DBI

The DBI scores in all groups did not differ. When comparing the treatment effects on DBI scores per patient with a mixed model, we found no differences between the intervention group and both *usual care* groups (Table 5 and 6). The subanalysis, excluding patients with a DBI score of 0 in the pre year, did not alter the results.

Costs

Mixed model comparison of average direct healthcare costs revealed no differences between the intervention group and *usual care* group in primary care costs, secondary care costs and medication costs (Table 7 and 8). Also, when looking more closely into secondary healthcare costs related to hospitalisations, we found no differences: adjusted ratio 0.82 (95% CI 0.64–1.06).

Table 5: Unadjusted Drug Burden Index[a] per high-risk patient

Study group	**INTERVENTION**		**USUAL CARE**		**USUAL CARE PLUS**	
Study period	**PRE**	**POST**	**PRE**	**POST**	**PRE**	**POST**
High-risk patients, *n*[b]	3,106	3,091	3,232	3,292	3,185	2,974
DBI per patient, *mean (SD)*	0.48 (0.64)	0.50 (0.63)	0.53 (0.63)	0.54 (0.64)	0.78 (0.68)	0.56 (0.67)
DBI categorised, *n patients (%)*						
0	1,485 (48)	1,425 (46)	1,379 (43)	1,354 (41)	1,331 (42)	1,233 (42)
0-1	1,158 (37)	1,173 (38)	1,311 (41)	1,342 (41)	1,218 (38)	1,177 (40)
>1	463 (15)	493 (16)	542 (17)	596 (18)	636 (20)	564 (19)

DBI Drug Burden Index; SD standard deviation

[a] Including all chronically used anticholinergic or sedative medications, excluding ATC-D, ATC-L, ATC-P, ATC-S and ATC-V.[50]

[b] Due to missing data, not all high-risk patients as included in the primary outcome analyses were included here.

Table 6: Adjusted treatment effect on lowering DBIs in high-risk patients[a]

Comparison of treatment effects (95% confidence interval)		**p-value**
Intervention group vs. usual care group	-0.02 (-0.07 – 0.02)	0.291
Intervention group vs. usual care plus group	-0.01 (-0.06 – 0.04)	0.609

DBI Drug Burden Index

[a] Using a linear mixed model, see Appendix 1.

Table 7: Crude costs per high-risk patient, in euros

Study group	**INTERVENTION**		**USUAL CARE**	
Study period	**PRE**	**POST**	**PRE**	**POST**
High-risk patients, *n*[a]	2,525	2,574	2,553	2,474
Primary care costs[b], *median (IQR)*	403 (232 – 560)	428 (246 – 602)	422 (233 – 581)	364 (228 – 560)
Secondary care costs[c], *median (IQR)*	977 (188 – 3,359)	840 (122 – 3,249)	1,148 (191 – 4,269)	843 (93 – 3,545)
Medication costs[d], *median (IQR)*	841 (441 – 1,581)	868 (450 – 1,479)	857 (435 – 1,532)	749 (400 – 1,383)

IQR Inter Quartile Range

[a] Due to using a different data source for these analyses, not all high-risk patients included in the primary outcome analyses were included here.

[b] Primary healthcare costs included consultations and home visits by GPs and general practice-based nurse specialists, additional proceedings, module fees and registration fees.

[c] Secondary healthcare costs included hospital care as remunerated in DOTs (these are defined remunerations for combinations of diagnoses and treatments, that particularly last longer than one day but maximally a year). Only those DOTs starting during the study period were included.

[d] Medication costs included medications prescribed both in primary and secondary care.

Table 8: Adjusted ratios of average healthcare costs in high-risk patients[a]

Ratio of healthcare costs in intervention group vs. usual care group (95% confidence interval)		**p-value**
Primary care costs	1.08 (0.99 – 1.17)	0.073
Secondary care costs	0.92 (0.65 – 1.29)	0.622
Medication costs	1.04 (0.98 – 1.10)	0.172

[a] Using linear mixed models, see Appendix 1.

DISCUSSION

This study demonstrates a lower rate of medication-related hospitalisations among high-risk patients in general practices with fully integrated NDPs compared to *usual care*. No difference with *usual care plus* practices was found. Also, no differences in DBI scores nor in direct healthcare costs were found. Despite the absence of an effect on DBI scores and costs, results on medication-related hospitalisations suggest that in order to improve medication safety, the current model of pharmaceutical care provision should be replaced by new concepts of pharmaceutical care provision, centred around full integration of pharmaceutical care in medical practice – such as the NDP care model.

Comparison with existing literature

To our knowledge, this is the first study evaluating the effect of NDPs integrated in general practice on medication-related hospitalisations. Studies measuring the impact of such NDP-led care on relevant clinical patient outcomes are sparse. Lowrie *et al*. reported no effect of NDP-led care on death or hospitalisation in patients with heart failure.[34] Maybe this lack of effect was due to the fact that this intervention had insufficient patient follow-up. Moreover, NDPs in Lowries study, so-called *non-specialist pharmacists*, only received a very short additional training.

Studies measuring the impact of NDP-led care on surrogate clinical outcomes (e.g. glycated haemoglobin, blood pressure and cholesterol levels) and the quality of medication use (e.g. appropriateness of prescribing and medication adherence) are more frequent, and generally demonstrate positive effects.[7,35] However, heterogeneity amongst interventions complicates valid comparison of results. Studies about specific interventions and targeting specific medications or specific conditions are more likely to show positive results than studies on complex interventions targeting multiple medications and/or multiple conditions.[36-40] We think, however, that comprehensive medication therapy management is typically needed in high-risk patients, in whom multiple medications and conditions impact each other.[41]

Measuring clinical effects of such NDP-led comprehensive medication therapy management, a complex intervention, is challenging. Full integration of NDPs in general practice seems key to enlarge effect on pharmaceutical care outcomes.[35] Also, taking integral responsibility for the patient's pharmacotherapy and providing follow-up consultations to monitor the patient is recognised to be essential.[42,43] Furthermore, education is needed to equip the NDPs with the necessary clinical knowledge, consultation skills and experience to work as part of the multidisciplinary general practice team.[44,45] We believe that these 3 aspects (the NDPs being fully integrated in the team, taking integral responsibility for the patient's pharmacotherapy and participating in additional education) enable the NDPs to significantly improve the quality of pharmaceutical care.

Interpretation of results

Differences in rates of medication-related hospitalisations should be interpreted with caution. We found a stronger increase of total acute hospitalisations in the *usual care* group than in the other two groups, when comparing the intervention year to the baseline year (see Table 2). Even after detailed analysis of the data, we could not explain this difference. It might be related to the practice population, or simply to chance. Nonetheless, as the number of total acute hospitalisations is closely related to the primary outcome, this quite marked increase of hospitalisations in the *usual care* group could have influenced (part of) the intervention effect.

Interestingly, medication-related hospitalisation outcomes in intervention and *usual care plus* practices did not differ. We think this is related to characteristics of the *usual care plus* practices that we did not take into account at the time of inclusion. The additional training in performing clinical medication review (the inclusion criterion for *usual care plus*) appeared to be no standalone feature but rather an expression of an already highly integrated pharmaceutical care-model. In the *usual care plus* practices, there was a strong pre-existing collaboration between GPs and community pharmacists, with joint information systems, regular (in)formal face-to-face meetings between GPs and pharmacists and a common focus upon medication therapy management. The main difference with the NDP-intervention practices was that in these practices NDPs were formally co-located in general practices and extensively trained in clinical knowledge, skills and communication.[12]

Regarding the DBI, we found no difference between the intervention and control groups. When interpreting this finding, several issues should be taken into account. First, due to technical difficulties in extracting the medications used per patient, we had missing data on DBI scores in both the pre and post period (in 17% and 18% of high-risk patients, respectively). Such large proportions of missing data put the comparison of DBIs at risk, minimising chances to find small differences. Second, we included all high-risk patients in the analysis, while not all patients received the intervention by the NDP, possibly diluting a potential effect.

Few studies used DBI-scores to evaluate effects of NDP-led interventions. A study in the Netherlands, researching effects of an intervention by a community pharmacist in collaboration with a GP, did also not find an effect on DBI-scores – even while this intervention was specifically tailored on improving the DBI.[26] On the contrary, 2 studies from Australia did find positive effects on DBI-scores following medication therapy management interventions by pharmacists in collaboration with GPs.[46,47] However, in 1 of these studies[46], total group effects were researched instead of an in-patient lowering of DBIs. The other study[47] did report an in-patient decrease of DBI-scores, but this reduction of 0.12 did not meet the 0.5 reduction we consider clinically relevant. So, effect of NDP-led care on reducing DBI-scores remains subject of research.

Regarding costs, we hypothesised in advance to find a shift in costs from secondary to primary care in intervention practices compared to *usual care*, as we expected fewer medication-related hospitalisations. However, the cost comparison

did not confirm this hypothesis. This might be related to the fact that we used cost reimbursement data of a health insurance company as the basis of the calculations. We could not individually link these data to our general practice database, hence individual cost comparison of medication-related hospitalisations was impossible. In addition, although such cost reimbursement data reflect actual expenditures, they do not precisely cover the actual provided care – at least not regarding secondary healthcare costs. In the Netherlands, secondary care is remunerated through so-called *DOTs* (defined remunerations for combinations of diagnoses and treatments), instead of through individual medical actions. Hence, any existing differences might be blurred, as remuneration data lack precision. This idea, that in our study actual existing differences might be blurred, is further supported by 2 studies reporting an (expected) reduction of costs after introduction of an NDP in primary care in the UK, based on measurements of actual used care-elements.[48,49] Based only on prescribing changes, Snell *et al*.[48] expected reductions in costs of about £90 (equivalent to about €99) per high-risk patient per year (resulting from a total of £46,000 costs savings and £9000 additionally spent on medication after introduction of NDPs in primary care). Including total primary care costs and taking investments into account, Bush *et al*.[49] reported that every £1 invested in NDP-care, would result in £4.73 savings; in total, saving on average £3052 per GP practice per month (about €3364). Few studies reporting on cost-effects of NDP-led care suggest that NDP-led care might reduce costs. We did not find such results, maybe due to the fact that we used cost reimbursement data instead of measurements of actual used care-elements. Future research including cost-effectiveness analyses may provide more insight.

Strengths and limitations

This study has several strengths. We covered a large patient population with in total 11 928 registered high-risk patients. The intervention was multifaceted, tailored to the needs of each general practice and performed in a real-life setting. We used a structured methodology to systematically identify medication-related hospitalisations (assessment by a multidisciplinary team, consensus meetings with experts and cross-checking of data) to limit the risk of subjectivity in judgement.

This study also has several limitations. The fact that we chose not to randomise puts the comparison at risk of bias, even though we corrected for several relevant baseline differences. We think, however, that randomisation would have put optimal performance of the NDPs at risk. A second limitation concerns the sample size calculation of the study. During our study, a new study reported an increased prevalence of medication-related hospitalisations: 10.4%[2] instead of the 4.5%[28] we used in our original calculations. In addition, the original sample size calculation was not adjusted for clustering. Future research should take these 2 elements into account. Third, regarding the primary outcome, the hospitalisations we identified were *possibly* medication-related, including various levels of certainty about the causality. To assess

definite causality (if that is even possible), data including interviews with involved doctors, pharmacists and patients would have been necessary.[50] In addition, we could not measure *preventability* of the medication-related hospitalisations due to the nature of available data. Fourth, flaws in the electronic medical records extraction resulted in the omission of an unknown number of deceased patients in our database. As the number of high-risk patients is the numerator in our primary outcome, these missing data may influence the absolute rates of medication-related hospitalisations among elderly with polypharmacy. However, as data collection was similar in all study groups, these missing data probably did not affect the between-group comparison. Fifth, we included all high-risk patients registered in the participating practices, instead of only patients who had a clinical medication review or consultation with the NDP. This might have diluted the measured effect. Last, the intervention period lasted only a year. Despite the fact that we added in advance a 3-month start-up period, this year might have been too short to show the full potential of the intervention.

Future research

Integration seems key to improve the quality of pharmaceutical care. This may either be done by introduction of the NDP, or by developing more *usual care plus* practices. The latter would involve investment in existing infrastructure and collaboration, which is likely to be a time consuming and nontransparent improvement process. In contrast, the integration of an NDP in general practice is a well described organisational intervention with a potentially rapid implementation process. Cost-effectiveness of both models should be investigated and implementation research should be continued. An intervention study with matched control patients could provide more insight into the effects of NDP-led care.

CONCLUSION

In practices with NDP-led care, we found a lower rate of medication-related hospitalisations compared to *usual care*. No difference with *usual care plus* was found. High-risk patients will benefit most from integrated pharmaceutical care. Full integration of an NDP in clinical practice, adequate training and integral responsibility are key conditions of success for this new concept of pharmaceutical care provision.

What is already known about this subject

- Elderly patients with polypharmacy are at risk of medication-related morbidity and mortality.
- Non-dispensing pharmacists integrated in general practice are reported to improve safety and effectiveness of pharmacotherapy in single diseases and proxy endpoints.

What this study adds

- This study demonstrates a lower risk on medication-related hospitalisations in patients with non-dispending pharmacist-led care compared to usual care.
- To optimise the quality of pharmacotherapy, pharmaceutical care needs to be fully integrated in primary care.

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ONLINE SUPPLEMENT S1 – APPENDIX 1

To compare treatment-effects on DBI between intervention and both control groups, a linear mixed model was used. A reduction of 0.5 or more was considered clinically relevant, hence a treatment-effect of at least -0.5 in comparison to both control groups was looked for. So, the DBI after the intervention period was modelled as a function of the DBI before the study period. The intervention effect was assessed by adding the variable 'study group' to the model. We adjusted for patients' age, sex, number of chronically used medications and number of comorbidities, degree of urbanisation and socioeconomic status in the same way as in the primary outcome model. Adjustment for clustering at practice level was also done as in the primary outcome model, by including a random intercept.

To compare costs in high-risk patients between the intervention and the usual care control group, for each cost category (i.e. direct primary care costs, direct secondary care costs and medication costs) a linear mixed model was used. First, costs were log-transformed, and to be able to include patients with 'no costs' (outcome zero), zeroes were replaced by a low amount of costs (randomly set at €0,55; shifting to other amounts did not alter the results). The linear mixed models then included adjustment for clustering and adjustment for measuring patients in both the baseline and intervention period, in the same way as done in the primary outcome model. The intervention effect was assessed, also similarly to the primary outcome model, with the interaction between study group and study period. Only adjustment for potential confounders differed slightly from the primary outcome model, as the insurance data did not cover all needed data: we again included age, sex, number of chronically used medications and socio-economic status, but could not include the number of comorbidities and the degree of urbanisation.

Chapter 4

Non-dispensing pharmacist integrated in the primary care team: effect on the quality of physician's prescribing, a non-randomised comparative study

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ABSTRACT

Background Especially in elderly with polypharmacy, medication can do harm. Clinical pharmacists integrated in primary care teams might improve quality of pharmaceutical care.

Objective To assess the effect of non-dispensing clinical pharmacists integrated in primary care teams on general practitioners' prescribing quality.

Setting This study was conducted in 25 primary care practices in the Netherlands.

Methods Non-randomised, controlled, multi-centre, complex intervention study with pre-post comparison. First, we identified potential prescribing quality indicators from the literature and assessed their feasibility, validity, acceptability, reliability and sensitivity to change. Also, an expert panel assessed the indicators' health impact. Next, using the final set of indicators, we measured the quality of prescribing in practices where non-dispensing pharmacists were integrated in the team (intervention group) compared to usual care (two control groups). Data were extracted anonymously from the healthcare records. Comparisons were made using mixed models correcting for potential confounders.

Main outcome measure Quality of prescribing, measured with prescribing quality indicators.

Results Of 388 eligible indicators reported in the literature we selected 8. In addition, two more indicators relevant for Dutch general practice were formulated by an expert panel. Scores on all 10 indicators improved in the intervention group after introduction of the non-dispensing pharmacist. However, when compared to control groups, prescribing quality improved solely on the indicator measuring monitoring of the renal function in patients using antihypertensive medication: relative risk of a monitored renal function in the intervention group compared to usual care: 1.03 (95% CI 1.01–1.05, p-value 0.010) and compared to usual care plus: 1.04 (1.01–1.06, p-value 0.004).

Conclusion This study did not demonstrate a consistent effect of the introduction of non-dispensing clinical pharmacists in the primary care team on the quality of physician's prescribing.

This study is part of the POINT-study, which was registered at The Netherlands National Trial Register with trial registration number NTR-4389.

Keywords Non-dispensing pharmacist, Pharmaceutical care, Prescribing, Process indicator, Quality

Impacts on practice

- Prescribing indicators might not capture the full effect of non-dispensing pharmacists integrated in primary care teams, when interventions are not specifically targeted upon these indicators.
- A non-dispensing pharmacist integrated in the primary care team improves the monitoring of renal function in patients using diuretics, compared to usual care.
- Future studies on complex, generic interventions should use a mixed methods design to evaluate the effects on quality of care.

BACKGROUND

To prevent medication-related harm in the expanding group of elderly with polypharmacy[1, 2], various innovations in the organisation of pharmaceutical care are currently implemented. Integration of clinical pharmacists in primary care teams potentially improves the quality and safety of pharmacotherapy and is currently being evaluated in various formats in Canada, Australia, the United Kingdom and Ireland[3, 4, 5, 6]. Also in the Netherlands a *non-dispensing clinical pharmacist* (*NDP*), providing patient-centred pharmaceutical care in close collaboration with the general practitioner (GP), was recently introduced[7].

Clinical pharmacy services provided by such pharmacists in primary care can be either *disease-specific*, tailored to a patient population with a specific medical condition; or *patient-centred*, when provided to a more heterogeneous patient population, such as patients with polypharmacy, patients prescribed at least one medication or patients at risk of medication problems[8].

So far, largest impact of this new care model was found when pharmacists were fully integrated into primary care teams, providing multifaceted interventions and follow up to patients, and with the possibility of face-to-face communication between pharmacist and GP[9, 10]. Effects are mainly found on reducing drug therapy problems and improving proxy outcomes (such as blood pressure control or decreasing HbA1c levels). Yet, effects on prescription quality indicators, commonly used for quality monitoring on practice level by regulators and insurers, is scarce.

Aim of the study

Despite the promising results, integration of pharmacists in primary care teams has not been adopted widely yet. In this study, we evaluated the effect of patient-centred care

delivered by NDPs integrated in primary care teams on medication safety on a practice level. Hereto, we compared NDP-led care with usual care on prescription outcomes, as indicator of quality of pharmaceutical patient care[11].

METHODS

This study was part of the Pharmacotherapy Optimisation through Integration of a Non-dispensing pharmacist in primary care Teams (POINT) study[7]: a non-randomised, controlled intervention study, comparing NDP-led care (intervention group) with two current models of pharmaceutical care (control groups).

The integration of an NDP in primary care teams should be considered as a complex intervention, as it comprises of different interacting components, targets multiple levels of organisation, has variable outcomes and needs to be tailored to the context in which it is implemented[12, 13]. Hence, its evaluation should be multidimensional, including a theoretical framework underlying the expected intervention effect, and assessment of feasibility, effectiveness and related process changes. The theoretical framework as well as results on feasibility and effectiveness have been described elsewhere[14, 15, 16]; in the present study we focus on the process changes as measured with indicators that can be derived from computerised healthcare records.

Ethics approval

The POINT protocol was reviewed by the Medical Ethical Committee of the University Medical Center Utrecht and was deemed not eligible for full assessment (METC protocol number 13-432C). Patient data were extracted anonymously, according to data protection regulations.

Intervention and control groups

For the POINT study, ten (PharmD) pharmacists were trained as NDPs in a 15-months training program[17]. These NDPs were attached to general practices, collaborating closely with the GPs while being fully integrated in the team. Their key activities were both on a patient level, providing clinical medication reviews and patient consultations for medication problems, as well as on a practice level, educating staff and implementing quality improvement projects. For these quality improvement projects, the NDPs were allowed to select different topics, tailored to the needs of the practice. The NDPs mainly focussed on care for elderly with polypharmacy, but provided pharmaceutical care for younger patients or those with less medications as well (especially in improvement projects). Their role was allowed to evolve during the trial and, if needed, to be adjusted to the needs of daily practice. Most NDPs were relatively at the beginning of their career, with working experience varying from less than 1 year (n = 3), 1–3 years (n = 5)

and between 5 and 10 years (n = 2); mainly in community pharmacies (n = 9). The NDPs were blinded for outcome measures (except for the primary outcome: medication-related hospital admissions) during the study period.

Intervention group practices were included only when they were explicitly willing to host an NDP, as willingness of all participating parties to improve pharmaceutical patient care has been recognised as a key condition for successfully implementing an NDP in primary care[3].

Two control groups consisted of the "usual care group", in which pharmaceutical care was provided by local community pharmacists, and the "usual care plus group", in which community pharmacists had an additional training[18, 19] in performing clinical medication reviews. Control group practices were matched to the practices in the intervention group as much as possible, with regard to practice size, degree of urbanisation, socioeconomic status and patients' age distribution. Full details of the design of the POINT-study have been described elsewhere[7].

