



## Potential clinical impact of pharmaceutical interventions in an interprofessional medication management program

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### ABSTRACT

**Introduction:** Medication reviews (MR) can improve medication safety, especially when followed by continuous medication management (MM). The interprofessional MM program ARMIN resulted in a significantly reduced mortality risk. To gain a deeper understanding of what contributed to this effect, we aimed to investigate the pharmaceutical interventions (PI) conducted by the community pharmacies and their communication with the physicians.

**Methods:** We conducted an intervention study in the ambulatory setting with a pre-post design and an observational period of approximately 6 months per patient to assess (1) number and types of drug-related problems (DRP) identified and solved, (2) to evaluate PIs conducted, (3) changes in the medication, (4) clinical and economic impact of the PIs, and (5) involvement of the physicians with respect to type and relevance of DRPs.

**Results:** 79 patients received 10.2 drugs at baseline (median: 9, range 5–26). (1) 420 DRPs were detected during the initial MR and 50 DRPs during MM. (2) 538 PIs were conducted. (3) Changes in the medication were observed in all patients. (4) 404 PIs (76.0%) were classified as successfully implemented. Of these, 84.2% had minor and 12.6% moderate clinical impact. Most of the PIs (81.9%) had no effect on costs. (5) In 42.2% ( $n = 227$ ) of PIs, the prescribing physician was contacted.

**Conclusion:** Within ARMIN it was possible to solve DRPs with PIs resulting in changes in medication and having a potential clinical impact. The implementation rate shows that intensive collaboration with clear responsibilities between CP and physician is crucial.

### 1. Introduction

Medication review (MR) interventions are designed to solve drug-related problems (DRPs)<sup>1</sup> and can improve medication safety and effectiveness.<sup>2–9</sup> Therefore, they have become an established pharmaceutical service in many countries worldwide,<sup>2,10</sup> such as the medicines use review in the United Kingdom,<sup>11,12</sup> clinical MR and home MR in Australia,<sup>13</sup> MedsCheck in Canada,<sup>14</sup> MR in Denmark,<sup>6</sup> Slovenia,<sup>15</sup> and Germany.<sup>16</sup>

Since there are no accepted international standards for these

services, there are differences in e.g. how, by whom, for what patients, and in which setting MR are provided. Despite all challenges to compare study results from different MR interventions, it was shown that a close interprofessional collaboration contributes to the success of MRs.<sup>17–19</sup> Reasons for this might be a facilitated communication or defined responsibilities that might result in a better acceptance of pharmaceutical interventions (PIs). Another shortcoming is that not all DRPs can be solved during an MR intervention as some DRPs need a follow-up to reach a solution and sustainable outcomes.<sup>20</sup>

For these reasons, a concept for an interprofessional, continuous

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medication management jointly conducted by physicians and community pharmacists (CPs) was implemented in two German states within the program ARMIN - Medicines Initiative Saxony-Thuringia (*Arzneimittelinitiative Sachsen-Thüringen*) from July 2016 to June 2022. This complex intervention consisted of an initial MR followed by continuous medication management and included generating and updating comprehensive, standardized medication plans for the patients.<sup>21</sup>

Altogether, almost 10,000 patients were enrolled in ARMIN. In this program, physicians, and CPs worked together with defined roles and responsibilities. The evaluation was conducted utilizing claims data and included all patients enrolled until the end of 2018 ( $n = 5033$ ) versus a propensity score-matched control group (10,039) with an average follow-up of  $30.0 \pm 9.7$  months. Over the observation period, 9.3% of the ARMIN participants and 12.9% of persons in the control group died (hazard ratio of the adjusted Cox regression, 0.84; 95% confidence interval [0.76; 0.94],  $P = 0.001$ ). This corresponded to a covariate-adjusted absolute risk reduction of 1.52% and a number needed to treat (NNT) of 66. Reasons for this outcome can only be assumed since it was a retrospective analysis not allowing for any causal relationships. It was discussed that the extensive utilization of healthcare services during the observation period, an increased participation in disease management programs, or earlier hospitalizations as well as an improvement in some medication safety indicators in the intervention group might have contributed to this effect.<sup>22</sup>

In the main evaluation, no data on the practical implementation of the interventions conducted in this program were available. Therefore, our study aimed to provide mechanistic insights by observing a convenient sample of patients over a 6-month period to assess:

- (1) number and types of DRPs identified and solved during the initial MR and the continuous management.

To gain a deeper understanding on the interaction between the health care professionals we further aimed to evaluate:

- (2) PIs conducted,
- (3) changes in the medication resulting from PIs,