Setting and patients

This study was performed in all 25 general practices that participated in the POINT-study. Patients registered in one of these practices, aged 50 years or older and using at least one type of chronic medication (defined as having 3 or more prescriptions per year of the same ATC-3-level medication) were included.

Study period

We did a pre-post comparison, comparing the prescribing quality during 2013 (pre period) with the prescribing quality in the intervention year, starting June 1st 2014 until May 31st 2015 (post period). The NDPs worked full time in the practices during the intervention year.

Outcome: quality of prescribing

To evaluate the GPs' prescribing quality, we used process indicators, as these have been reported most sensitive to differences in quality of care: they are easier to interpret than outcome indicators, and are usually more sensitive to small differences[20].

Selection of indicators

We collected indicators from literature and policy documents. Indicators were assessed step-wise, including assessment of feasibility, validity, acceptability, reliability and sensitivity to change (Box 1)[11] and health impact. Additional indicators were formulated if needed. For details of the selection procedure, see Online Supplement 1.

Box 1. Criteria that quality indicators were assessed on[11]

Criteria	Description
Feasibility	Whether the data needed to calculate the indicator were available in our database
Validity	Whether the content of the indicator was clinically relevant, based upon current guidelines and scientific publications
Acceptability	Whether assessment of the indicator was acceptable for both the patient and the healthcare provider
Reliability	Whether other factors than the prescribing behaviour of the GP could influence the outcome of the indicator, and whether these factors would differ between the study groups
Sensitivity to change	Whether the indicator would detect changes and differences in quality of care

Data collection

We used anonymised healthcare data routinely extracted from the GPs' electronic medical records. These data comprised of basic patient characteristics, such as sex and age, and contained all prescribed medications, registered comorbidities and lab tests performed during the study periods. We also collected data on the five months prior to both periods, as for some indicators a timeframe of more than one year was required.

Sample size calculation

No separate sample size calculation was performed. Data were considered a secondary outcome measurement of the POINT-study, for which a sample size calculation on the primary outcome (medication-related hospitalisations) was performed[7]. Outcomes on the primary outcome have been described elsewhere[16].

Analysis

Scores on indicators are reported as percentages. Differences in scores over time were reported per study group, but as practices were not randomised, those differences should not be formally compared. Hence, performance per indicator was compared between study groups using mixed models. For a detailed description of the mixed models, see Online Supplement 2. The Consort-checklist for non-randomised trials was used for writing the manuscript (see Online Supplement 3)[21].

RESULTS

Indicators of prescribing quality

The PubMed-search yielded 42 articles, of which 16 were considered relevant. From these, 318 indicators were included. From professional and policy literature we collected an additional 141 indicators. After removing duplicates, 388 indicators remained for assessment, resulting in 8 eligible indicators (see Fig. 1). Of those, two concerned long-term medication use. Because of the nature of our intervention, we needed to alter the definition of 'long-term' used in these two indicators in order to enable the indicators to adequately capture change in prescribing quality.

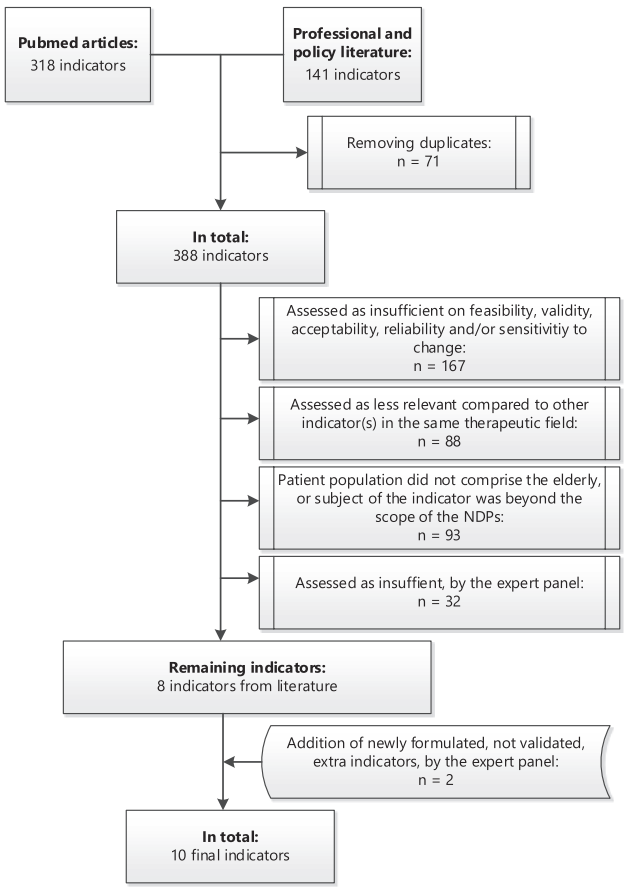

Fig. 1. Flowchart of assessment of indicators

Two additional indicators were formulated by the expert panel. The ten final indicators are summed in Box 2.

Box 2. Final set of prescribing quality indicators, per category.

Underprescribing[a]		
1.	PPIs and NSAIDs	Patients aged 70 years or older using non-selective NSAIDs (denominator), using a PPI (numerator)
2.	LDL in CVD history	Patients aged younger than 80 years, with a history of cardiovascular disease and at least one measurement of LDL (denominator), having their last LDL-measurement being 2.5 mmol/L or lower with or without statin treatment (numerator)
Dosing error[b]		
3.	HCT dose	Patients aged 80 years or older using hydrochlorothiazide (denominator), of which the dose is 25mg/day or higher (numerator)
4.	Digoxin dose	Patients aged 70 years or older and using digoxin (denominator), of which the dose is over 0.125mg/day (if aged 71-85 years) or over 0.0625mg/day (if aged 86+) (numerator)
Therapeutic duplication[b]		
5.	ACEi and ATII-RA	Patients using one or more antihypertensive medications on a chronic basis (denominator), who use both an ACE-inhibitor and an AT-II-antagonist chronically (numerator)
Contra-indicated[b]		
6.	NSAIDs in CVD history	Patients with a history of cardiovascular disease (denominator), using COX-2 selective NSAIDs (numerator)
Medication not effective[b]		
7.	Benzodiazepines	Patients aged 65 years or older (denominator), using benzodiazepines for >300 days per year (numerator)
Overprescribing[b]		
8.	Antidepressants	All patients (denominator), using antidepressants for >450 days during period of 17 months (numerator)
Inadequate monitoring[a]		
9.	Diuretics and renal function	Patients using diuretics and/or RAS-inhibitors (denominator), with known renal function and known potassium levels (numerator)
10.	Thyroid medication and function	Patients using thyroid medication (denominator), with known thyroid function (numerator)

NSAID Non Steroid Anti-Inflammatory Drug, PPI Proton Pump Inhibitor, LDL Low Density Lipoprotein, mg milligrams, ACEi Angiotensin-Converting Enzyme inhibitor, ATII-RA Angiotensin II type 2 receptor antagonist, CVD Cardiovascular Disease, COX-2 Cyclo-oxygenase-2, RAS Renin-Angiotensin System.
Although categories describe potential prescription errors, indicators are formulated as both undesirable care (and hence indeed potential erroneous prescribing) and desirable care (and hence potential correct prescribing):
[a] This category contains indicators representing desirable care, hence a higher score is generally preferable;
[b] This category contains indicators representing undesirable care, hence a lower score is generally preferable.
All indicators were assessed for the pre and the post period, selecting element of the indicator from that specific study period.
'Using' was defined as having one or more prescriptions of the medication named.
'Using on a chronic basis' was defined as having three or more prescriptions of the medication named.
Indicators No. 3. and 5. were formulated by the expert panel, and are hence not validated. Indicators No. 7. and 8. contain altered durations of medication use compared to the original indicators, in order to make them susceptible to eventual change.

Participating practices

One NDP stopped during the study period, so we evaluated prescribing quality of 9 practices in the intervention group. In the control groups, for the usual care group 10 practices and for the usual care plus group 6 practices were included. Intervention and control practices were comparable with respect to practice characteristics and patient demographics, except for practice size (see Table 1).

Fidelity of the intervention

All NDPs implemented quality improvement projects in their practices, but content and scheduling of these projects varied: some projects were implemented right after the NDPs started working in the practice, but others were (partly) implemented only two months before the intervention period ended. This may have limited their effect. The number of projects per practice ranged from 1 to 14 (median 10). Box 3 gives an overview of the covered topics. Six topics matched with clinical themes of the final indicator set.

Quality of prescribing

In the intervention group, all indicators of desirable prescribing improved, while those measuring undesirable prescribing decreased (Table 2). In the control groups comparable trends were seen, but not for all indicators (for details, see Online Supplement 4).

After correction for potential confounders and taking the baseline differences into account in mixed models, 4 out of 10 indicators differed between intervention and control group (Table 3, and described in detail in Online Supplement 4).

Table 1. Baseline characteristics of practices and patient populations

	INTERVENTION (n=9 practices)	**USUAL CARE** (n=10 practices)	**USUAL CARE PLUS** (n=6 practices)
Practice characteristics			
Patients aged ≥18 years, *median (IQR)*	8669 (4765 – 10,689)	5973 (5371 – 6646)	6907 (4474 – 13,981)
Patients aged ≥50 years and using ≥1 medication chronically, *median (IQR)*	1899 (1262 – 2301)	1711 (1211 – 2369)	1768 (1480 – 3888)
Degree of urbanisation[a], *mean ± SD (range)*	1.8±1.1 (1-4)	2.1±0.7 (1-3)	2.2±0.8 (1-3)
Socioeconomic status[b], *mean ± SD (range)*	0.9± 1.0 (-1.2-2.2)	0.6± 0.9 (-2.1-1.7)	0.6± 0.5 (0-1.2)
Healthcare centre, *n (%)*	7 (78)	7 (70)	3 (50)
Indoor pharmacy[c], *n (%)*	6 (67)	6 (60)	4 (67)
Patient characteristics			
Patients aged ≥50 years and using ≥1 medication chronically, *n*	15,864	17,609	14,459
Male sex, *n (%)*	7166 (45.2)	7966 (45.2)	6564 (45.4)
Age in years, *median (IQR)*	63 (55 – 72)	63 (55 – 72)	63 (55 – 71)
Number of chronic medications per patient, *median (IQR)*	3 (2 – 5)	3 (1 – 5)	3 (2 – 5)
Number of comorbidities[d] per patient, *median (IQR)*	2 (1 – 4)	2 (1 – 4)	3 (1 – 4)

n number, IQR inter quartile range, SD standard deviation

[a] Using a five point scale of degree of urbanisation (in which 1 = highly urbanised area, 5 = rural area)[22]

[b] Data from Dutch Social and Cultural Planning Office, using status scores of zip code area of the general practice (in which a higher score represents a higher status)[23]

[c] Being a pharmacy located in the same building as where the general practice is located.

[d] Using the UK Quality and Outcomes Framework and overview of chronic diseases developed by the Dutch National Institute for health and Environment[24, 25]

Box 3. Topics of quality improvement projects, implemented by the NDPs (n)

	NDPs that implemented the project *(n)*
Projects that intervened on specific quality prescribing	
Underprescribing of PPIs in patients using NSAIDs[a]	6
Underprescribing of inhalation corticosteroids in patients with asthma	5
Underprescribing of statins in patients with a history of cardiovascular disease[a]	4
Underprescribing of calcium and vitamin d in patients using bisphosphonates	4
Underprescribing of vitamin D in patients aged over 70 years	4
Therapeutic duplication of ACEi and AT-II antagonist[a]	6
Contra-indicated NSAIDS in patients with a history of cardiovascular disease[a]	8
Overuse of benzodiazepines[a]	4
Overuse of bisphosphonates	4
Overuse of paracetamol-codeine	1
Overprescribing of antidepressants[a]	1
Overprescribing of alpha-blockers in patients with LUTS	6
Overprescribing of acetylsalicylic acid for primary cardiovascular risk prevention	5
Overprescribing of inhalation corticosteroids in patients with COPD	1
Overprescribing of triptans and starting preventive medication in patients with chronic migraine headache	5
Overprescribing of PPIs	3
Second-line antibiotics	1
First-choice RAS-acting agents in new users	1
Projects that intervened on comprehensive quality prescribing	
Medication reconciliation after hospital discharge, taking all used medications into account	5
Compliance with prescribing quality indicators measuring effective prescribing in primary care, defined by the Dutch Institute for Rational Use of Medicine (IVM)	2
Projects that intervened on organisation of care, underlying quality prescribing	
Optimise the organisation of referring to fellow GP with additional expertise in a specific (medication) field	1
Optimise the exchange of information on medication prescriptions and medication lists between care providers	2
Optimise registration of contra indications in the medical record	1
Optimise the exchange of information on renal function between GP practice and community pharmacy	1

[a] Topic is represented in the eventual selection of quality prescribing indicators

Table 2. Quality indicators of prescribing: percentages per study group and per study period and delta, uncorrected data

Study group	INTERVENTION			USUAL CARE			USUAL CARE PLUS		
Study period[a]	pre	post	Δ	pre	post	Δ	pre	post	Δ
Underprescribing [b]									
1. PPIs and NSAIDs	634 / 769 (82.4)	596 / 710 (83.9)	+1.5	621 / 766 (81.1)	619 / 714 (86.7)	+5.6	619 / 690 (89.7)	551 / 595 (92.6)	+2.9
2. LDL in CVD history	651 / 1270 (51.3)	798 / 1416 (56.4)	+5.1	757 / 1307 (57.9)	818 / 1490 (54.9)	-3.0	602 / 979 (61.5)	648 / 1124 (57.7)	-3.8
Dosing error [c]									
3. HCT dose	127 / 499 (25.5)	95 / 453 (21.0)	-4.5	149 / 525 (28.4)	124 / 509 (24.4)	-4.0	114 / 372 (30.6)	89 / 316 (28.2)	-2.5
4. Digoxin dose	58 / 175 (33.1)	48 / 182 (26.4)	-6.8	47 / 128 (36.7)	44 / 150 (29.3)	-7.4	81 / 212 (38.2)	57 / 219 (26.0)	-12.2
Therapeutic duplication [c]									
5. ACEi and ATII-RA	89 / 5858 (1.5)	77 / 6336 (1.2)	-0.3	71 / 6664 (1.1)	72 / 7281 (1.0)	-0.1	131 / 6223 (2.1)	105 / 6396 (1.6)	-0.5
Contra-indicated [c]									
6. NSAIDs in CVD history	420 / 3097 (13.6)	301 / 3378 (8.9)	-4.7	378 / 3398 (11.1)	264 / 3815 (6.9)	-4.2	365 / 2678 (13.6)	202 / 2893 (7.0)	-6.6
Medication not effective [c]									
7. Benzodiazepines	408 / 7391 (5.5)	389 / 7320 (5.3)	-0.2	401 / 7750 (5.2)	402 / 7645 (5.3)	+0.1	316 / 6527 (4.8)	342 / 6332 (5.4)	+0.6
Overprescribing [c]									
8. Antidepressants	621 / 15864 (3.9)	613 / 15935 (3.8)	-0.1	667 / 17609 (3.8)	658 / 17693 (3.7)	-0.1	709 / 14459 (4.9)	699 / 14283 (4.9)	0.0
Inadequate monitoring [b]									
9. Diuretics monitoring	4401 / 6697 (65.7)	4897 / 7098 (69.0)	+3.3	4735 / 7384 (64.1)	5079 / 7815 (65.0)	+0.9	4275 / 6620 (64.6)	4402 / 6751 (65.2)	+0.6
10. Thyroid monitoring	629 / 968 (65.0)	665 / 996 (66.8)	+1.8	682 / 1023 (66.7)	721 / 1084 (66.5)	-0.2	608 / 925 (65.7)	661 / 979 (67.5)	+1.8

n number, Δ difference, PPI Proton Pump Inhibitor, NSAID Non Steroid Anti-Inflammatory Drug, LDL Low Density Lipoprotein, CVD Cardiovascular Disease, HCT Hydrochlorothiazide, ACEi Angiotensin-Converting Enzyme inhibitor, ATII-RA Angiotensin II type 2 receptor antagonist.
Indicators are represented as n numerator / n denominator (%) for the pre- and post-period, and for the % the difference between both periods is given. No correction for potential confounders was done

[a] Pre-period: the year prior to the intervention year, namely 1 January 2013 until 31 December 2013; Post-period: the year in which the intervention was conducted, namely 1 June 2014 until 31 May 2015.

[b] This category contains indicators representing desirable care, hence on average applies: the higher the percentage, the better

[c] This category contains indicators representing undesirable care, hence on average applies: the lower the percentage, the better

Table 3. Quality indicators of prescribing in the intervention year: comparison between intervention and control groups, corrected for potential confounders (Relative Risks, 95% CI, p-value)

	Intervention vs. usual care in post-year		**Intervention vs. usual care plus in post-year**	
Underprescribing [a]				
1. PPIs and NSAIDs	0.96 (0.92 - 1.00)	0.066	**0.91 (0.87 – 0.94)**	<0.001
2. LDL in CVD history	1.02 (0.96 - 1.09)	0.504	0.99 (0.92 - 1.05)	0.661
Dosing error [b]				
3. HCT dose	0.85 (0.60 - 1.21)	0.373	*0.71 (0.52 - 0.97)*	0.030
4. Digoxin dose	0.92 (0.65 - 1.31)	0.652	1.07 (0.67 - 1.70)	0.780
Therapeutic dulication [b]				
5. ACEi and ATII-RA	1.24 (0.88 - 1.75)	0.223	0.94 (0.58 - 1.54)	0.808
Contra-indicated [b]				
6. NSAIDs in CVD history	**1.27 (1.01 - 1.61)**	0.044	**1.33 (1.05 - 1.69)**	0.019
Medication not effective [b]				
7. Benzodiazepines	1.04 (0.78 - 1.39)	0.797	1.03 (0.77 - 1.38)	0.849
Overprescribing [b]				
8. Antidepressants	1.03 (0.83 - 1.28)	0.791	0.78 (0.59 - 1.03)	0.077
Inadequate monitoring [a]				
9. Diuretics monitoring	*1.03 (1.01 - 1.05)*	0.010	*1.04 (1.01 - 1.06)*	0.004
10. Thyroid monitoring	1.00 (0.94 - 1.06)	0.873	0.99 (0.93 - 1.05)	0.697

Differences on scores of indicators are represented as adjusted relative risks with corresponding 95% confidence intervals and p-values. Numbers result from the mixed models, correcting for potential confounders (on patient level: age, sex, the number of medications used and the number of comorbidities; on practice level: socioeconomic status and degree of urbanisation) and if needed, correction for clustering on practice level using random intercepts

[a] Indicator represents desirable care, hence a corrected relative risk greater than 1 resembles a positive intervention effect compared to the control group (in italics if statistically significant), and a relative risk below 1 resembles a negative intervention effect compared to the control group (in bold if statistically significant).

[b] Indicator represents undesirable care, hence a corrected relative risk lower than 1 resembles a positive intervention effect compared to the control group (in italics if statistically significant), and a relative risk greater than 1 resembles a negative intervention effect compared to the control group (in bold if statistically significant).

DISCUSSION

We assessed the effect of NDPs integrated in primary care teams on the quality of GP prescribing, using 10 selected indicators of prescribing quality. Although the scores of all quality indicators improved in the intervention group, and not in the control groups, we could not demonstrate a consistent favourable effect of NDP introduction on prescribing quality after correction for baseline differences and potential confounders.

Comparison with existing literature

To our knowledge, only few studies have used process indicators to assess effects of integrating an NDP in primary care teams. In Canada, the effect of integrating a team of a pharmacist and nurse practitioners in primary care was measured using indicators on quality of care for chronic disease management[26]. Most of these indicators concerned prescribing (for example: recommended aspirin in patients with coronary artery disease), but some regarded physical examinations (for example: feet examination in patients with diabetes). Comparable to our study, all indicators improved over time after introduction of the intervention, when examined within the intervention group alone (except for two indicators in which performance was considered relatively high already at baseline). In contrast to our study, the performance of the intervention group was subsequently compared to a control group using a composite indicator. This showed a result in favour of the intervention group. We did not use a composite indicator, as a composite is very dependent on the way it is constructed: differently constructed composite scores can even result into different conclusions being drawn about quality, especially when they include a wide range of medical conditions, different numbers of indicators triggered by a patient and when they include both frequently and more rarely triggered indicators[27].

In a United Kingdom-based study, the effect of a pharmacist-led information technology intervention in primary care on prescribing quality was assessed[28]. In comparison to a control group receiving only simple feedback, significant differences in favour of the intervention group for seven of the 12 measured indicators were found. This result may be explained by the fact that the pharmacist-led information technology intervention was specifically targeted on the measured indicators, while in our study NDP-led care was mainly broadly implemented: focussing on specific interventions can increase the potential to detect change. Although the quality improvement projects implemented by the NDPs were targeted at specific patients groups, the variation in projects among practices was still substantial (see Table 2). Although this variation was explicitly allowed, the resulting heterogeneity and dilution may explain the absence of a consistent effect on the prescribing quality indicators.

Interpretation of results

We did not find a consistent effect of the integration of NDPs in primary care teams on prescription indicators. Although prescription indicators are considered a suitable measurement for medication safety effects, they may be too specific to assess the true effect of a heterogeneous intervention such as patient-centred NDP-led care.

Still, we found some specific effects that resulted from the NDP intervention: in practices with an integrated NDP, the renal function was monitored more frequently in patients using antihypertensives, compared to in usual care practices. We think this is a result from the clinical medication reviews performed by NDPs, as renal function monitoring was not frequently part of the quality improvement projects. This finding adds to the evidence that the quality of clinical pharmacy services improves when the pharmacist is embedded in clinical practice: NDPs are fully integrated in primary care teams, whilst community pharmacists operate separately from general practice teams. This is also illustrated by a previous finding that recommendations given by NDPs were more frequently followed by GPs, compared to recommendations by community pharmacists[29].

In contrast, we found that in the intervention group patients with a history of cardiovascular disease were prescribed NSAIDs more often as compared to control groups. As almost all NDPs had the use of NSAIDs in CVD patients incorporated in their quality improvement projects (n = 8), this does appear as an unexpected negative outcome. However, we suggest this may be related to the composition of the indicator: whilst quality improvement projects were implemented *during* the intervention year, the indicator measured NSAID-use with a single prescription *at any time* in the intervention year. Hence, it could be that the indicator underestimated the intervention effect, as changes following interventions in patients *after* a first prescription were not captured by the indicator anymore.

Strengths and limitations

This study has several strengths. We thoroughly assessed a broad selection of indicators, in order to achieve a reliable set to measure the effect of a non-dispensing pharmacist in primary care teams on GPs' prescribing. Furthermore, the intervention was multifaceted and tailored to the practice and patients' needs, in a real-world clinical environment. Including patients on a practice level might increase generalisability of results.

Some limitations need to be taken into account as well. First of all, the fact that we—deliberately—chose not to randomise participating practices, may have biased the comparison between the study groups. We corrected for this using mixed models, adjusting for potential relevant baseline characteristics, however bias can't be fully ruled out.

Second, two limitations concern the use of indicators to measure quality. These limitations are in fact characteristics of indicators that are important to be aware of

when interpreting data on indicators, and hence are more a general constraint of using indicators as outcome measurement rather than a specific limitation of this study. First, an indicator can measure only a part of the care provided; it will never reflect the total quality of care. By selecting a *set* of indicators, we tried to gain a wider insight into the quality of prescribing during the provision of NDP-led pharmaceutical care; however, it is still possible that pharmaceutical care improved despite the fact that we couldn't measure it. Second, evidence based practice requires personalised decisions, sometimes deviating from guidelines. Therefore, optimal prescription outcomes for individual patients may not be optimally reflected in mean indicator scores: "the higher (or the lower) score the better" may not be the aim for every individual[30].

Last, limitations concerning the use of routine healthcare data need to be discussed. First, routine healthcare data are registered for healthcare use, not for research purposes. If data are not registered by GPs, they cannot be measured when using routine healthcare data[31]. Hence, they may reflect quality of registration more than quality of care provided. Second, as data of all patients registered in the practice are extracted, the problem of missing values arises as patients can 'enter' the dataset when newly registering and 'leave' the dataset when deregistering. Overall, mixed models can handle missing data quite well, but this might still influence our findings. In line with this limitation is the problem of populations changing over time, which changes the case mix of practices. If characteristics of this case mix are related to the indicator, this might influence indicator findings. We tried to exclude such influence as much as possible during the assessment of indicators, however it might still be present to some extent[32]. Another problem of using data of *all* patients registered in the practice is that a final intervention effect might be diluted: in the intervention group, we could not distinguish patients who had received an NDP-led intervention from patients who had no NDP-led intervention. Especially our choice to include a rather broad patient population (aged 50 years and older, using one or more chronic medications) might add to this potential dilution phenomenon. However, as we wanted to measure the complete intervention effect, we preferred this broader patient population over a more detailed population such as patients aged 65 years and older, with polypharmacy), even though the latter may reduce the dilution problem.

So, using extensive data sets such as routinely collected healthcare data is not without limitations. We tried to counter these limitations by applying the same method in each study group and selecting indicators that are least susceptible to misinterpretation. However, we believe interpreting findings based on indicators measured in routine registry data remains uncertain. As a consequence, one should be aware of the above mentioned constraints that might put findings and comparisons at risk.

Implications for practice

This sub study, focused on measuring the impact of an NDP integrated in primary care with currently used quality indicators, showed no consistent effect of the intervention. Whether this indicates that the NDP does not adequately target the main prescribing problems in GP practice, or that the quality indicators used did not capture the NDP's effectiveness around these problems remains unsolved. Taking results from the other sub studies of the POINT project into account[16, 29, 33], the latter option may be plausible as our intervention should be considered as complex[13, 34].

CONCLUSION

We assessed the effect of NDPs integrated in primary care teams on the quality of prescribing by GPs, using a compiled set of indicators. Although scores on all prescribing quality indicators improved after introduction of the NDP, we could not demonstrate a consistent improvement in prescribing quality in comparison with usual pharmaceutical care. To evaluate such a complex intervention however, in addition to measuring effects on quality, the "how" and "why" of (absence) of effects needs to be addressed as well to fully understand these results.

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ONLINE SUPPLEMENT S1 – SELECTION OF INDICATORS

Literature search

To collect earlier reported indicators, we searched Pubmed and policy documents from government and professional organisations. We searched (mainly Dutch) reports and documents by the Dutch Ministry of Health, Welfare and Sport; the Royal Dutch Pharmacists Association (KNMP); the Dutch College of General Practitioners (NHG); and the Netherlands institute for health services research (NIVEL).

Search strategy:

indicator*[Title] AND prescri*[Title/Abstract] AND (general practice[Title/Abstract] OR primary care[Title/Abstract] OR family practice[Title/Abstract]) AND (full text[sb] AND English[lang]

Assessment of indicators

Duplicate indicators were removed. The remaining set of indicators was assessed stepwise. First, all indicators were evaluated on feasibility, validity, acceptability, reliability and sensitivity to change [11] (Box 1) by two researchers (ZdW and AH). Acceptability was not formally assessed, for all indicators were deemed acceptable as we planned to use routinely collected healthcare data – with no burden or whatsoever to the patient or the healthcare professional. If indicators did not fulfil one or more criteria, they were excluded from further analysis. Second, indicators meeting all criteria were compared on their clinical themes. In case of overlap, the indicator(s) deemed most clinically relevant was selected. Third, indicators concerning health topics beyond the scope of the NDP in primary care were excluded (for example: cancer treatment). Finally, the indicators were presented to an expert panel, consisting of two experienced GPs (NdW, DZ) and an experienced community pharmacist (MB). They selected the indicators with the highest health impact, defined as a combination of a substantial risk of patient harm, and high frequency of occurrence in daily GP practice. In addition, the expert panel checked whether all important aspects of pharmacotherapy were covered. If not, additional indicators were formulated by the expert panel to cover the missing themes, based on evidence and expert opinion. These were not formally validated.

ONLINE SUPPLEMENT S2 – DESCRIPTION OF THE MIXED MODELS

Per indicator, we assessed whether patients met the prescribing conditions (dichotomous outcome) in the intervention group compared to the control groups, using an interaction-term between study group and study period. We corrected for several potential confounders, both on the patient level (age, sex, the number of medications and the number of comorbidities), as well as on the practice level (socioeconomic status and degree of urbanisation). Also, we corrected for clustering on practice level using random intercepts, and for repeated patient measurements using random residuals. In case practice clustering-effects were absent, random intercepts were removed. Using a Poisson-distribution, log-link and Robust standard errors, the mixed models resulted in relative risks comparing performances between study groups on each indicator, with 95% confidence intervals.

Analyses were performed with SAS® software, Version 9.4 for Windows, and IBM SPSS Statistics for Windows, Version 23.0 (Armonk, NY).

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No*2
Title and abstract			
	1a	Identification as a randomised trial in the title	Title
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	Abstract
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	Background
	2b	Specific objectives or hypotheses	Aim of the study
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	Methods
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	n/a
Participants	4a	Eligibility criteria for participants	Setting and patients
	4b	Settings and locations where the data were collected	Setting and patients, Data collection
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Intervention and control groups
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	Outcome: quality of prescribing, Selection of indicators, Box 2, S1
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n/a

Sample size	7a	How sample size was determined	Sample size calculation
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n/a
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	n/a (Intervention and control groups)
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	n/a (Intervention and control groups)
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	n/a (Intervention and control groups)
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	n/a
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	Intervention and control groups
	11b	If relevant, description of the similarity of interventions	Intervention and control groups
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	Analysis, S2
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	n/a
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Table 2
	13b	For each group, losses and exclusions after randomisation, together with reasons	n/a (Strengths and limitations)
Recruitment	14a	Dates defining the periods of recruitment and follow-up	Study period

CONSORT 2010 checklist

	14b	Why the trial ended or was stopped	n/a
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Table 2
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Table 2 and 3
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Table 2 and 3
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	n/a
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	n/a
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	Strengths and limitations
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	Strengths and limitations
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	Interpretation of results
Other information			
Registration	23	Registration number and name of trial registry	Below keywords
Protocol	24	Where the full trial protocol can be accessed, if available	Intervention and control groups
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	Funding

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

*[2] Instead of page numbers the related section headings/subheadings where the sections/topics are reported are listed, as page numbers of the manuscript might change in the print.

ONLINE SUPPLEMENT S4 – DETAILED DESCRIPTION OF RESULTS ON QUALITY OF PRESCRIBING

Uncorrected data In the intervention group, all indicators of desirable prescribing improved, while those measuring undesirable prescribing decreased (Table 2). In the control groups comparable trends were seen, but not for all indicators. The proportion of cardiovascular disease patients meeting the LDL-target level increased in the intervention group, but decreased in the two control groups. The proportion of patients using antihypertensive drugs that had their renal function checked increased more in the intervention group than in the control groups. Small differences were seen between intervention and control groups in the proportions of patients with benzodiazepines overuse (decrease in the intervention group, increase in both control groups) and PPI-NSAID co-prescription (increased more in both control groups than in the intervention group).

Corrected data After correction for potential confounders and taking the baseline differences into account in mixed models, 4 out of 10 indicators differed between intervention and control group (Table 3). The relative risk of having the renal function checked during use of antihypertensive medication (desired prescribing), was higher in the intervention than in the two control groups (RR 1.03, 95%CI [1.01-1.05] compared to usual care and RR 1.04, 95% CI [1.01 – 1.06] compared to usual care plus). The relative risk of dosing errors of hydrochlorothiazide among elderly (undesired prescribing) was lower in the intervention group than in the usual care plus group (RR 0.71, 95% CI [0.52 – 0.97]), but not different to the usual care group (RR 0.85, 95%CI [0.60 – 1.21]). The relative risk of co-prescription of PPI and NSAID (desired prescribing) was lower in the intervention than in the usual care plus group (RR 0.91, 95% CI [0.87 – 0.94]) but not different from the usual care group (RR 0.96, 95% CI [0.92 – 1.00]). The relative risk of prescribed diclofenac in patients with cardiovascular disease (undesired prescribing) was higher in the intervention group compared to both control groups (RR 1.27, 95% CI [1.01 – 1.61] compared to usual care and RR 1.33, 95% CI [1.05 – 1.69] compared to usual care plus).

The model with the NDP in primary care: when, why and how is it effective?

Chapter 5

Clinical medication reviews by non-dispensing pharmacists integrated in primary care: patients' evaluations

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Submitted

ABSTRACT

Background: Non-dispensing pharmacists are integrated in primary care teams, were they provide pharmaceutical care and conduct clinical medication reviews.

Aim: To evaluate patients' satisfaction and achievement of patient-specific goals after a clinical medication review by non-dispensing pharmacists integrated in primary care teams.

Design and setting: A cross-sectional observational study in Dutch primary care.

Method: We compared elderly with polypharmacy who received a clinical medication review by a non-dispensing pharmacist (CMR-group) with elderly with polypharmacy who did not (control group). The primary outcome was medication satisfaction , using the TSQM 2.0 questionnaire. We triangulated this outcome with two observational outcomes measured solely in the CMR-group: satisfaction with the service provided during the medication review (questionnaire) and attainment of patient-specific goals (records review).

Results: Questionnaires were returned by 169 patients (response rate 47%): 88 CMR-patients and 81 control patients. The CMR- and control groups did not differ in overall medication satisfaction; yet fewer patients in the CMR-group reported to experience side effects (12.4% vs. 26.9%, p-value 0.02). This was supported by medical records review: 46% of the set goals concerned reduction of side effects, of which 40% was attained during follow-up. Patients consented with 96% of proposed interventions.

Conclusion: Patients with a clinical medication review by a non-dispensing pharmacist integrated in the primary care team are satisfied with the pharmaceutical care provided, consent with most proposals by NDPs to attain patient-specific pharmacotherapy-related goals and experience fewer side effects after the review compared to controls.

Keywords: non-dispensing pharmacist – primary health care – general practice – patient perspective – medication review – goal attainment scaling – patient-outcome

How this fits in

What is already known:

- NDPs integrated in primary care improve medication safety in elderly with polypharmacy
- Patients are generally satisfied with service provided by those NDPs

What this study adds:

- Patients experience less side effects after a CMR and follow-up provided by an NDP fully integrated in primary care teams
- Triangulation with measuring patients' goal attainment deepens insight in the meaning of quantitatively measured patients' satisfaction outcomes concerning care provision by NDPs

INTRODUCTION

With the aging of the population, both multimorbidity and polypharmacy increase, resulting in a larger population at risk of medication harms. To cope with this, a new model of pharmaceutical care provision in primary care is being implemented, with a *non-dispensing clinical pharmacist* (NDP) integrated in the primary care team. [1–4] This new model performs optimally when full integration is achieved, including follow-up and face-to-face communication between NDP and general practitioner (GP). [5,6]

In the Netherlands, the NDP in primary care was recently introduced in the POINT-study. [7] A key activity of the NDP is performing clinical medication reviews (CMRs): extensive analyses of patients' medication needs and related problems with active involvement of the patient. [8,9] Such CMRs are found effective to identify and solve drug therapy problems. [10–13] Community pharmacists perform CMRs as well, but as they are not fully integrated in general practice, communication and alignment with GPs is less as compared to NDP's.

There is an emerging interest in what this new integrated care model brings to patients. In most studies, patients' satisfaction with NDP-led care is high. [3,14–16] However, satisfaction scores are dependent on prior expectations, and in isolation they do not optimally capture the quality of care as perceived by the patient as they do not provide insight in what or why patients are satisfied. [16,17] We found two interview studies deepening such insight, finding that patients appreciated to have time with the

pharmacist to discuss their medications and felt that the pharmacist improved patients' understanding of their medications and optimised the drug therapy. [18,19]

In this study we aimed to add to understanding patients' evaluations of the NDP integrated in primary care teams by triangulating (1) satisfaction scores about the quality of pharmaceutical care, (2) controlled satisfaction scores about medication used and (3) evaluation of attained goals as set during NDP-provided CMRs. [20]

METHOD

This observational, cross-sectional study is part of the Pharmacotherapy Optimisation through Integration of a Non-dispensing pharmacist in a primary care Team (POINT) project, see Box 1. [7]

Setting

All nine general practices in the intervention group of the POINT project participated in this study. Practices were located in a middle region of the Netherlands.

Box 1. The POINT-project

In this project, nine NDPs provided pharmaceutical care while being fully integrated in primary care teams between March 1st 2014 and May 31st 2015. The first three months were considered a start-up period. 1 The NDPs were concurrently trained in consultation skills and clinical knowledge in a Clinical Pharmacy Training Program. [21]
The effect of the NDP-implementation was evaluated in a non-randomised clinical trial, comparing three groups: the intervention group, where pharmaceutical care was provided by the NDPs fully integrated in the primary care team, and two control groups, where pharmaceutical care was provided as usual by community pharmacists (usual care group) and by community pharmacists with an additional training in performing CMRs (usual care plus group). [22,23]
In the intervention group, the NDPs had three main tasks: 1. providing individual patient care, mainly by conducting CMRs as well as by pro-actively addressing specific medication problems in consultation hours (for example: persistent pain after the use of multiple analgesics), 2. improving the quality of pharmaceutical care in the practice, by developing quality improvement projects on a practice level and 3. providing education to general practice team members on pharmacotherapy.
Endpoints of the trial were medication-related hospitalisations, drug burden index, costs [4], and prescribing quality [article under review]. For details about the design and intervention of the POINT project, we refer to the study protocol. [7]

Patients

Patients at risk of medication problems were invited for CMR. Inclusion criteria were: older age, concurrent use of multiple medications and presence of one or more additional frailty factors (such as medication adherence problems, impaired kidney function, increased risk of falls, cognitive impairment). [24]

At 10 and 15 months after the NDPs started working in the practices, each NDP was asked to invite the last 10 patients scheduled with a completed CMR to participate in this study (180 patients in total). In addition, NDPs contacted 20 patients who were not yet invited for a CMR at the end of the intervention period, but where on the waiting list and would have had a CMR if the intervention had lasted longer (also 180 patients in total).

The intervention

The NDPs conducted CMRs in patients at risk of medication problems and provided follow-up. [25] Outcomes of CMRs were discussed with the GP, and the NDP and GP jointly developed a treatment plan addressing the patients' needs. During follow-up, the NDP guided the patient while keeping the GP informed or more actively involved, if needed.

Effects of other activities of the NDPs (individual consultations, quality management and education) were not evaluated in the present study.

Control comparison

Patients who had a CMR (CMR-group) were compared to patients who not yet had a CMR (control group) but where otherwise identical on eligibility criteria as described above.

Data collection

Patients were asked to return a questionnaire, comprising of baseline characteristics and the questionnaires as described under *Outcomes and measurements*. In addition, anonymised medical records were collected of patients who returned questionnaires.

Outcomes and measurements

We evaluated the CMR on three outcomes: 1. patients' satisfaction with the NDP-provided service (descriptive), 2. patients' satisfaction with the medications used (comparison); 3. goal attainment as set during the CMR (descriptive). Outcomes 1 and 3 were measured only in the CMR-group; outcome 2 was compared between the CMR- and the control group.

1. Patients' satisfaction with the service provided by the NDP

Patients in the CMR-group were asked about their satisfaction with the consultations with the NDP. We used the questionnaire of Baker *et al*. on satisfaction with GP-provided service, earlier adjusted to measure pharmacist-provided service; we further adjusted it to fit NDP-provided service. [26,27] We translated this adjusted version into Dutch, according to criteria of the COSMIN-checklist. [28] Following each question we included free text space, enabling patients to elaborate on their response. For the final questionnaire in Dutch, see Supplementary Box 1.

2. Patients' satisfaction with the medications used

Patients in both groups were asked about their satisfaction with the medication they used. We used the validated Treatment Satisfaction Questionnaire for Medication (TSQM, version II) in Dutch. [29] This questionnaire comprises of questions with 7-point Likert scale answers. Besides a global satisfaction score, the TSQM covers effectiveness, convenience and side effects (only scored if experienced). In addition, we asked patients to rate each medication they used separately, with scores ranging from one to ten.

3. Attainment of patient-specific goals

We used the principle of Goal Attainment Scaling (GAS) [30] when assessing the patients' medical records: patient-specific goals set during CMR were identified, proposals by NDPs to attain them were determined and attainment during follow-up was scored (by a sixth year medical student and researcher VMS). As medical records typically consist of open text data with high variability in wording, we could not reliably *scale* eventual attainment of goals; we decided to score attainment dichotomously as either reported improvement or no improvement.

Analyses

Data were analysed using IBM SPSS Statistics for Windows, Version 21.0. Descriptive measures were reported as well as t-tests and chi-square tests for comparisons. A p-value below 0.05 was considered significant. The 95% confidence intervals of risk differences were calculated using an online tool. [31] If data were missing, this was reported and patients were excluded from the analysis. In addition to these quantitative measurements, we used the concept of triangulation: a scientific approach frequently used in qualitative research, now applied in quantitative research, to gain a more comprehensive understanding of the effects on patients. [20]

Regarding patients' satisfaction with medication used, a subanalysis was planned upfront, excluding patients in the control group who had a medication review by their community pharmacist. [32]

RESULTS

Participating patients

Of 360 patients invited (180 with a CMR and 180 who were scheduled for it), 169 returned questionnaires (47%): 88 patients in the CMR- and 81 patients in the control group. The groups were comparable regarding age, sex and mean number of medications used (Table 1). In the control group, 20 patients (25%) reported to have had a medication review by a community pharmacist in the past year. Of patients who did not return questionnaires, no information on baseline characteristics was available.

Table 1. Baseline characteristics of participants

	CMR-group (n=88)	Control group (n=81)
Mean age in years (SD)	74.1 (10.3)	73.5 (7.4)*
Male sex, n (%)	35 (39.8)	39 (48.1)*
Mean number of medications used (SD)	8.1 (2.7)	8.3 (2.8)
Medication review by community pharmacist	n/a	
yes, n (%)		20 (24.7)**
no, n (%)		54 (66.7)
unknown to patient, n (%)		2 (2.5)

n number, SD Standard Deviation, n/a not applicable, CMR Clinical Medication Review
* For three patients, data were missing. ** For five patients, data were missing.

Patients' satisfaction with the service provided by the NDP

In general, most patients were fully satisfied with their visit to the NDP (88.1%; Table 2). Also, most patients thought the NDP gave clear explanations (86.9%) and thoroughly examined the situation (83.3%). Responses on the amount of time spent with the NDP and on divulging personal information varied (Table 2). Free text comments elaborating on responses were rarely provided.

Patients' satisfaction with the medications used

Patients who had a CMR did not differ from control group patients in satisfaction with the medications used, nor in perceived effectiveness and convenience (Table 3). However, less patients in the CMR-group reported to experience side effects: 10 patients (12.4%) compared to 21 patients (26.9%) in the control group (risk difference -14.6%, 95% confidence interval [-26.8; -2.4]). Patients in the CMR-group rated side effects lower than patients in the control group (Table 3).

Excluding those in the control group who had a medication review by a community pharmacist in the past year (n=20) did not significantly change the results. Satisfaction with the distinct medications was quite homogeneous for the majority of patients: 75% of patients in the CMR-group and 69% in the control group rated each medication identically, or with 1 or 2 points difference on a 10-point scale.

Attainment of patient-specific goals

In the medical records of the 88 patients in the CMR-group, 222 goals were identified (mean per patient 2.5, SD 2.0). The mean duration of follow-up was 85 days (SD 72 days). Goals identified mainly regarded the reduction of experienced side effects (n = 101, 45.5%; Table 4).

The NDPs proposed an intervention for 200 of the set goals (90.1%). Patients consented with 192 proposals (96.0%). Interventions included: start new medication, stop current medication, switch to other medication or adjust dosage or usage. Also, NDPs provided counselling. In case multiple goals were to be obtained in one patient and concurrent intervention was undesirable, NDPs sometimes proposed to postpone an intervention until the most urgent goal was reached. During follow-up, 107 goals were attained (55.7%), whereas 41 were not (21.4%). For the remaining goals, attainment was (yet) unknown.

Additional actions by the NDP

Patient records demonstrated that NDPs also addressed medication-related questions and worries of patients (n=20) and referred patients to the GP for goals that were not medication-related (n=30). Finally, NDPs identified multiple drug therapy problems that did not match patient-specific goals, but were considered necessary for adjustment or optimisation of pharmacotherapy according to current quality standards (n=240 in total; mean (SD) per patient 2.7 (1.6)). More details on these and other medication-related problems can be found elsewhere. [33]

Table 2. Satisfaction with service provided by the NDP *

Statement	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree	*Missing data*
I am fully satisfied with my visit to the NDP	0	0	10 (11.9)	49 (58.3)	25 (29.8)	*0*
The NDP gave me a clear explanation about my medication	0	0	10 (11.9)	50 (59.5)	23 (27.4)	*1 (1.2)*
Some things could have been better during my visit to the NDP	14 (16.7)	28 (33.3)	34 (40.5)	3 (3.6)	3 (3.6)	*2 (2.4)*
The NDP thoroughly examined me, my situation, and my medical file	0	0	14 (16.7)	51 (60.7)	19 (22.6)	*0*
The NDP showed interest in me as a person, and not only in my medication	0	1 (1.2)	10 (11.9)	52 (61.9)	19 (22.6)	*2 (2.4)*
I have a better understanding about my medication following my visit to the NDP	0	5 (6.0)	23 (27.4)	44 (52.4)	9 (10.7)	*3 (3.6)*
I had a strong feeling that the NDP understood my situation and concerns	0	1 (1.2)	14 (16.7)	51 (60.7)	16 (19.0)	*2 (2.4)*
I would have liked to have spent more time with the NDP	1 (1.2)	18 (21.4)	42 (50.0)	16 (19.0)	3 (3.6)	*4 (4.8)*
I would find it difficult to divulge very personal information to the NDP	11 (13.1)	28 (33.3)	24 (28.6)	16 (19.0)	2 (2.4)	*3 (3.6)*

NDP non-dispensing pharmacist.
* Results reported as n (%), of 84 patients in the intervention group (4 did not fill out this part of the questionnaire).

Table 3. Satisfaction with used medication, TSQM scores* ‡

	CMR-group (n=87)	Control group (n=81)	p-value
Global satisfaction score, *mean (SD)*	67.1 (11.2)	67.4 (13.4)	0.85[a]
Effectiveness score, *mean (SD)*	66.0 (13.1)	64.6 (15.1)	0.52[a]
Convenience score, *mean (SD)*	66.5 (13.4)	67.9 (14.5)	0.53[a]
Experienced any side effects, *n patients*	10	21	0.02[b]
Side effects score, *mean (SD)*	64.8 (14.3)	75.8 (15.0)	0.08[a]

TSQM Treatment Satisfaction Questionnaire for Medication, SD Standard Deviation, n number, CMR Clinical Medication Review

* TSQM scores range from 0 (not satisfied) to 100 (totally satisfied).

‡ TSQM scores were missing in one patient in the CMR-group, who stated that "the total package of medicines is okay". Furthermore, TSQM scores were missing per section: for Global satisfaction in 2 CMR- and 3 control patients; for Effectiveness in 3 CMR- and 2 control patients; for Side effects in 1 CMR- and 1 control patient. Data on experiencing side effects were missing in 6 CMR- and 3 control patients.

[a] Students t-test, [b] Chi-square test.

Table 4. Goals identified and attainment, per category *

Goals	Set	Intervention proposed	Patient consented	Attained
Reduce experienced side effect	101 (45.5)	89 (88.1)	87 (97.8)	40 (46.0)
Reduce complaints due to insufficient or untreated condition	60 (27.0)	54 (90.0)	49 (90.7)	20 (40.8)
Increase ease of medication usage	41 (18.5)	38 (92.7)	37 (97.4)	34 (91.9)
Quit medication use	20 (9.0)	19 (95.0)	19 (100)	13 (68.4)
Total	222 (100)	200 (90.1)	192 (96.0)	107 (55.7)

* Results are reported as n (%)

DISCUSSION

Summary

We found that CMRs conducted by an NDP integrated in primary care teams were generally well evaluated by patients: patients were very satisfied about the pharmaceutical care provided. Medication satisfaction did not differ between patients who did and did not have a CMR, though patients with CMR reported less frequently to experience side effects. Patient-specific goals set during the CMR improved in almost 60%, with the reduction of side effects being the most frequently set goal (46% of goals). Triangulating these results, we believe our findings validly suggest that NDPs are better able to positively mitigate medication side effects than care as usual. This supports

earlier findings of the added value to patients of an NDP integrated in primary care teams.

Strengths and limitations

The main strength of this study is the triangulation of several patient-reported and patient-centred outcomes, including a comparison with control patients. [20] Although triangulation of quantitative data is uncommon, we believe it provides a better insight in the subject under study.

Some limitations need to be considered. First, we used a cross-sectional design with a non-randomised control group comparison, hence chances are that the difference in experienced side effects is not attributable to the intervention but simply to chance. However, findings from our medical records review suggest that a reduction of side effects following a CMR by an NDP is likely. Second, although 47% of patients returned questionnaires, which is quite high, the risk of selective response remains. As we have no information of non-responders, we cannot compare responders with non-responders. Third, we used the TSQM to assess satisfaction with multiple medications at once, while this questionnaire has been validated to evaluate satisfaction with a single medication only. [29] For this reason, we asked patients to additionally provide satisfaction scores for their distinct medications. Here, we found rather homogeneous satisfaction scores for the majority of patients. Lastly, we applied the principle of GAS retrospectively, using open text data from medical records. Although we considered the medical records of CMR consultations and follow-up appointments a reliable source for this GAS [34], the high variability in wording might have limited the detailing of the findings.

Comparison with existing literature

We found that patients were satisfied and experienced less side effects compared to controls after a CMR and follow-up by an NDP. High satisfaction scores on NDP-provided service have been reported before. [3,14–16] To our knowledge (the principle of) GAS has not been researched before in NDP-led care. For community pharmacist-led CMRs, GAS was used previously by Verdoorn *et al*. to assess the effects of CMRs: per patient, on average 1.4 goals were set (SD 0.5). [35] This in contrast to our mean of 2.5 goals per patient (SD 2.0). The study of Verdoorn *et al*. reported the community pharmacists to be "unfamiliar with the concept of GAS". We think this difference in number of set goals might endorse the effectivity of and *need for additional education* for pharmacists who perform CMRs to improve consultation skills and clinical knowledge, as in primary care the concept of GAS as an approach during consultations is rather standard.

Looking more closely into our satisfaction scores shows alignment with the GAS-results: most patients thought the NDP gave clear explanations (86.9%) and thoroughly

examined the situation (83.3%), which was resembled in findings during record review, where we found that besides aiming to attain set goals, the NDPs answered questions and addressed worries. Similarly, two other studies found that patients reported the improved understanding and awareness of medication, and the reassurance provided by NDPs as patient benefits resulting from CMRs by NDPs. [18,19]

Lastly, we found patients having different opinions about whether it was difficult to divulge personal information to the NDP. Hereon, Tan's study mentioned the fact that the NDP was *integrated in the primary care practice* as essential to gain trust: "patients felt comfortable seeing the pharmacist in the clinic and appreciated the privacy in consulting rooms. By being affiliated and present within the clinic, rapport and trust with the pharmacist were more easily built." [19] Furthermore, some pharmacist attributes were reported that were deemed important too: "being personable, flexible and have sound interpersonal and communication skills". [19] In other words, an NDP needs to be a healthcare provider, equipped with the necessary skillset to work in general practice. As in our study all NDPs were fully integrated in the primary care teams, perhaps differences in the extent to which the NDPs took on this new role of healthcare provider might explain the diversity in patient responses. [36,37]

Implications for research and practice

Our findings demonstrate that from a patients' perspective NDPs integrated in primary care teams have a positive effect on pharmaceutical care, and encourage further implementation of this new care model. Our findings add to the existing evidence that the intervention is acceptable for patients and well appreciated. Further research to substantiate these findings would be valuable as we believe that expanding the POINT-model into primary care practice could benefit the quality and safety of elderly patients' medication.

CONCLUSION

Most patients are fully satisfied with the CMRs and follow-up provided by NDPs that are fully integrated in primary care teams. A vast majority of patients consents with NDPs' proposed interventions for attaining patient-specific treatment goals. After NDP-led CMR and follow-up, patients experience less side effects compared to controls.

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ONLINE SUPPLEMENT S1

Patient questionnaire on satisfaction with provided service (in Dutch)

1. Ik ben tevreden met het gesprek met de apotheker-farmacotherapeut.
▫ Zeer mee oneens ▫ Mee oneens ▫ Neutraal ▫ Mee eens ▫ Zeer mee eens

Eventuele toevoeging:

---

2. De apotheker-farmacotherapeut gaf mij duidelijke uitleg over mijn medicijnen.
▫ Zeer mee oneens ▫ Mee oneens ▫ Neutraal ▫ Mee eens ▫ Zeer mee eens

Eventuele toevoeging:

---

3. Tijdens mijn bezoek aan de apotheker-farmacotherapeut hadden sommige dingen beter gekund.
▫ Zeer mee oneens ▫ Mee oneens ▫ Neutraal ▫ Mee eens ▫ Zeer mee eens

Eventuele toevoeging:

---

4. De apotheker-farmacotherapeut was goed op de hoogte van mijn situatie.
▫ Zeer mee oneens ▫ Mee oneens ▫ Neutraal ▫ Mee eens ▫ Zeer mee eens

Eventuele toevoeging:

---

5. De apotheker-farmacotherapeut toonde interesse in mij als persoon en niet alleen in mijn medicijnen.
▫ Zeer mee oneens ▫ Mee oneens ▫ Neutraal ▫ Mee eens ▫ Zeer mee eens

Eventuele toevoeging:

---

6. Ik heb een beter begrip gekregen van (een deel van) mijn medicijnen door het gesprek met de apotheker-farmacotherapeut.

▫ Zeer mee oneens ▫ Mee oneens ▫ Neutraal ▫ Mee eens ▫ Zeer mee eens

Eventuele toevoeging:

---

7. Ik had het gevoel dat de apotheker-farmacotherapeut begreep wat belangrijk was voor mij.

▫ Zeer mee oneens ▫ Mee oneens ▫ Neutraal ▫ Mee eens ▫ Zeer mee eens

Eventuele toevoeging:

---

8. Ik had graag meer tijd gehad met de apotheker-farmacotherapeut.

▫ Zeer mee oneens ▫ Mee oneens ▫ Neutraal ▫ Mee eens ▫ Zeer mee eens

Eventuele toevoeging:

---

9. Ik zou het moeilijk vinden om hele persoonlijke dingen aan deze apotheker-farmacotherapeut te vertellen.

▫ Zeer mee oneens ▫ Mee oneens ▫ Neutraal ▫ Mee eens ▫ Zeer mee eens

Eventuele toevoeging:

Chapter 6

Non-dispensing pharmacists integrated in primary care practice; a realist evaluation of a new interprofessional model

VM Sloeserwij, E de Groot, JJ de Gier, NJ de Wit, AA de Bont, DLM Zwart

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Submitted

ABSTRACT

Background: A new interprofessional model with a non-dispensing pharmacist integrated in primary care practice teams seems promising to improve quality of pharmaceutical care. However, results of interventions are dependent on the context in which they are implemented. Understanding when, why and how the model works may increase chances of successful broader implementation in other general practices with their own, different context. Earlier theories suggested that the model works by the addition of new knowledge to current practices. Yet, as establishing new interprofessional models in existing healthcare organisations is challenging, the addition of new professional knowledge alone may not always be enough for successful implementation.

Methods: We used the realist evaluation approach for this qualitative study that was part of the Pharmacotherapy Optimisation through Integration of a Non-dispensing pharmacist in primary care Teams (POINT) project. We interviewed 18 general practitioners who (had) worked closely with a non-dispensing pharmacist. Interview data were analysed in iterative, cyclic processes.

Results: In a context where general practitioners acknowledge the need for improvement and are willing to engage in this development, working mechanisms are triggered: non-dispensing pharmacists add new knowledge to current primary care practice and via discursive actions both general practitioners and non-dispensing pharmacists evolve in what they consider appropriate, legitimate and thinkable in their work situations: they align their professional identities.

Conclusions: We enriched existing theories on when, why and how the interprofessional model works: not only the addition of new knowledge is crucial but also alignment of the general practitioners' and non-dispensing pharmacists' professional identities in discursive actions. In general practices that want to use this healthcare model, general practitioners need to be aware that, to induce those mechanisms, addressing the pharmaceutical needs of all their patients is an interprofessional endeavour. Both general practitioners and non-dispensing pharmacists then will explore and reflect on what they consider appropriate, legitimate and thinkable in carrying out their professional roles.

Trial registration: The POINT project was pre-registered in The Netherlands National Trial Register, with Trial registration number NTR-4389.

Keywords: interprofessional model; non-dispensing pharmacist; primary care; realist evaluation; quality improvement

BACKGROUND

Current primary healthcare models seem unable to adequately address the pharmaceutical needs of a growing population at risk of medication problems – mostly elderly with polypharmacy[1,2]. Hence, new models are emerging worldwide in which pharmaceutical care is organised differently. In Canada, Australia, the United Kingdom, Ireland and the Netherlands *non-dispensing clinical pharmacists* (NDPs) were integrated in primary care teams, providing pharmaceutical care in close collaboration with the general practitioner (GP).[3–7] This new interprofessional model appears to improve quality and safety of pharmaceutical care: in practices with fully integrated NDPs, drug therapy problems are adequately addressed and less medication-related hospitalisations occur.[8–10]

It has been recognised that implementing promising interventions in a new context does not automatically provide the same results, as their success can be highly dependent on the context in which the intervention is introduced.[11] This holds especially in case of complex interventions with multiple components [12] that require social interaction between professionals: such interventions could work well in one context, but not at all in another.[13] So, in addition to answering the question *whether* the interprofessional model improves quality of care with quantitative studies, we need to understand *how and why* this improvement is obtained (so-called working mechanisms) and *when* (so-called context elements). These understandings could help to better interpret results found so far and could increase chances of success with broader implementation of the model in other practice settings.

Earlier theories on how and why new interprofessional models in healthcare could improve quality of care suggested *the addition of new knowledge* to existing organisational structures as a potential working mechanism.[14–16] For the introduction of clinical pharmacists in primary care teams, this has also been recognised.[17] However, establishing new interprofessional models in existing healthcare organisations is challenging and interprofessional collaboration is not self-evident.[18] Hence, addition of new professional knowledge alone may not always be enough for successful implementation.

When we introduced the interprofessional model in the Netherlands in the Pharmacotherapy Optimisation through Integration of a Non-dispensing pharmacist integrated in primary care Teams (POINT) project[7], our pre-set theory was that the addition of new knowledge was key.[19] To make optimum use of this additional knowledge brought into the practices by NDPs, it was deemed essential that the patient and not the drug should be central in applying pharmaceutical knowledge. Therefore, NDPs were additionally trained in communication, consultation and clinical reasoning skills.[19,20]

In the present study, we challenge and refine our theory on *when, why and how* the interprofessional model works, using a realist evaluation approach.

METHODS

Setting

In the Netherlands, primary care is provided by a team, consisting of GPs, practice assistants and practice nurse(s) for chronic disease management and mental health. These primary care teams are increasingly located in multidisciplinary health centres, including a community pharmacy. Pharmaceutical care is provided in collaboration between GPs and community pharmacists.

Although already implemented in other countries, the interprofessional model with an NDP integrated in primary care teams is a novel approach in the Netherlands. In the POINT project, where this study was part of, outcomes of the model were measured in ten primary care practices.[7] The practices were selected when they were explicitly willing to host an NDP and to cooperate in the development and evaluation of the new role of NDP. Also, the practices needed to have a consultation room available for the NDP and to provide the NDP access to the GPs' electronic medical records.

After an introduction period of three months, the NDPs worked full time in the practices from June 2014 until May 2015, while concurrently being trained in a 15-month Clinical Pharmacy Training Program based on interprofessional workplace learning, to develop skills in communication and clinical reasoning.[20] One NDP was unable to finish the training program. Of the remaining nine NDPs, five continued working as an NDP in the general practice after the intervention period ended.

Box 1. Description of the NDP in the POINT project

During the POINT project, the NDPs were given integral responsibility for the pharmaceutical care in the practice. They intervened at the *patient level*, performing clinical medication reviews with elderly patients who use multiple medications and holding individual consultations for patients with specific drug therapy problems; and at the *practice level*, organising quality improvement projects and educating GPs and staff members on pharmacotherapy. The general outline of how NDPs were expected to fulfil their role was pre-specified, but NDPs were encouraged to develop their role during the study and to tailor it to the practice' needs.

The training and professional identity development of the NDPs were described earlier.[20,21] Quantitative evaluations demonstrated that implementation of the NDPs in primary care teams resulted in improved quality and safety of pharmaceutical care: we found a lower risk of medication-related hospitalisations amongst elderly patients with polypharmacy, compared to usual care[10] and that NDPs identified and adequately addressed drug therapy problems[22].

Methodological approach: realist evaluation

To evaluate the interprofessional model with an NDP integrated in primary care teams, which can be considered a complex intervention, we chose a realist evaluation (RE) approach.[11] An RE aims to explain how and why an intervention works, for whom and under what circumstances.[23] From the RE perspective, taking the context explicitly into account yields important information when evaluating intervention effects, as RE recognises that a social intervention alters and can be altered by the context in which it is introduced. The combination of the intervention and its specific context are then thought to trigger mechanisms, which in turn produce both intended and unintended outcomes (**Figure 1**: framework of so-called CMO-configurations).

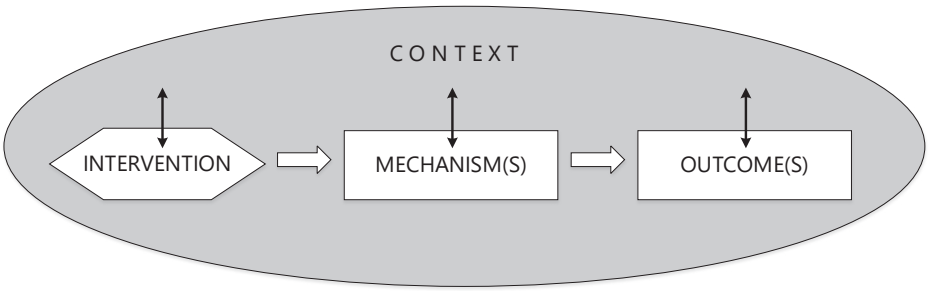

Figure 1. CMO framework

Elements on context, mechanisms and outcomes were inferred from the interviews. Context-elements were defined as "actors or factors that are external to the intervention, present or occurring even if the intervention does not lead to an outcome, and which may have influence on the outcome"[24] and mechanism-elements as underlying processes or structures, usually hidden, which operate in particular contexts and generate outcomes[25]. Combining these elements, we formulated theories on when, why and how the interprofessional model of an NDP integrated in primary care teams improves pharmaceutical care – an outcome based on findings of earlier quantitative analyses in the POINT project.[10,22]

Recruitment and data collection

We interviewed GPs from the practices where an NDP had worked during the POINT project. To guarantee information-rich interviews, we used 'intensity sampling' and 'snowball sampling' methods: we invited the nine GPs who supervised the NDPs at the workplace (intensity sampling) and asked them which colleague GP (still) had a close working-relationship with the NDP in daily practice, and/or a distinct opinion on the NDP (snowball sampling).[26] In total, 18 GPs were interviewed.

Semi-structured interviews were conducted between March and June 2018 by one researcher (VMS, a PhD student and GP trainee, who alternates between periods of doing research and following primary care training) accompanied by a 6th year medical student. Interviews lasted between 30 and 45 minutes and took place at the GPs' practices. All interviews were audio-recorded, transcribed verbatim and anonymised.

The topic list used for the interviews consisted of open questions, and was designed inspired by the RE framework.[27,28] For this, participants were asked to describe their experiences with the intervention, rather than asked for their opinions about the NDP. The topic list was adjusted where necessary after a pilot interview, to ensure that each topic was properly highlighted (see Online Supplement S1 for the topic list).

Data analysis

We analysed the interviews using the CMO-configuration heuristic.[11] All interview transcripts were coded independently by two researchers (VMS and a 6th year medical student), using NVivo version 11.13 to organise the data. First, codes were given that were close to the text. Codes were regularly discussed within the research team (VMS, EdG, DZ, AdB), resulting in refined coding and suggestions for the identification of additional codes and themes. Discrepancies and ambiguities in coding and interpretation were resolved in discussion. In line with earlier realist evaluations[29,30], with this iterative, cyclical analysis we identified elements on context and mechanisms that, combined with outcomes previously found in our quantitative analyses [10,22] resulted in a CMO configuration that refined and deepened our pre-set theory. Results were repeatedly compared to existing literature, to enhance credibility of the findings. The SQUIRE checklist was followed while writing the manuscript.[31]

Ethics approval

All interviewees provided written informed consent for participation in the present sub study of the POINT project. The POINT project was exempted of formal medical-ethical approval by the Medical Ethical Committee University Medical Centre Utrecht (METC protocol number 13-432C).

RESULTS

We conceptualised the results from the interviews into a CMO configuration: in a context where GPs acknowledge the **need for improvement** [C] and are **willing to engage** in this improvement [C], the GPs recognise the **addition of new knowledge** to current primary care [M] but also, they and NDPs **align their professional identities** via discursive actions [M]. As a result, the **quality** of pharmaceutical care provided

in the primary care practice is **improved**, as experienced by GPs and earlier shown in quantitative studies [10,22] [O].

We will discuss these contexts, mechanisms and outcome in more detail now.

Need for improvement

The GPs felt ***room for improvement*** in providing pharmaceutical care in their practices; both in time to provide pharmaceutical care (practice level) as well as in pharmaceutical knowledge (personal level). Importantly, GPs were ***willing to engage*** in this improvement. Especially the fact that primary care is getting more complex urged the need for change, as one GP put it:

> *"[as a GP] you need to know of a lot. Especially as secondary care is increasingly transferred to primary care, it is all just becoming very specialised, so yes we do need extra knowledge."* (PR2GP7)

This acknowledgement of the need for improvement was further endorsed by the experienced decline in quality of pharmaceutical care after the NDP left their practice. Returning to the traditional model with only the community pharmacist, often instigated by a lack of financial reimbursement for the interprofessional model with the NDP by healthcare insurers, felt like "*it all collapsed in ruins*" (PR1GP1).

Aligning professional identities through discursive actions

With the introduction of the NDP into their practices, the GPs recognised that NDPs ***brought new knowledge*** into their clinical practice:

> *"By his background, [the NDP] provides depth, he can explain in detail on what the medicine does with the body, or interactions with other medicines, and I think… as a GP your pharmaceutical knowledge is more shallow."* (PR3GP17)

> *"She [the NDP] linked that to her knowledge on medications, to taper off medications or to find an alternative, so she of course has the knowledge that I as a GP have not."* (PR1GP1)

In addition, we found that over time GPs and NDPs changed the way they consorted. These changes were related to their professional identities. A professional identity can be defined in terms of 'spaces of action', being "what professional actors find appropriate, legitimate and thinkable in their work situations, given the existing cultural conditions". [32] Spaces of action are not fixed. New spaces of action can be co-constructed and boundaries between interprofessional spaces of action can be

redrawn, as spaces of action are the result of everyday work interactions, so-called ***discursive actions***. In these discursive actions, the professional identities of both GPs and NDPs started to change – not in a random direction, but they were getting together. This process of ***aligning professional identities*** started both explicitly and implicitly: GPs and NDPs became aware of what the other considers appropriate, legitimate and thinkable and started sharing ideas about this, thereby re-drawing and aligning their professional identities.

By working as an interprofessional team, the GP and NDP grew closer together and learned to speak the same language. This was observed by a GP for an NDP who over time increasingly ***incorporated the context*** of the patient in his evidence-based considerations:

> *"I think that a pharmacist really has to get used to being located in the primary care setting. General practitioners are kind of strange people, doctors think differently. (…) You know, in the beginning you have to get used to that and then (…) what a real difference is, is whether you see a list with medications or whether you see the patient using them. (…) That is the translation from practice to the medications, and that is the translation a pharmacist needs to complete, mainly in the beginning."* (PR7GP12)

Meanwhile, the GPs – besides appreciating the additional knowledge brought by the NDPs – increasingly ***valued differences in work approaches***: NDPs work pro-actively while GPs work mainly reactively. Two ways of collaboration were identified, for specific and complex care; in both, ***providing shared care*** is key, and being aligned enables GPs and NDPs to recognise, acknowledge and utilise the others' expertise.

For specific care – patients with a single pharmaceutical care problem – the GPs entrusted patients to the NDP or consulted the NDP for advice. In these situations, the GP agreed with the NDP's recommendations often easily, without much discussion. For example, in a patient with persistent pain who was referred to the NDP by the GP, the GP stated:

> *"you know, when [NDP] says that starting Pregabalin is the best option now, then I think Oh, good idea, well, let's do that; as I do trust her, yes."* (PR9GP9)

For complex care – patients with pharmaceutical care problems being part of complex comprehensive care – the GPs recognised the importance of combining both their own and the NDPs expertise actively and worked along the lines of collaborative care, with the GP and NDP having face-to-face meetings. This was common in care for elderly patients with polypharmacy, for whom clinical medication reviews were performed. One GP described the importance of interprofessional collaboration in discussing such complex clinical medication review outcomes:

> *"Sometimes, you [as a GP] think, what else is going on there? And then I wonder… she [the NDP] is trained as a pharmacist, and she looks through certain glasses. And I look through slightly different glasses. I definitely think these glasses are complementary, but I feel that sometimes there is a need for my broader scope, […] to see the wider picture, not focusing solely on the medication. Sometimes it is priority to make sure someone can stay home, or has a good quality of life, rather than to control the blood pressure; there is more to life than a controlled blood pressure."* (PR5GP6)

Over time, GPs ***started to think and feel differently*** about ***sharing (part) of their responsibility*** with the NDPs. The GPs gradually entrusted parts of the provided care to NDPs, but meanwhile remained convinced that they should be able to provide the NDP-led care themselves – even though they recognised they actually would not be able to, especially in the complexification of care:

> *"She [NDP] is better at it [providing pharmaceutical care] than I am. But I, as a GP, should be able to do it, too. […] That is how it always has been. Whether it stays like that, I don't know."* (PR9GP10)

> *"No, I think I cannot do all that what they [NDPs] can. […] I think that I should be able to do clinical medication reviews, but I am not sure whether I would be able to do it that good, no."* (PR6GP11)

> *"So, I wouldn't be able to do the same [as the NDP], even if I could take the same amount of time for the patient, because I do not have the knowledge."* (PR1GP1)

Alignment of identities took place through ***discursive actions***: as the GPs and NDPs talked in the corridors or during short daily meetings, about specific patients and their context or about pharmacotherapeutic considerations. Alignment took time and was highly supported by the communication and clinical reasoning skills acquired by the NDPs during the training program, as NDPs learned there to put the patient instead of the drug in the centre of their considerations, facilitating the NDPs' identity changes.

Both in practices with good relations with the (dispensing) community pharmacy and in practices where relations were less optimal, alignment of identities between GPs and NDPs occurred. The fact that this alignment occurred through discursive actions might explain why previous collaboration with community pharmacists did not yield the same results: discursively aligning what is appropriate, legitimate and thinkable did not occur with community pharmacists. One GP illustrated how he experienced the discourse with the NDP and with the community pharmacist differently:

> *"To collaborate with someone with both medical knowledge as well as pharmaceutical background, that results in a nice cooperation. I sometimes visit the community pharmacist but that is different. You still have… then it is often all about logistics, while with [NDP] you notice that she just does much more with patients and, well, she has a much more medical background."* (PR8GP13)

Improved quality of care

The alignment of professional identities and the addition of knowledge contributed to the formation of a new, interprofessional model of pharmaceutical care, in which GPs and NDPs work closely together. Combining their expertise, while appreciating and trusting each other and speaking the same language, resulted in both perceived improvement of pharmaceutical care, as well as objectively demonstrated improvement outcomes. [10,22] The newly formed model is not just another model of providing pharmaceutical care, but one in which interprofessional collaboration between GP and NDP comes into its own, as recognised by this GP:

> *"Together, they make a very strong team."* (PR1GP1)

DISCUSSION

In a context where GPs acknowledge the need for improvement and are willing to engage in this improvement, working mechanisms are triggered: NDPs add new knowledge to current primary care and via discursive actions both GPs and NDPs change in what they consider appropriate, legitimate and thinkable in their work situations: they align their professional identities. This contributes to the formation of an interprofessional healthcare model, in which shared care is provided by GPs and NDPs that is perceived to be, and measurably, of improved quality compared to usual care.

When designing the NDP model, we assumed the addition of new knowledge by the NDPs to general practice to be a potential working mechanism[19] – in line with previous theories.[14–16] However, it has been recognised before that additional knowledge is often not optimally utilised, because of interprofessional conflicts that limit its effectiveness in heterogeneous groups.[18,33] For the interprofessional model with an NDP integrated in primary care practices, the appreciation by GPs of additional knowledge provided by the NDPs was recognised before in a study investigating stakeholder experiences with this model in the United Kingdom.[17] Also, in this study the potential risk of conflicts hampering effective interprofessional collaboration was recognised: a GP compared the "perceived threat to professional boundaries and identity to that observed during the introduction of nurse practitioners, although suggested that this sentiment might be stronger since *everything a nurse can do a GP can probably*

do, whereas anything a pharmacist can do the GP probably can't".[17] In contrast to these findings, we observed a positive development between GPs and NDPs: indeed, professional boundaries needed to be redrawn, and (interprofessional) identity work was needed, yet as this resulted in the ***alignment of professional identities*** it allowed for instead of hampered effective interprofessional collaboration.

Moreover, we think the process of professional identity alignment is essential to make the healthcare model work. It is important to highlight that this process is difficult, for both GPs and NDPs, and that it takes time. Understanding how the process takes place could help to optimise broader implementation of the model: then, the needed means could be facilitated. We found that ***discursive actions*** were the means for the identity aligning process to take place; for example: knocking on each other's door for ad hoc consultations during the day, coffee break meetings, asking the other to shortly fly in during a patient consultation to assess the patients' pharmacotherapy directly together, or quick questions via digital notes in the patient records system. In those moments, GPs and NDPs discussed specific patients and their context or pharmacotherapeutic considerations, thereby questioning each other's routine, asking questions like "why do you do what you do?". These discursive actions made GPs and NDPs both explicitly and implicitly reconsider what they thought appropriate, legitimate and thinkable in their work situations: the identity aligning process could take place.

Earlier studies already recognised 'proximity' between GPs and pharmacists, and them both working 'on-site' as important elements to enable interprofessional collaboration.[17,34] A study in Canada on GPs' experiences with prescribing pharmacists (both community pharmacists and NDPs, so-called team pharmacists) reported that "the proximity of team pharmacists allowed physicians to develop trust and mutual respect with pharmacists; however, proximity alone did not facilitate collaboration. […] All participants were hesitant to trust pharmacists with whom they were unfamiliar, especially in community settings."[34] So, besides the need for proximity, this study stressed that GPs and pharmacists need to be familiar with each other. Another study, in the United Kingdom, reported that "a strong preference was expressed [by GPs] for the pharmacy team to be located *in house all day* (PG5). In practices where the pharmacy team was located on-site, participants reported easy personal access and the ability to ask informal questions. Where the pharmacy team was located off-site, however, they were viewed as *a separate entity* (GP7) and aspects of communication were lost."[17] We agree with those studies that proximity and working on-site are important, but we think that in this proximity GPs and NDPs not only need to get familiar but need to *align their professional identities*, which, in our view, incorporates deeper underlying mechanisms taking place than simply getting to know each other: it requires both parties to change. Yet, we think proximity and working on-site describe the essential conditions that are needed for this alignment process to take place: they allow for discursive actions to occur. The fact that collaboration with the NDP-like pharmacists was perceived easier than with community pharmacists by the Canadian

GPs could imply that alignment of professional identities already had started between them, too. Also in our study, a difference between collaborating with NDPs and community pharmacists was perceived by GPs; so, we hypothesise that despite (often) proximity between GPs and community pharmacists and (often) knowing each other, the community pharmacists and GPs may not have *aligned their professional identities*, whereas NDPs and GPs had.

In literature on interprofessional teams it was recognised before that in such discursive actions the process on identity formation can be started: professional identity formation is a social activity, and professional identities are explored in relation with others.[35] We think that additional training further facilitates this aligning process. The need for additional training of pharmacists to work in general practice was recognised before[17,36], yet we would like to specifically stress the need for additional *interprofessional* training, like workplace learning, as interprofessional learning and working are essential to achieve effective interprofessional team work, and also here informal conversations hold key opportunities to achieve such.[37,38]

Over time, in the process of aligning identities the GPs started to reconsider responsibilities. Worldwide, GPs feel responsible for the integral care provided to patients, including pharmaceutical care – clearly in the following quote of a Canadian GP: "*If they [pharmacists] are going to make clinical decisions about a patient, and they [pharmacists] don't call me [to get my consent], that's inappropriate*".[34] Yet, the same GPs had less problems with such decisions with NDP-like pharmacists who "did not need to seek approval prior to prescribing whereas community pharmacists should."[34] Being and feeling responsible is thus a core aspect of GPs' professional identity, but needs to be (partly) reconsidered when aligning this identity with the NDPs' professional identity. Although this is a difficult process, we think that talking to and discussing with one another provides a first step into further exploring how to relate to such reconsiderations and changes.

Moreover, we think this change is *necessary* – as there is a need for change of current pharmaceutical care models in primary care settings. Especially as the number of elderly patients with chronic conditions rises, GPs generally recognise that primary care requires a more diverse skill mix, and pharmacists' expertise is suggested to be of additional value here.[39,40] Yet, we found some differences between GPs in our study in acknowledging the level of the problem at hand. Although all GPs acknowledged there was a ***need for improvement*** of the pharmaceutical care provided in their practices, some GPs considered this need on the practice level only, recognising a lack of time to provide pharmaceutical care as the main problem, while others incorporated their own personal level in the problem too, feeling a gap in their own knowledge to provide pharmaceutical care. As thoughts on (partly) sharing responsibility were not crystallised during our study yet, we cannot link these differences in contexts to eventual differences in formation of the model; yet we would like to stress the importance of stakeholders acknowledging the problem at hand, as this is known to be key for the implemented intervention to result in success.[41]

Strengths and limitations

While many evaluations of interventions aim to standardise the context in which the intervention is implemented, we did not standardise but instead regarded this context by using a realist evaluation approach. Taking the context into account provided additional insight into elements that could help with successful implementation of the model in other practices with their own context.

Some limitations need to be considered too. First, due to logistic reasons there was quite a large time frame between the ending of the intervention period (May 2015) and the interviews (March until June 2018). During this time, five of the nine practices the NDPs continued working after the intervention period ended while in the other practices the NDPs stopped, bringing different stories to the fore. Second, there was only little contrast between the interviews regarding enthusiasm for the new model. This might be related to the selection of GPs and practices willing to engage to begin with. However, this limits possibilities to contrast different contexts. Last, we chose to include GPs only, for feasibility reasons. To get a broader overview of the context in which the NDPs were integrated, insights in the perspective of the full general practice team would have had added value. Findings would have been even richer had we interviewed practice assistants and nurses as well.

Implications for future pharmaceutical care and future research

For successful future implementation of the interprofessional model, we want to highlight several elements. First, we want to point out that the alignment of professional identities described in this article is the result of a *process* that takes time: simply placing an NDP in primary care teams, let alone a community pharmacist without additional training, will not suffice. Second, this alignment occurred in discursive actions. This finding stresses the need for integration of NDPs *in the primary care practice* and explains why mechanisms do not occur *in community pharmacy*: discursive actions take place in daily activities, and need physical interaction. Co-location is hence a key condition for the intervention to succeed. In addition, we think that the additional training in communication, consultation and clinical reasoning skills for NDPs further aided the process of aligning identities. Third, in order to start the aligning process, GPs need to be *open for change*. If they are not (i.e. if they do not acknowledge the need for improvement), work needs to be done there as otherwise the interprofessional model will most likely yield no results.

Future follow-up research should investigate the sustainability of impact of this interprofessional model on quality of pharmacotherapy in primary care and on the workload of GPs, as well as the perspectives on the model of other stakeholders, such as policy makers, governmental bodies, professional organisations and healthcare insurers. We suggest that especially cost effectiveness and financial sustainability should be focus of research, as the need for adequate financing has been reported by GPs in our study as well as in earlier research on comparable models.[39]

CONCLUSION

The new interprofessional model with the NDP integrated in primary care practice teams not only works through addition of new knowledge in general practice, but also via professional identities alignment of NDP and GP. This is essentially different from traditional pharmaceutical care models, in which pharmacists and GPs work separately. To induce these mechanisms when broader implementing the interprofessional model with NDPs, GPs need to acknowledge that addressing the pharmaceutical needs of their patients is an interprofessional endeavour. Then, both GPs and NDPs will explore and reflect on what they consider appropriate, legitimate and thinkable in carrying out their professional roles for collaboratively providing the best pharmacotherapy for their patients.

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ONLINE SUPPLEMENT S1

Interview guide – translated into English (original version in Dutch)

Introduction

Before the interview:

- check and record the interviewees' consent with the audiotape recording
- thank the interviewee for his or her participation

A short introduction to the interview:

- reminding the interviewee of his/her involvement in the POINT study, with integration of the NDP in his/her practice during 2014/2015
- in case the NDP continued working in the GP practice, name this

Interview guide

NB: During the interview, ask follow-up questions such as "could you provide examples?", "could you illustrate that?", "like what, for example?"

1. Fidelity of the intervention and the context in which the intervention was implemented.

Q1.1: Could you describe how pharmaceutical care is currently organised in your practice?

Q1.2: Please describe what was changed in this organisation by the arrival of the NDP? Either positively or negatively.

The NDP was "designed" to be a healthcare provider on the patient level (performing medication reviews, holding consultation hours) and on the practice level (doing quality improvement projects, educating practice staff). During the intervention year, the NDP and practices were allowed to tailor the NDP's role to the practice needs. Could you tell more about the NDP in your specific practice?

Q1.3: Do you have some examples of care problems where the NDP got/still gets involved?

2. How does the NDP work in this practice, for this organisation

Q2.1: What changed after the intervention period ended (and the NDP left your practice)?

Q2.2: Could you describe your collaboration with the community pharmacist, compared with collaborating with the NDP?

How is this collaboration now, after the study, compared to the situation before?

Q2.3: Please describe pharmaceutical care that is provided by you, as a GP, compared to pharmaceutical care provided by the NDP? Are there differences in approaches, in care plans?

Q2.4: *IF THE NDP STOPPED:* If there were no constraints by time or money, how should pharmaceutical care in your practice look like if it was up to you?

IF THE NDP CONTINUED: this question is transferred

3. Sustainability: the future of the NDP in primary care

Q3.1: *IF THE NDP STOPPED:* After the intervention period ended, the NDP left your practice. Can you describe the backgrounds thereof, illustrate how that went?

IF THE NDP CONTINUED: After the intervention period ended, your practice started to employ the NDP. Can you describe the backgrounds thereof, illustrate how that went?

Q3.2: *IF THE NDP STOPPED:* What would be needed for your practice to employ an NDP? Or more broadly: to optimise pharmaceutical care?
Are there specific elements hampering improvements, or facilitating them?

IF THE NDP CONTINUED: If there were no constraints by time or money, how should pharmaceutical care in your practice look like if it was up to you? Are there specific elements hampering improvements, or facilitating them?

4. Outcome: the additional value of an NDP in this practice, in this organisation

Q4.1: Could you describe what the NDP brought to your practice?
Did all of the staff perceive the integration of the NDP in the same way, or were there differences?

Closing:

Q5.1: Is there anything else that you want to discuss that we didn't cover yet?
Thank the interviewee for his or her participation and time and stop recording.

Chapter 7

General discussion

In this thesis, we evaluated the introduction of an interprofessional model with a non-dispensing pharmacist (NDP) integrated in primary care teams. In this model, the NDP provides integral pharmaceutical care while working closely together with the general practitioner (GP).

Evaluation of such a complex intervention should include both outcome and process evaluations derived from quantitative and qualitative approaches: quantitative research to provide effect sizes, and qualitative research to provide information on how the intervention could be replicated in another context, in such a way that trial outcomes could be expected to be reproduced. [1] Hence, we aimed both to answer the question *what* the effects of the model are on improving quality and safety of pharmaceutical care, as well as to investigate *when, why and how* improvement could be obtained.

The main findings in relation to our study questions were:

What are the interprofessional model's effects?

In our quantitative analyses, we demonstrated that the interprofessional model improves quality and safety of pharmaceutical care in the primary care setting, i.e. the NDP integrated in primary care results in a lower risk of medication-related hospitalisations in elderly with polypharmacy, compared to usual care (Chapter 3). It was also shown that NDP-led care improved the process outcome of renal function monitoring in patients using antihypertensives, again compared to usual care (Chapter 4). However, we found no difference between the interprofessional healthcare model and usual care on overall quality of GPs' prescribing (Chapter 4), nor in drug burden and healthcare costs (Chapter 3).

When, why and how is the model effective?

From our qualitative analyses, we inferred an understanding of when, why and how the interprofessional model could result in improved quality of care. From interviews with GPs, we unravelled relevant context elements and mechanisms that could be triggered by the intervention (Chapter 6). When GPs acknowledged the need for improvement of pharmaceutical care provided in their practices and were willing to engage in this improvement, the model triggered working mechanisms. The NDPs brought new knowledge into current primary care. This knowledge could be utilised over time, as both GPs and NDPs changed in what they considered appropriate, legitimate and thinkable in their work: they aligned their professional identities. For NDPs, this meant that they incorporated the patients' context more often in their evidence-based considerations – which resonated in patients generally being satisfied with the service provided and less frequently experiencing side-effects, compared to patients who had not received NDP-led care (Chapter 5). For GPs, alignment of professional identities entailed valuing differences in working approaches and, over time, starting to change their opinions about shared responsibility in patient care. The alignment of professional

identities took place in discursive actions: in corridor talking and during short daily meetings in the primary care practice. These interactions do less frequently occur between GPs and community pharmacists, and identity alignment does not happen.

Combining above findings, we conclude that the interprofessional model works – in contrast to the fundamentally different traditional models of pharmaceutical care. We consider the interprofessional model as the fundament of future pharmaceutical care.

Taking a closer look at the interprofessional model's effects

To enable better understanding and interpretation of the quantitative results, some specific challenges need to be addressed.

First, obviously we did *not randomise* but instead used a controlled pre-post design to compare our intervention with two control groups. Consequently, the strength of the evidence is suboptimal (evidence level III instead of II). [2] Yet, the choice for a more pragmatic design was a deliberate one. As stated in Chapter 2, we considered willingness of all participating parties to improve pharmaceutical care a key condition for the successful implementation of the intervention – as had been recognised before during the implementation of a comparable model in Canada[3]. Indeed, as inferred from our qualitative analyses described in Chapter 6, this willingness turned out to be an essential contextual element to make the model work. In addition, given the limited time and financial resources, randomisation was not feasible. Yet, we reckon that using the MRC framework for evaluating complex interventions[1] provided a solid base for answering our questions, even in a non-randomised design.

Second, we chose *medication-related hospitalisations* (HARMs) as primary outcome measurement to assess the impact of the interprofessional model on safety of pharmaceutical care (Chapter 3). Prior studies had reported on the number of HARMs, and concluded that a substantial part of these HARMs is preventable. [4,5] Yet, assessing the 'medication-relatedness' of hospitalisations proved to be complex. Especially in elderly with multimorbidity who use multiple different medications, the cause of hospitalisations is often multifaceted. For example: a woman aged 82 years was admitted because of a traumatic hip fracture, unable to remember exactly what happened – concurrently using two antihypertensives, a sleeping pill and a stomach protector. Despite all kinds of algorithms to assess the probability of an adverse drug reaction [6,7], one could debate whether any of these pills actually *caused* hospitalisation.

The *preventability* of these HARMs is even harder to assess. For example, how to value HARMs related to side effects that were consciously accepted during prescribing? As we used retrospective data, we concluded that we could not reliably assess preventability.

The challenges in the assessment of medication-relatedness of hospitalisations urge for modesty in ambitions to reduce HARMs. They also call for other indicators to measure the effect of quality improvement interventions. For example, goal attainment

scaling could provide a standardised method resulting in patient-specific outcomes that do more justice to the effects of the individualised approach of the NDP-led care model and might be better able to capture eventual effects. [8,9] Last but not least, the challenges stress the need for a qualitative explanation of the background of HARMs. We aimed to incorporate the measurement-uncertainty by reporting "possible" HARMs, and used an adjusted algorithm that had been used to assess medication-relatedness of hospitalisations before. [10] As this method was used in all study groups, the comparison remains valid: the interprofessional healthcare model resulted in a lower risk of HARMs compared to usual care. Yet, we would discourage the extrapolation of the unadjusted numbers and percentages we reported, as these have a high level of uncertainty.

Third, we used *prescription indicators* (Chapter 4), as process indicators of quality of pharmaceutical care. Prescription indicators are originally developed to assess and improve quality of provided care in individual community pharmacies and collaborating general practices. Over the past decades, these indicators are increasingly used by healthcare insurers to determine remuneration fees. [11] Hence, the choice for prescription indicators as secondary outcome measurement fitted into both scientific and policy developments. We found no overall effect of the intervention when comparing scores between the interprofessional and traditional pharmaceutical care models (Chapter 4). This lack of effect can have multiple explanations – the first one being that the intervention had no effect on improving quality of care indeed. However, as we did find a potential reduction on HARMs (Chapter 3), and showed that side-effects were less frequently experienced by patients after NDP-led medication reviews (Chapter 5) we –in hindsight– question the suitability of prescription indicators to measure the effect of a quality improvement intervention such as this interprofessional healthcare model. Analogue, we also question the use of indicators in remuneration procedures of healthcare insurers. Especially in valuing quality of care, we would suggest the use of different checkpoints, such as an assessment of the quality improvement projects executed in an individual practice (including quantity, effectiveness and reasoning behind the choices).

Knowing when, why and how the NDP-model is effective; the context of pharmaceutical care

I. The model works because GPs and NDPs align their professional identities

Although the interprofessional model is new in the Netherlands, it has previously been introduced and researched (sometimes in slightly different forms) at different places across the world. [3,12–15] These studies provided promising results as well as insight into when, why and how the model could work. Elements essential to make the model work were: 1. *full integration* of the pharmacist in the primary care team, with close collaboration with the GP, [16,17] 2. *additional education* for the pharmacist to become a clinical patient-centred care provider, by learning and developing communication and

clinical skills [18,19] and 3. *shared responsibility* between the pharmacist and GP over the pharmaceutical care provided. [19,20]

Underlying these three key elements, the input of ***new knowledge*** by NDPs into primary care practices has been thought to increase quality of care. This was also theorised in the initial program theory for the POINT project. [21] In our qualitative research, we inferred from interviews with GPs who engaged in the model that this "addition of new knowledge"-mechanism was indeed triggered when NDPs were introduced in their practices (Chapter 6). This has been recognised before in a comparable model in the United Kingdom [22] as well as in other settings. [23–25] Yet, it has also been stated that the addition of knowledge alone often is not enough to result into quality improvement, especially when it is brought by a "new" professional: interprofessional collaboration can face conflicts that limit the effectiveness of the heterogeneous group. [26,27] So, another mechanism is needed to secure effective use of the added new knowledge.

We found that the additional knowledge could only be utilised as concurrently a process took place in which GPs and NDPs ***aligned their professional identities*** (Chapter 6). We think that this second mechanism incorporates the earlier mentioned key elements and provides insight into *what happens* that makes the model work when those key elements are present. 'Professional identity alignment' concerns the process that both GPs and NDPs go through when they start working together in this interprofessional model: they change in what they consider appropriate, legitimate and thinkable in their work situations. With both professionals having their professional identity changed from their original identity –not in a random direction but *aligned* onto one another– the model becomes truly and effectively interprofessional. As stated, this process of alignment incorporates the three key elements mentioned. We think that the elements are no standalone features, but are needed together to enable the process of identity alignment to take place. We would like to take a closer look at them, to further illustrate what the identity alignment entails and how and when it could be reproduced.

The first key element is *full integration* of NDPs in primary care teams. Earlier studies on the interprofessional model concluded that proximity between GP and pharmacist (being part of the team and working in the same location) was an enabling factor to improve collaboration and to build trust. [22,28] Based on our findings, we deem full integration essential not only because it improves collaboration and builds trust, but because it facilitates ***discursive actions*** to occur. Discursive actions concern everyday work interactions, including informal encounters: e.g. face-to-face discussing patients' care plans, coffee corner and corridor talking. In those moments, both implicitly and explicitly, the process of identity formation and adaptation can take place: professional identities are explored and shaped in relation with others. [29] In other words: discursive actions are the means needed for the process of identity alignment to occur (and thus to enable effective use of new knowledge).

These discursive actions and related identity alignment do not occur between GPs and community pharmacists in traditional care settings, even though they often

work in the same building. This contrast was well depicted by a GP participating in the POINT project: "*To collaborate with [the NDP,] someone with both medical knowledge as well as pharmaceutical background, that results in a nice cooperation. I sometimes visit the community pharmacist but that is different. You still have… then it is often all about logistics, while with [the NDP] you notice that she just does much more with patients and, well, she has a much more medical background*." (Chapter 6). The quote clearly highlights that full integration involves more than a shared location. Also, the quote stresses the importance of the second key element: additional education.

The second key element, *additional education* for pharmacists, again was recognised in earlier studies: the need for (postgraduate) education was reported essential to enable pharmacists to work in primary care. [22,30] In the POINT project, a 15-month interprofessional workplace learning program was especially designed for pharmacists to become NDPs. [18] In this program, the NDP-trainees were taught communication-, consultation- and clinical reasoning skills during the teaching days. The other days they worked in the general practice, where the interprofessional workplace learning method further facilitated discursive actions to occur and hence contributed to the professional identity alignment. For NDPs, those identity work processes incorporated –besides aligning to the GPs' professional identity– even the formation of a fully new professional identity. [31]

The third key element is *shared responsibility* between GP and NDP over the pharmaceutical care provided. Again, this confirmed an earlier study on the interprofessional model; illustrated by a pharmacist saying "*I'd like to actually work with the physician rather than [asking] 'are you ok with this?*" [32] Yet, sharing responsibility is no obvious nor automatic consequence when GPs and NDPs work together. Their traditional view on professional responsibility differs widely. General practitioners, as generalists, feel ultimately responsible for patient care and see themselves as main prescribers. [28] For NDPs, traditionally used to taking a more supporting role, taking this responsibility is new, as stated by one of our NDPs: "*as a pharmacist you are always responsible for the patient, even when only dispensing. But during the [POINT] study we made recommendations for pharmacotherapy, we didn't just suggest it to the GP but carried it out too*." [31] Hence, sharing responsibility requires both professionals to reconsider what is appropriate, legitimate and thinkable in bearing and sharing responsibility. This change for NDPs was described elsewhere. [20,31] We looked into this process for GPs and found that the process of identity alignment made GPs start to think differently on sharing responsibility (Chapter 6). However, this process still has to be completed. We observed a careful start of interprofessional collaboration between GPs and NDPs, including sharing of responsibilities concerning pharmacotherapy. Yet, we believe that to reach fully effective and reciprocal sharing of responsibilities needs more time to develop.

II. The model only works when the need for change is acknowledged

A prerequisite for the mechanisms of "addition of new knowledge" and "alignment of professional identities" to be triggered, is a context where GPs ***acknowledge the need for improvement*** of the pharmaceutical care provided in their practice (Chapter 6). The quality of collaboration between GPs and community pharmacists had no role in triggering the working mechanisms (both suboptimal and optimal experienced collaboration situations were included). Therefore, we conclude that the interprofessional model can work everywhere – as long as GPs acknowledge the need for improvement.

It should be noted here that, of course, our explicit selection of general practices where GPs were willing to engage in the improvement project added importantly to this context of "acknowledged need for improvement". Across practices in the Netherlands, such willingness will differ. Hence, specific attention should be given to engaging GPs in acknowledging the problem being addressed by the model, to achieve successful broader implementation. Here, we want to highlight that among the GPs interviewed in our study –although all willing to engage in the improvement project– the level on which they acknowledged a need for improvement differed. Some GPs considered the need on the practice level only, feeling a lack of time to provide proper pharmaceutical care. Others recognised a need for improvement on the personal, healthcare provider level too, experiencing a gap in their own pharmaceutical knowledge to answer to the increasing complexity of pharmaceutical care (Chapter 6). Despite these differences, we found the mechanisms as described to occur in both cases. Yet, it is conceivable that not acknowledging a need for change on the personal, healthcare provider level hinders professional identity alignment, as then there seems no need to change one's own identity.

Key characteristics of the interprofessional model

Combining qualitative and quantitative results, the *key characteristics* that make the interprofessional model work are:

1. the GP and NDP ***together provide shared pharmaceutical care*** in a ***fully integrated*** care setting that is of improved quality compared to the care provided in usual care settings
2. the GP and NDP ***have their identities aligned*** – a process that takes place in the primary care practice and that is further supported by ***additional education*** for the NDPs, resulting in a fundamentally different collaboration compared to traditional care settings
3. the GP and NDP ***acknowledge the need for improvement***, and are willing to engage in the change required – eventually ***sharing responsibility*** over the provided care.

Our findings highlight that the interprofessional model with NDPs integrated in primary care teams is, after a process of change, fundamentally different from primary

care teams collaborating with community pharmacists in traditional primary care settings.

Where does the model stand now? A shared ambition for change, but stakeholders are stuck in the current system

Worldwide, amongst GPs the need for change of the current pharmaceutical care is increasingly acknowledged. Key driver is the fact that primary care is getting more complex with the increasing number of elderly patients with polypharmacy and chronic conditions. [33] Pharmacists are acknowledged as potentially complementing the current skills mix in primary care [34], especially when working as "general practice-based pharmacists". [35]

Pharmacists also feel the need for change, to develop from being drug-centred towards being patient-centred. [36] The importance of providing pharmaceutical care is generally recognised amongst pharmacists, yet they differ in terms of willingness to take on these patient care roles and responsibilities, as well in relinquishing their drug distribution roles. [32,37]

So, although the need for improvement and the wish to change is present among both GPs and pharmacists, the change from the traditional towards the interprofessional model hasn't been made. We reckon that GPs and pharmacists are stuck in the current system.

This seems also the case in the Netherlands. The need to improve pharmaceutical care was stressed in two reports on preventable HARMs in 2008. [4,5] Results were directly translated into recommendations to optimise pharmaceutical care. [38] To further improve the organisation of pharmaceutical care, in 2012 a multidisciplinary guideline was developed in which the joint provision of pharmaceutical care by GPs and community pharmacists was urged – focussing on performing clinical medication reviews. [39] However, this guideline is still insufficiently implemented. [40] An assessment among stakeholders to identify barriers in guideline adherence provided important messages: "*the pharmacist is often not recognised as a caregiver*", "*unclear whether the GP, pharmacist or patient takes or should take the lead*", and multiple examples of challenges in the collaboration between GP and pharmacist, such as ICT problems (for example, reports on changes following a medication review are lost, as information is not fully shared between GPs and pharmacists, resulting in stopped medications being prescribed again). [41] Also, the fact that community pharmacists are still largely financially dependent on reimbursements for their dispensing tasks hampers adherence to the guideline: "*stopping medication for patients with their medication in weekly dosing systems has important financial consequences, hence is often not effected. A remuneration for this specific patient population could help hereon*". [41]

These barriers have been recognised before to hamper improvement of pharmaceutical care in traditional care models. [42–45] Yet, instead of searching for a solution to these problems, the conclusion of the aforementioned assessment was that

"adhering to the guideline was not effective nor achievable in the current healthcare system". [46] Both the results from the stakeholder assessment, as well as the poor effects of clinical medication reviews as reported in international and national literature [47–50] were brought forward to further endorse this conclusion. This resulted in a "light" version of the guideline stating, "clinical medication reviews should not be regarded as a panacea to solve all polypharmacy related problems" and "the focus should be on improving ICT instead of on medication reviews". [46]

We disagree with these conclusions, for two reasons.

First, we think ICT improvements alone will not change the current pharmaceutical care provision. Improving ICT can add to the quality of pharmaceutical care: obviously, having access to *all* required information provides important quality gains. In fact, we think this information should optimally also include information on dispensed medication: to guarantee quality of the entire chain of pharmaceutical care, the dispensing process should be aligned to the pharmaceutical care provision in primary care too. Yet, providing the data alone will not be enough, as the data will still need to be interpreted. In Finland, healthcare data on primary and secondary care including pharmacy data are accessible to all care providers and patients in an online repository. [51] Although this is quite impressive, and may bring major benefits, interpretation of the data still requires broader multidisciplinary competency.

Second, we question the focus on clinical medication reviews. We stress that clinical medication reviews do have the potential to improve quality of pharmaceutical care, especially when part of full pharmaceutical care provision: it has been recognised before that pharmaceutical care improvements are most effective when they consist of *multifaceted interventions*, rather than medication reviews performed (or provision of education, for that matter) in isolation. [17] Contrasting a recent RCT measuring effects of clinical medication reviews by community pharmacists in the Netherlands with our main findings further illustrates that the context in which these reviews are placed is essential for its potential to achieve success: in the first context, medication reviews yielded no effect on total number of health problems or health-related quality of life [52], while we found (with the provision of medication reviews in elderly with polypharmacy being one of the main tasks of the NDPs) a positive effect on the clinical outcome medication-related hospitalisations.

The interprofessional model could overcome most barriers mentioned above. However, even with interprofessional collaboration the problems of insufficient time and reimbursement will continue to exist. While NDPs obviously provide fulltime pharmaceutical care, GPs will still have to invest time in providing shared care. Some of the GPs interviewed in our study considered this investment much more efficient than aiming to provide pharmaceutical care themselves; yet others stated that the model means additional workload. In return however, GPs experienced increased job satisfaction. Future research could investigate whether the interprofessional model eventually could save GPs time as well. The problem of insufficient reimbursement fully remains, and has been recognised an important barrier elsewhere too. [53]

Interestingly, changing the current pharmaceutical care model is also what stakeholders regarded necessary to optimise guideline adherence: besides "*better mutual cooperation*", "*improved finance*" and "*pharmacists and GPs should be as much as possible located 'under one roof'*", the need was stressed to "*invoke integral healthcare models with adjusted financing, organisation, administration and care provision, to enable network care.*" [41]

Recommendations for broader implementation of the interprofessional model

Lastly, we would like to discuss some actions to be taken by stakeholders in order to improve the current system of pharmaceutical care (depicted in **Figure 1**).

I. Professional organisations of GPs and pharmacists: start with the model, by putting the three key characteristics into practice

- Communicate that current pharmaceutical care needs improvement and put the interprofessional model on the agenda for the coming 5 years. Stimulate the professional dialogue; discuss the consequences of our results for sharing responsibilities between GPs and NDPs, and the complementary responsibilities of community pharmacists; and convince the field to rethink pharmaceutical care in primary care.
- Facilitate the professional identity alignment-process: fully integrate the NDPs into the primary care teams (e.g. facilitate a consultation room, shared use of ICT systems including the patient records, aligned agendas of GPs and NDPs), and prepare (the field) for the need to invest time and to reconsider professional standards and values, as well as for increased job satisfaction. Provide support for both GPs and NDPs during this process; for pharmacists by furthermore adopting the already developed training program [18], including interprofessional learning, to become NDPs.

II. Policy makers, healthcare insurers and healthcare inspectorate: provide a solid foundation for the model, by ensuring adequate financing and monitoring truly on quality

- Acknowledge the NDP as healthcare provider and ensure finances for their post-graduate training by the state to guarantee sufficient NDP-trainees and future NDPs.
- Allocate appropriate budget for NDP-care, including reimbursement of both direct and indirect patient care. Although we could not demonstrate a reduction in direct healthcare costs yet (Chapter 3), investing in this quality improvement in primary care could pay off on the long term.

- Redesign ways to monitor the quality of pharmaceutical care: focus on interprofessional collaboration and quality improvement initiatives instead of using current indicators.

III. Academia and patient organisations: further optimise the model, by continuous follow-up research

- Facilitate follow-up research to further improve the model during implementation. Use patient-centred measures to identify true intervention effects, and apply the MRC guidelines for evaluating complex interventions: acknowledge the complex nature of this quality improvement model by choosing appropriate research methods. Patients should have a prominent role here.
- Review the curricula of Medicine and Pharmacy and integrate interprofessional learning.

The NDP integrated in primary care practices: the future

The interprofessional model differs fundamentally from traditional pharmaceutical care models. We demonstrated *that* and *how* the model improves pharmaceutical care in the primary care setting – here, the fundamental differences play a key role. The introduction of the model has proven to be feasible in Dutch primary care. Still, shifting towards the model will require investments. Nonetheless, this thesis POINTs out that the interprofessional model with NDPs fully integrated in primary care teams is the fundament of future pharmaceutical care.

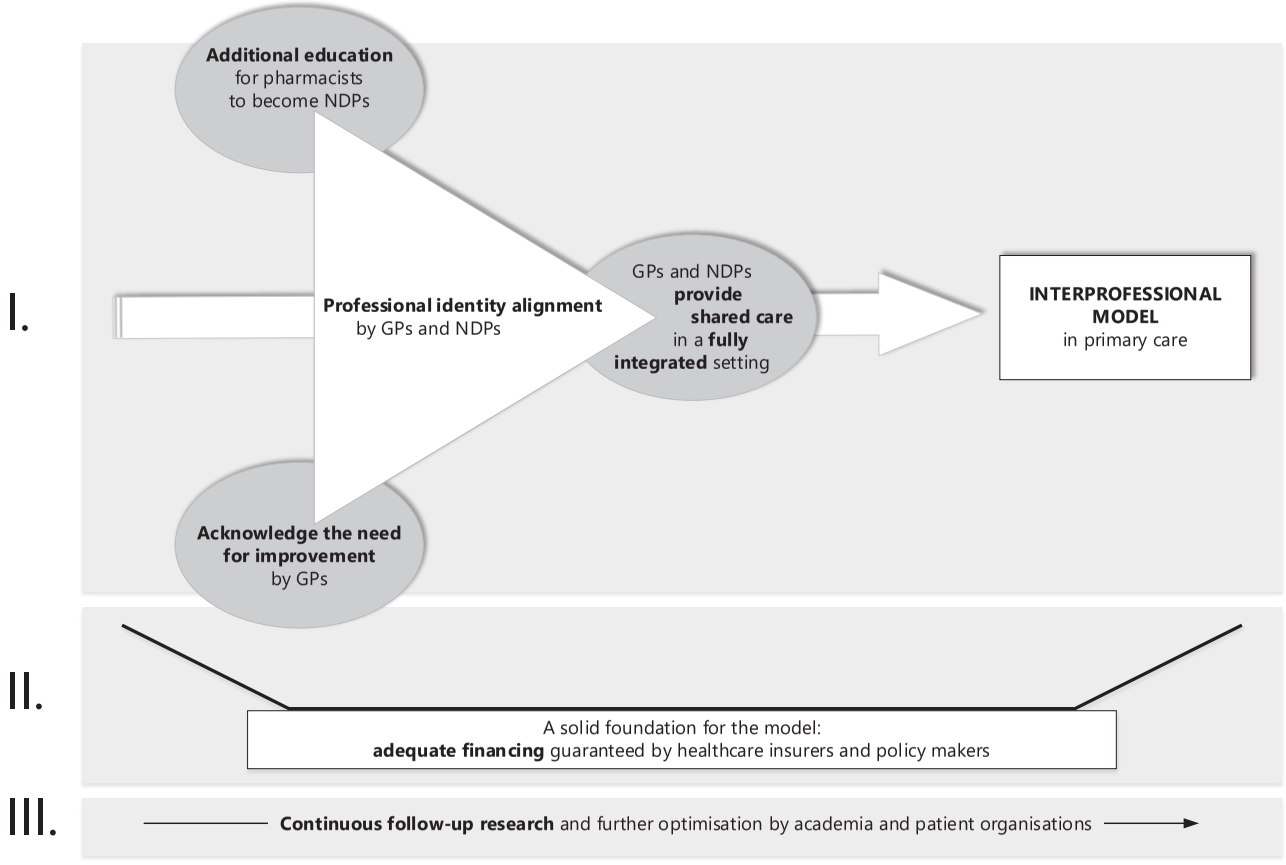

Figure 1. Requirements for broader implementation of the interprofessional model by different stakeholders

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SUMMARY

Providing safe and effective pharmacotherapy is an essential element of primary care. Generally, medication is very effective. However, medication can also cause harm. The highest risk of such medication-related harm is among elderly patients using multiple medications – a population that is currently growing. Optimising pharmacotherapy in these patients to minimise harm is important, yet complex. The fact that secondary care is increasingly transferred to primary care further adds to this complexity. Currently, this complex care problem is inadequately addressed.

Optimally, pharmaceutical care should be performed in close collaboration between the general practitioner (GP), the pharmacist and the patient. Yet, several well-known barriers hamper this joint provision of care: collaboration between pharmacists and GPs is often suboptimal; pharmacists have no access to relevant patient records and lack clinical knowledge and communication skills to provide good pharmaceutical care; and both pharmacists and GPs lack sufficient time and reimbursement to provide pharmaceutical care.

A new interprofessional model of pharmaceutical care provision with a *non-dispensing pharmacist* (NDP) integrated in primary care teams might address above barriers. In ***Chapter 1***, this model is introduced. An NDP is a clinical pharmacist working fulltime in the general practice, completely separated from the community pharmacy and its dispensing tasks. As part of the general practice team, the NDP provides full-time patient care in close collaboration with the GP. Patient care includes both activities on the *patient level* and on *the practice level*. On the patient level, activities include performing medication reviews for elderly with polypharmacy and holding consultation hours for patients with specific medication-related problems. On the practice level, activities consist of providing quality improvement projects and educating the practice staff.

The general aim of this thesis is to evaluate this interprofessional care model. First, we assess *what* the effects of the model are on improving quality and safety of current pharmaceutical care. Then, we investigate *when, why and how* the model could be effective.

To answer these questions, the Pharmacotherapy Optimisation through Integration of a Non-dispensing pharmacist in primary care Teams (POINT) project was conducted. ***Chapter 2*** describes the design of the POINT project: a non-randomised controlled intervention study, comparing the interprofessional model with an NDP integrated in primary care practice (*intervention group*) with to two current models of pharmaceutical care, where GPs collaborate with community pharmacists as usual (control group "*usual care*") and with community pharmacists who had done an additional training in performing clinical medication reviews (control group "*usual care plus*"). During the project, both quantitative and qualitative research was conducted.

For the intervention group, ten NDPs were fully integrated in general practices and provided full-time pharmaceutical care, while being additionally trained in an especially designed 15-month clinical pharmacy training program. For the control

groups, general practices were matched as much as possible to the intervention practices. The methodological decisions and challenges in evaluating a complex intervention such as the POINT project are described in this chapter.

Chapter 3 and ***Chapter 4*** describe *what* the effects of the interprofessional model are on improving quality and safety of pharmaceutical care.

Medication harm is diverse – ranging from mild side effects to hospitalisation or even death. Prior research had reported on medication-related hospitalisations (HARMs) and deemed almost fifty percent of those to be preventable. Hence, the number of HARMs was set as primary outcome measurement to assess safety improvement. ***Chapter 3*** reports the effect of the model on HARMs in elderly patients with polypharmacy. Secondary outcome measurements include drug burden and direct healthcare costs.

In the intervention period of the POINT project (June 2014 until May 2015), 822 possible HARMs were identified among 11.281 high-risk patients. We used mixed models to compare the intervention with both control groups: after adjusting for clustering, potential confounders and taking the baseline measurements into account, we found a rate ratio of HARMs of 0.68 (95% Confidence Interval 0.57–0.82) in the intervention group compared to usual care, and 1.05 (95% CI 0.73–1.52) compared to usual care plus. We conclude that the interprofessional model lowers the risk of HARMs in elderly patients with polypharmacy compared to usual care. No difference with usual care plus was found. For drug burden and costs, no differences between the intervention and both control groups were found.

Besides effects on direct clinical outcomes such as HARMs, quality improvement interventions could have effect on process outcomes. Hence, ***Chapter 4*** reports the model's effect on prescribing quality of GPs, measured with quality prescribing indicators. We searched indicators from the literature and assessed their feasibility, validity, acceptability, reliability and sensitivity to change. We selected ten indicators. Scores on all indicators improved in the intervention group after introduction of the NDP. However, compared to the two control groups in mixed models, prescribing quality improved solely on the indicator measuring monitoring of the renal function in patients using antihypertensive medication. Although this finding could indicate that the interprofessional model indeed has no overall effect on GPs' prescribing quality, we question whether the use of prescription indicators is suitable for assessing the effect of a complex intervention such as this interprofessional NDP-led care model.

Following these reports on the effect of the model on improving quality of care, ***Chapter 5*** and ***Chapter 6*** provide insight into *when, why and how* the model works.

In ***Chapter 5***, we investigate patients' perspectives on clinical medication reviews performed by NDPs in the interprofessional care model. The aim of the study was to deepen the insight into what the model could bring about to patients, as this had been sparsely studied so far despite the patients' important role in pharmaceutical

care provision. Using questionnaires and medical records review, we measured and triangulated three outcomes. First, patients were satisfied with the pharmaceutical care provided by the NDPs. Second, patients consented with most proposals (96%) by the NDPs to attain patient-specific pharmacotherapy-related goals, of which 46% concerned the reduction of side effects – 40% of those goals were attained. Third, patients experienced fewer side effects after the medication review compared to controls. Combining these outcomes, we conclude that patients are open to the new model, and that NDPs seem able to effectively mitigate patients' side effects.

In addition to examining patient perspectives, ***Chapter 6*** reports the GPs' perspective on the interprofessional model. We interviewed 18 GPs who worked with the NDPs during the POINT project. To evaluate these interviews, the realist evaluation approach was used. With a realist evaluation, the context in which an intervention is placed is explicitly taken into account, as this is thought to provide essential information: depending on the context in which it is placed, an intervention can trigger working mechanisms that in turn result in outcomes. Hence, an intervention can be effective in one context, but not at all in another. Therefore, insight into context-elements and related working mechanisms could improve chances of success when further implementing the intervention in different contexts.

We found that an essential context element was that GPs acknowledged the need for improvement of the pharmaceutical care provided in their practice. In this context, two working mechanisms could be triggered: NDPs added new knowledge to the practice, and both GPs and NDPs evolved in what they consider appropriate, legitimate and thinkable in their work situations – in other words, they aligned their professional identities. For NDPs, this meant that they increasingly incorporated the patients' context into their evidence-based considerations. For GPs, this meant that they increasingly valued differences in work approaches between themselves and NDPs, and eventually started to think and feel differently over sharing (part of) their responsibility of provided care with the NDPs.

Aligning of professional identities took place through discursive actions: in coffee corner talking and while discussing patients. Effectivity of discursive actions was further facilitated by the additional training of NDPs. Such discursive actions seem in general not to occur between GPs and community pharmacists, what could explain why the aligning process did evolve between GPs and NDPs but seems not to take place between GPs and community pharmacists.

We conclude that for successful broader implementation of the model, these findings underline the importance of (1) GPs to acknowledge the need for improvement, (2) NDPs to be integrated in the primary care team to enable and allow discursive actions between GPs and NDPs to occur and (3) additional training of NDPs to further facilitate identity alignment.

Last, in ***Chapter 7***, we discuss our findings. As the interprofessional model should be considered a complex intervention, we stress the need for the evaluation to include

both quantitative research (to provide effect sizes), and qualitative research (to provide information on how the intervention could be replicated in another context, in such a way that trial outcomes could be expected to be reproduced). In this Chapter, we first discuss some methodological challenges encountered in the quantitative part of our research. Next, we dive into our research on when, why and how the model could work. Integrating our findings with international literature on comparable models worldwide, we provide three key characteristics that make the model work:

1. the GP and NDP *together provide shared pharmaceutical care,* in a *fully integrated* care setting;
2. the GP and NDP *have their professional identities aligned*, a process taking place in the primary care practice and further supported by *additional education* for the NDPs;
3. the GP and NDP *acknowledge the need for improvement* and eventual *share responsibility* over the provided care.

This results in a model that is fundamentally different from traditional models of pharmaceutical care provision, with improved quality and safety of provided care.

We then focus on the current situation worldwide and in the Netherlands specifically. We conclude that stakeholders want to improve pharmaceutical care, yet are stuck in the current system with its known barriers that can be overcome by the interprofessional model. Feasibility of the model and enthusiasm by the field is moreover shown by the fact that five NDPs continued working in the general practices after the intervention period ended.

Finally, we provide recommendations to stakeholders in the field on how to sustain and further implement this new interprofessional model and the associated improved quality of care.

SAMENVATTING

Een belangrijk onderdeel van huisartsgeneeskunde is farmacotherapie: behandeling met medicatie. Hoewel medicatie meestal erg effectief is, kan het ook schade opleveren. Ouderen die langdurig meerdere medicijnen gebruiken lopen het grootste risico op dergelijke medicatie-schade. Deze hoog-risico patiëntengroep groeit. Om medicatie-schade in deze groep patiënten tot een minimum te beperken is het belangrijk om hun farmacotherapie te optimaliseren; maar dat is complex. De toenemende verschuiving van tweedelijns naar eerstelijns zorg versterkt de complexiteit van farmacotherapie verder. Op dit moment wordt dit complexe zorgprobleem onvoldoende aangepakt.

Farmacotherapeutische zorg is optimaal wanneer de huisarts, apotheker en de patiënt nauw met elkaar samenwerken. Meerdere zaken staan deze samenwerking echter in de weg: apothekers en huisartsen werken dikwijls suboptimaal samen; apothekers hebben geen toegang tot patiëntendossiers en missen klinische kennis en communicatievaardigheden die nodig zijn om goede farmacotherapeutische zorg te kunnen leveren; en zowel apothekers als huisartsen hebben onvoldoende tijd en financiële vergoedingen om deze zorg te kunnen leveren.

Een nieuw interprofessioneel model om farmacotherapeutische zorg te leveren, met een in de huisartspraktijk geïntegreerde *apotheker-farmacotherapeut* (zonder apotheek), zou bovenstaande problemen kunnen beantwoorden. In ***Hoofdstuk 1*** wordt dit model geïntroduceerd. Een apotheker-farmacotherapeut is een klinische apotheker die fulltime in de huisartspraktijk werkt, volledig apart van de openbare apotheek en de bijbehorende medicatie-uitgifte taken. De apotheker-farmacotherapeut is onderdeel van het team, en levert in nauwe samenwerking met de huisarts fulltime patiëntenzorg. Patiëntenzorg vindt plaats op zowel *patiënt*- als op *praktijkniveau*. Op patiëntniveau betekent dit het uitvoeren van medicatiebeoordelingen uitvoeren voor ouderen met polyfarmacie en het draaien van spreekuren voor patiënten met specifieke medicatie-gerelateerde problemen. Op praktijkniveau omvat dit het uitvoeren van kwaliteitsprojecten en het opleiden van praktijkpersoneel.

Het doel van dit proefschrift is om het interprofessionele model met een in de huisartspraktijk geïntegreerde apotheker-farmacotherapeut te evalueren. Eerst wordt onderzocht *wat* het effect van het model is op het verbeteren van de kwaliteit en veiligheid van de farmacotherapeutische zorg. Daarna volgt onderzoek naar *wanneer, waarom en hoe* het model effectief kan zijn.

Om deze vragen te beantwoorden werd het POINT-project opgezet: Pharmacotherapy Optimisation through Integration of a Non-dispensing pharmacist in primary care Teams (optimalisatie van farmacotherapie door de integratie van een apotheker-farmacotherapeut zonder apotheek in de huisartspraktijk). ***Hoofdstuk 2*** beschrijft het design van het POINT-project: een niet-gerandomiseerde, gecontroleerde interventiestudie, waarin het interprofessionele model (de *interventiegroep*) vergeleken wordt met twee traditionele modellen van farmacotherapeutische zorg, waarin huisartsen samenwerken met openbaar apothekers (de controlegroep "*gebruikelijke zorg*") en met openbaar apothekers die een landelijk gecertificeerde training hebben

gevolgd om medicatiebeoordelingen uit te voeren (de controlegroep "*gebruikelijke zorg plus*"). Het project bevatte zowel kwantitatief als kwalitatief onderzoek.

Voor de interventiegroep werden tien apotheker-farmacotherapeuten volledig in huisartspraktijken geïntegreerd. Zij leverden fulltime farmacotherapeutische zorg, waarbij zij aanvullend getraind werden in een speciaal daartoe ontwikkeld 15 maanden durend training programma. Met dit programma trainden en verbeterden de apotheker-farmacotherapeuten hun vaardigheden op het gebied van patiënt-consultatie, klinisch redeneren en interprofessionele samenwerking. Voor de controlegroepen werden huisartspraktijken geselecteerd die qua praktijkkarakteristieken zoveel mogelijk overeenkwamen met de praktijken in de interventiegroep. In dit hoofdstuk beschrijven we de methodologische keuzes en uitdagingen om een complexe interventie als het POINT-project te evalueren.

Hoofdstuk 3 en ***Hoofdstuk 4*** beschrijven <u>*wat*</u> de effecten van het interprofessionele model zijn op het vergroten van de kwaliteit en veiligheid van farmacotherapeutische zorg.

Medicatieschade is een breed begrip: het loopt uiteen van milde bijwerkingen tot ziekenhuisopnames en zelfs overlijden. Eerder onderzoek naar dergelijke medicatie-gerelateerde ziekenhuisopnames rapporteerde dat bijna vijftig procent potentieel vermijdbaar was. Het aantal medicatie-gerelateerde ziekenhuisopnames werd daarom gekozen als primair uitkomstmaat om eventuele verbetering van farmacotherapeutische zorg te meten. ***Hoofdstuk 3*** toont het effect van het interprofessionele model op deze medicatie-gerelateerde ziekenhuisopnames, gemeten in oudere patiënten met polyfarmacie. Secundaire uitkomstmaten omvatten de "medicatielast" (drug burden index) en directe zorgkosten.

Er werden in de interventieperiode van het POINT-project (juni 2014 – mei 2015) 822 mogelijke medicatie-gerelateerde ziekenhuisopnames gevonden bij 11.281 hoog-risicopatiënten. We vergeleken de interventiegroep met de controlegroepen met behulp van "mixed effect modellen": na correctie voor clustering, voor mogelijke verstorende factoren en na het meenemen van baseline-metingen, vonden we een *rate ratio* van medicatie-gerelateerde ziekenhuisopnames van 0.68 (95% betrouwbaarheidsinterval 0.57–0.82) in de interventiegroep vergeleken met "gebruikelijke zorg", en van 1.05 (95% BI 0.73–1.52) vergeleken met "gebruikelijke zorg plus". We concluderen dat het interprofessionele model het risico op medicatie-gerelateerde ziekenhuisopnames in ouderen met polyfarmacie verlaagt, vergeleken met gebruikelijke zorg. We vonden geen verschil met de gebruikelijke zorg plus praktijken. In medicatielast en zorgkosten werd geen verschil gevonden tussen de interventiegroep en beide controlegroepen.

Behalve op klinische uitkomsten als medicatie-gerelateerde ziekenhuisopnames, kunnen interventies om de kwaliteit van zorg te verbeteren effect hebben op procesmaten. In ***Hoofdstuk 4*** beschrijven we het effect van het model op de kwaliteit van voorschrijven door huisartsen, gemeten met indicatoren. We beoordeelden indicatoren afkomstig

uit de literatuur op hun haalbaarheid, validiteit, aanvaardbaarheid, betrouwbaarheid en gevoeligheid voor verandering. Tien indicatoren werden geselecteerd. Scores op alle indicatoren verbeterden nadat de apotheker-farmacotherapeut in de interventiepraktijken was geïntegreerd. Echter, in de vergelijking met de twee controlegroepen in mixed effect modellen verbeterde de kwaliteit van voorschrijven slechts op één indicator: in het monitoren van de nierfunctie in patiënten die antihypertensie-medicatie gebruiken. Deze bevinding kan natuurlijk betekenen dat het interprofessionele model geen overkoepelend effect heeft op de kwaliteit van voorschrijven door huisartsen, echter wij betwijfelen of indicatoren geschikt zijn om het effect te meten van een complexe interventie zoals dit interprofessionele model met een geïntegreerde apotheker-farmacotherapeut.

Na de beschrijving van de effecten van het model op het verhogen van de kwaliteit van zorg, geven ***Hoofdstuk 5*** en ***Hoofdstuk 6*** inzicht in *wanneer, waarom en hoe* het model werkt.

In ***Hoofdstuk 5*** beschrijven we het patiënten perspectief op de klinische medicatiebeoordelingen die de apotheker-farmacotherapeuten in het interprofessionele model hebben uitgevoerd. Het doel van deze studie was om meer inzicht te verkrijgen in wat het model voor patiënten oplevert; ondanks dat patiënten een belangrijke rol hebben in het leveren van effectieve farmacotherapeutische zorg, is dit namelijk nog weinig onderzocht. Met vragenlijstonderzoek en de beoordeling van medische dossiers onderzochten en trianguleerden we drie uitkomsten. Allereerst waren patiënten tevreden met de door de apotheker-farmacotherapeuten geleverde zorg. Ten tweede stemden patiënten in met de meeste voorstellen (96%) van de apotheker-farmacotherapeuten om patiënt-specifieke opgestelde doelen te behalen. Van deze doelen betrof 46% het verminderen van bijwerkingen; en daarvan werd 40% behaald. Ten derde ervoeren patiënten minder bijwerkingen na de medicatiebeoordeling, vergeleken met controlepatiënten zonder medicatiebeoordeling. Op basis van deze resultaten concluderen we dat patiënten open staan voor het nieuwe model en dat hun bijwerkingen effectief verminderd lijken te kunnen worden door de apotheker-farmacotherapeut.

Naast het patiënten perspectief, toont ***Hoofdstuk 6*** het perspectief van de huisarts op het interprofessionele model. We interviewden 18 huisartsen die gedurende het POINT-project met de apotheker-farmacotherapeuten hadden gewerkt, en gebruikten de methode van realistische evaluatie om deze te evalueren. Met een realistische evaluatie wordt de context waarin een interventie geïmplementeerd wordt expliciet onderzocht: afhankelijk van de context kan een interventie namelijk wel of niet werkingsmechanismen activeren, die vervolgens resulteren in uitkomsten. Zodoende kan een interventie effectief zijn in de ene context, maar totaal ineffectief in een andere. Inzicht in de context en gerelateerde werkingsmechanismen kan daarom helpen om de interventie succesvol in verschillende contexten te implementeren.

Een essentieel context-element bleek dat huisartsen erkenden dat er verbetering nodig was van de farmacotherapeutische zorg zoals die in hun praktijk geleverd werd. Wanneer dat erkend werd, konden twee werkingsmechanismen geactiveerd worden: apotheker-farmacotherapeuten voegden nieuwe kennis toe aan de huisartspraktijk, en zowel huisartsen als apotheker-farmacotherapeuten veranderden in wat zij passend, legitiem en denkbaar vonden in hun werk – zij stemden hun professionele identiteiten op elkaar af. Voor apotheker-farmacotherapeuten betekende dit dat zij in toenemende mate de context van de patiënt meenamen in hun overwegingen. Voor huisartsen betekende dit dat zij steeds meer de verschillen in werkwijze van apotheker-farmacotherapeuten en zichzelf gingen waarderen, en dat zij in de loop van de tijd anders gingen denken over het delen van verantwoordelijkheid over de gezamenlijk met de apotheker-farmacotherapeut geleverde zorg.

Het afstemmen van professionele identiteiten gebeurde in zogenaamde discursieve acties: contact tijdens bijvoorbeeld koffiepauzes en patiëntbesprekingen. De effectiviteit van deze discursieve acties werd verder versterkt door de training van de apotheker-farmacotherapeuten. Over het algemeen lijken zulke discursieve acties tussen huisartsen en openbaar apothekers niet voor te komen, wat zou kunnen verklaren waarom het proces van afstemming wél tussen huisartsen en apotheker-farmacotherapeuten ontstond, maar niet tussen huisartsen en openbaar apothekers lijkt plaats te vinden.

We concluderen dat deze studie onderstreept wat nodig is voor succesvolle verdere implementatie van het model: (1) dat de huisarts de noodzaak voor verbetering erkent, (2) dat de apotheker-farmacotherapeut integreert in de huisartsenpraktijk zodat discursieve acties tussen de huisarts en apotheker-farmacotherapeut kunnen plaatsvinden, en (3) dat de apotheker-farmacotherapeut een aanvullende training volgt om het proces van identiteitsafstemming verder te ondersteunen.

In ***Hoofdstuk 7*** tenslotte, bediscussiëren we onze bevindingen. We benadrukken het belang om het interprofessionele model – dat gezien moet worden als een complexe interventie – te evalueren met zowel kwantitatief onderzoek (om effecten aan te tonen) als kwalitatief onderzoek (om informatie te genereren hoe de interventie in een andere context eenzelfde effect kan genereren). In dit Hoofdstuk gaan we allereerst dieper in op enkele methodologische uitdagingen in het kwantitatieve deel van ons onderzoek. Daarna verdiepen we ons onderzoek over wanneer, waarom en hoe het model werkt. We combineren onze bevindingen met die uit internationaal onderzoek naar vergelijkbare interprofessionele modellen en formuleren drie kern-eigenschappen van het model waardoor het werkt:

1. de huisarts en apotheker-farmacotherapeut *leveren samen farmacotherapeutische zorg*, in een *volledig geïntegreerde* setting
2. de huisarts en apotheker-farmacotherapeut *hebben hun professionele identiteiten op elkaar afgestemd* in een proces dat in de huisartspraktijk plaatsvindt en wordt ondersteund door de *aanvullende scholing* van apotheker-farmacotherapeuten

3. de huisarts en apotheker-farmacotherapeut *erkennen de noodzaak tot verbetering* van de huidige zorg, en *delen uiteindelijk verantwoordelijkheid* over de geleverde zorg.

Dit resulteert in een model dat fundamenteel verschillend is van huidige, traditionele modellen van farmacotherapeutische zorg; met verbeterde kwaliteit en veiligheid van zorg.

Vervolgens, kijkend naar de situatie wereldwijd en in Nederland specifiek, stellen we dat huisartsen en apothekers de farmacotherapeutische zorg wel willen veranderen, maar vastzitten in het huidige zorgsysteem met haar bekende knelpunten. Knelpunten die met het interprofessionele model verholpen kunnen worden. Bovendien blijkt uit het feit dat vijf apotheker-farmacotherapeuten na de interventieperiode werkzaam bleven in de huisartspraktijk, dat het model haalbaar is en het veld enthousiast.

Tenslotte beschrijven we enkele aanbevelingen om dit nieuwe interprofessionele model en de gerelateerde verbeterde kwaliteit van zorg te behouden, en verder te implementeren.


DANKWOORD

ABSTRACT

Achtergrond: Een proefschrift heeft altijd maar één naam op de omslag, maar komt tot stand met dank aan veel méér mensen. Die worden naar goed gebruik bedankt in het dankwoord.

Methoden: Van dit proefschrift is dit het enige hoofdstuk dat ik in mijn eentje schreef – om al die anderen die meehielpen aan de andere stukken, van harte te bedanken!

Resultaten: Niet verrassend, maar hoogstwaarschijnlijk wordt het resultaat het meest gelezen hoofdstuk van dit boekje.

Discussie: Het afronden van dit proefschrift (inclusief het schrijven van dit Dankwoord) gebeurt in Corona-tijd. De geldende maatregelen zorgen dat 'even langsgaan' om een boekje af te geven (en te bedanken) niet mogelijk is. Daarom op deze plek, als papieren vervanging van een fysieke groet en woord van dank, nogmaals: bedankt!

Conclusie: Wát een mooi AIOTHO-traject (arts-in-opleiding-tot-huisarts-en-onderzoeker) was dit! Ik heb er erg van genoten, met als kers op de taart dit mooie proefschrift!

ACHTERGROND

Mijn promotietraject begon met een vliegende start: het onderzoek naar een apotheker-farmacotherapeut in de huisartspraktijk was al begonnen toen ik als promovenda startte. Ik waardeer ontzettend hoe ik vanaf het begin welkom was en opgenomen werd in het POINT-onderzoeksteam.

Dat team bestond, net als de interventie zelf, uit "verschillende componenten": onderzoekers vanuit de huisartsgeneeskunde, farmacie en sociologie. Als AIOTHO (arts-in-opleiding-tot-huisarts-en-onderzoeker) beschreef ik de interventie vanuit het huisartsenperspectief, maar ik heb ontzettend veel geleerd én genoten van de combinatie van al deze vakgebieden!

Niek, je visie op de farmacotherapeutische zorg in de huisartspraktijk en je ideeën hoe die te onderzoeken (niet alles behoeft een RCT) waren leerzaam en inspirerend. In de maandelijkse overleggen wist jij de kern snel en scherp te benoemen, waardoor ik weer richting had en verder kon. Dank bovendien voor je sterke tekstuele feedback waarmee de manuscripten steeds weer verbeterden – leuke denk- en schrijfprocessen waren dat! **Han**, met al je kennis over de ontwikkelingen op het gebied van farmacotherapeutische zorg schetste je voor mij de context waarbinnen ons project plaatsvond, vanuit het apothekers-perspectief. Onze gesprekjes over vakanties (over de hoeveelheid sneeuw in Zuid-Duitsland) en oppassen op kleinkinderen waren een fijne start van de maandelijkse overleggen. Veel dank, ik heb van onze samenwerking genoten! **Dorien**, met plezier kijk ik terug op alle overleggen en overlegjes die we hadden: even uitwisselen hoe onze drukke levens (vaak vol met veel moois) verlopen en daarna aan de slag met de meest uiteenlopende onderdelen uit dit boekje. Dank dat je me leerde om hobbels in perspectief te plaatsen en vervolgens op te lossen – ongeacht het probleem. Dankjewel, en wellicht kunnen we in de toekomst samen nog meer hobbels vereffenen!

Naast uit mijn promotieteam bestond het POINT-onderzoeksteam uit:

Antoinette, je liet me kennismaken met een voor mij compleet nieuwe wetenschapsmethodiek: het kwalitatieve onderzoek! Ik heb erg genoten van onze overleggen, waarin ik steevast op een nieuwe manier naar de materie leerde kijken. Veel dank daarvoor! **Marcel**, het was goed om het project met een bril vanuit de openbare apotheek te kunnen bezien. Dank bovendien voor het laagdrempelig kunnen overleggen, ondanks je drukke agenda. **Anne**, je liefde voor het project werkte aanstekelijk. Dank dat je daarbij ruimte liet voor mij en mijn ideeën, ook al sprong ik op een al volop rijdende trein. Hoewel je door je gezondheid niet meer zo betrokken kon zijn bij het project, bedank ik je graag voor je desondanks onverminderde positiviteit over het project en mijn stappen daarin.

Ankie, lieve POINTer-sister en -buddy, nóg een kartonnen proefschrift dat in een boek veranderd is! Een promotie-traject zou wat mij betreft altíjd twee promovendi moeten laten samenwerken, en zeker als dat met een promovenda is als jij. Onderzoek doen samen met jou was een feest! Dank voor het vele samen lachen en de discussies,

alle lasagnes, de HARM-grappen… Sinds je in Engeland woont heb ik je zeker gemist, maar des te meer voel ik mij vereerd dat je bij de afronding van dit project als paranimf aan mijn zijde wil staan! **Judith**, je versterkte het team precies op het goede moment en veranderde het HARM-project dat eindeloos leek te duren in louter 'groene vinkjes-vakjes'. Dank voor je tip om in het promotietraject ook de kleine mijlpalen als zodanig te herkennen, en erop te proosten.

Met dit team onderzochten we een in Nederland nieuw farmacotherapeutisch zorgmodel. Dat model heeft drie belangrijke spelers: de apotheker-farmacotherapeut, de huisarts en de patiënt. Ik ben dan ook veel dank verschuldigd aan de apothekers die **apotheker-farmacotherapeut** werden: P**eter**, **Valérie**, **Tense**, **Bart**, **Sanneke**, **Harriëtte**, **Mirjam**, **Josephine** en **Ankie**. Het inkijkje op één van jullie onderwijsdagen en met sommigen van jullie een dagje in de huisartspraktijk, maakten dat de papieren interventie voor mij ging leven – en hoe! Dank daarvoor! **Simone**, dank voor het samen met Anne opleiden van de apotheker-farmacotherapeuten.

Eveneens veel dank aan de **huisartsen en hun praktijken** die de apotheker-farmacotherapeuten verwelkomden. In sommige gevallen zelfs zonder hem of haar daarna te laten gaan! En veel dank aan de **huisartsen en hun praktijken** die deel wilden nemen aan de POINT-studie als controlepraktijk. Ten slotte veel dank aan **alle patiënten** die open stonden voor de zorg door de apotheker-farmacotherapeut in hun huisartspraktijk.

METHODEN

Om onze onderzoeksvragen te beantwoorden, deden we kwantitatief en kwalitatief onderzoek. De hulp van nog vele anderen was hierbij onmisbaar.

Het kwantitatieve onderzoek

…begon met data verzamelen…

Er deden 26 huisartspraktijken mee aan het POINT-onderzoek. **Nicole**, dank voor al je werk bij de gigantische klus om de data van alle praktijken leesbaar aan ons aan te leveren! Wat hebben we gestoeid om de juiste zaken "eruit te trekken"… maar het is gelukt! Dank voor je altijd gezellige e-mails die de data-perikelen opfleurden.

Eveneens veel dank voor de oplossingen en inspanningen om de data compleet te maken, geleverd door: **Julia**, **Hugo** en **Erwin** (UMC Utrecht), **Anneke**, **Vera** en **Arjen** (Zorg-groep Almere), **Henk** en **Margot** (Leiden-cluster), **Raynor** (Pharmapartners) en **Patrick** (Farmacie UU).

Alle **geneeskundestudenten** die meegeholpen hebben bij de enorme dataverzameling van de ziekenhuisopnames; Aletta, Frits, Leroy, Wouter, Chantal, Eline, Lydia, Tanly, Martijn en Marleen, dank jullie wel!

Dank aan **alle patiënten** die vragenlijsten invulden.

…die data moesten beoordeeld worden…

Peter en **Sanne**, dank voor het versterken van het HARM-beoordelings-team! Ik heb genoten van onze discussies waarin de samenwerking tussen huisarts en apotheker-farmacotherapeut wederom terugkwam.

…en vervolgens geanalyseerd.

Hans, dank voor je begeleiding als supervisor vanuit de master epidemiologie bij de analyse van de HARMs. Ik heb genoten van je enthousiasme over de analyse die alles behalve een standaard epidemiologische vergelijking was. Het samen zoeken naar een zo goed mogelijk model om dit bijzondere studie-design te analyseren heb ik enorm gewaardeerd.

Peter, wederom een voor mij nieuwe dimensie werd door jou aan het project toegevoegd: die van pure statistiek, syntaxen en SAS. Ik heb, mede dankzij de master-vakken, een beetje geleerd je taal te spreken en waardeerde erg hoe jij vice versa de mijne probeerde te begrijpen. Het was erg fijn jou als expert aan boord te hebben! Dank voor je vele oplossingen en alle uitleg, vergezeld van de mooiste (droge!) vergelijkingen om de voor mij soms taaie statistiek begrijpelijk te maken.

Katja en **Heleen**, dank voor het meedenken met de analyse van de drug burden index vanuit Groningen! **Ardine**, dank voor het meedenken met de kosten-analyse. De mini-spoedcursus over kosten-onderzoek heeft mij veel geholpen!

Het kwalitatieve onderzoek

…begon ook met data-verzameling…

En wel in de vorm van interviews. Dank aan alle **huisartsen** die tijd maakten om hun ervaringen te delen!

…gevolgd door wederom beoordeling en analyse van die data.

Esther, door jou leerde ik de realist evaluation kennen. Wat een mooie onderzoeksvorm! Je leerde me de taal van kwalitatief onderzoek lezen en schrijven en gaf me naast mijn kwantitatieve een kwalitatieve onderzoeksbril mee, wat beide heeft verrijkt – ik ben je daar heel dankbaar voor! Dank bovendien dat je me introduceerde bij de **realist evaluation-group**: dank allen voor het hartelijke welkom, het meedenken en samen sparren over deze onderzoeksmethode.

Zowel binnen het kwantitatieve als het kwalitatieve onderzoek deden meerdere **geneeskundestudenten** hun wetenschappelijke stage. Dank voor de gesprekken, frisse blikken en fijne samenwerking Frits, Leroy, Luc, Fokeline en Annemiek!

RESULTATEN

Dit alles resulteerde in verschillende "uitkomsten". Allereerst meerdere wetenschappelijke artikelen, die gebundeld zijn in dit proefschrift. Dat werd beoordeeld door de **leescommissie**; dank daarvoor prof. dr. A.C.G. Egberts, prof. dr. H.E. Westerveld, prof. dr. A.K. Mantel-Teeuwisse, prof. dr. T.J.M. Verheij en prof. dr. L. van Dijk.

Naast in artikelen, vertelde ik over onze bevindingen op verschillende congressen. Het eerste congresbezoek was al in de maand nadat ik begonnen was aan het onderzoek, samen met jou, **Ankie**, in Mechelen het PCNE. Als bijna enige dokter tussen de apothekers was dit een fantastische start van dit mooie traject! Daarna volgden de WONCA en NHG-wetenschapsdagen – beide met meerdere mede-**aiotho's**. Dank allen voor de mooie dagen in verschillende Nederlandse steden, Istanbul en Krakow (met het surprise-ei ter ere van mijn zwangerschap, die dit congresreisje nóg bijzonderder maakte!).

DISCUSSIE

De hiervoor beschreven resultaten werden positief beïnvloed door de context waarin ik het onderzoek uitvoerde. Met veel plezier werkte ik in het Julius Centrum. Dank aan **alle Julianen** voor de Kerst- en Paas-lunches, de vragen tijdens Julius-seminars, de vergadervrije-week-ontmoetingen. Dank ook **Abdel**, voor de verse munt voor thee en de altijd vrolijke koffie-groet in de ochtend; **Coby** en **Henk**, voor de organisatorische ondersteuning; **Esther, Jinke** en **Monique** voor het zoeken naar momenten in altijd volle agenda's.

Een klein maar gezellig groepje binnen het Julius vormden de "**patiëntveiligers**" – dank voor de etentjes en recent de digitale koffie's! Ook de **HAG**-overleggen waren fijn om onderling uit te wisselen en te sparren – dank allen. En ten slotte, alle **kamergenoten in STR6.101**, dank voor de vele lunchwandelingen, escape room ontsnappingen, week/cake-starts, mooie steunende leuzen op de whiteboards aan de muur, koffie-momenten om successen maar ook frustraties te delen… jullie maakten dit traject naast leuk vooral erg gezellig!

De Julius-context wisselde ik regelmatig af met een andere: die van de huisartspraktijk. **Liesbeth**, **Sarie** en **Marie-Louise**, dank voor jullie meedenken en flexibiliteit bij het dikwijls wijzigen van mijn planning! **Caroline** en **Marieke**, het eerste jaar van de opleiding deed ik in jullie praktijk. Het was een fijne plek en naast dat ik de beginselen van het huisarts-zijn bij jullie heb geleerd, was het goed de theorie van het onderzoek met de praktijk af te wisselen! Dank jullie wel!

Ten slotte, naast fijne mensen op beide werkplekken, waren en zijn mijn vrienden en familie zeer belangrijk. Wat een geluk heb ik met jullie allemaal om mij heen! De **Cartesianen**, **Il-7**, **group-4**-met-aanhang, **Eric**; heel veel goede en fijne gesprekken, lachen, wandelingen, Catannen, weekendjes, etentjes, muziek… dank allemaal!

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CONCLUSIE

Wat een prachtig traject was het! Nogmaals allemaal ontzettend bedankt (ook zij die ik per ongeluk vergeet – hopelijk wordt mij dat vergeven, want een erratum op dit stuk wordt ingewikkeld…). En dan nu: PROOST!

LIST OF PUBLICATIONS

This dissertation

Hazen ACM[Ω], **Sloeserwij VM**[Ω], Zwart DLM, de Bont AA, Bouvy ML, de Gier JJ, de Wit NJ, Leendertse AJ. Design of the POINT study: Pharmacotherapy Optimisation through Integration of a Non-dispensing pharmacist in a primary care Team (POINT). *BMC Fam Pract*. 2015;16:76.

Sloeserwij VM[Ω], Hazen ACM[Ω], Zwart DLM, Leendertse AJ, Poldervaart JM, de Bont AA, de Gier JJ, Bouvy ML, de Wit NJ. Effects of non-dispensing pharmacists integrated in general practice on medication-related hospitalisations. *Br J Clin Pharmacol*. 2019; 1-11. DOI: 10.1111/bcp.14041

Sloeserwij VM, Zwart DLM, Hazen ACM, Poldervaart JM, Leendertse AJ, de Bont AA, Bouvy ML, de Wit NJ, de Gier JJ. Non-dispensing pharmacist integrated in the primary care team: effect on the quality of physician's prescribing, a non-randomised comparative study. *Int J Clin Pharm*. 2020;42:1293-1303. DOI: 10.1007/s11096-020-01075-4

Sloeserwij VM, Zwart DLM, Hazen ACM, Poldervaart JM, Bouvy ML, de Gier JJ, de Wit NJ. Clinical medication reviews by non-dispensing pharmacists integrated in primary care: patients' evaluations. Manuscript submitted for publication.

Sloeserwij VM, de Groot E, de Gier JJ, de Wit NJ, de Bont AA, Zwart DLM. Non-dispensing pharmacists integrated in primary care practice; a realist evaluation of a new interprofessional model. Manuscript submitted for publication.

[Ω] *Contributed equally*

Other publications

Hazen ACM, van der Wal A, **Sloeserwij VM**, Zwart DLM, de Gier JJ, de Wit NJ, Leendertse AJ, Bouvy ML, de Bont AA. Controversy and consensus on a clinical pharmacist in primary care practice in the Netherlands: a Q study. *Int J Clin Pharm*. 2016;38(5):1250-60.

Sloeserwij VM. Een apotheker-farmacotherapeut in de praktijk. *HenW*. 2017;1:47.

ABOUT THE AUTHOR

Vivianne Sloeserwij was born on April 20st 1990 in Woerden, the Netherlands. In 2008 she completed secondary school at the Minkema College (Gymnasium) and started medical school at Utrecht University, UMC Utrecht. During her studies, Vivianne followed the Descartes College honours programme, a 2-year interdisciplinary honours programme on the philosophy of science.

After graduating in 2014, she started her PhD trajectory on the effects of a non-dispensing pharmacist integrated in primary care teams, supervised by prof. dr. N.J. de Wit, prof. dr. J.J. de Gier and dr. D.L.M. Zwart (Julius Center for Health Sciences and Primary Care, UMC Utrecht). Major part of her work as a PhD student was the evaluation of the Pharmacotherapy Optimisation through Integration of a Non-dispensing pharmacist in primary care Teams (POINT) study. After a year, Vivianne combined this project with the General Practice vocational training at Utrecht University in a so-called AIOTHO-trajectory. During her PhD, she attended several classes of the postgraduate master Epidemiology. Also, she joined and organised realist evaluation meetings with researchers from across the country. She presented her work at several international and national conferences, including Wonca and the NHG Wetenschapsdag.

Vivianne will complete the General Practice vocational training to work as a general practitioner. She lives in Kamerik with her fiancé Andrik and their children Laure and Willem.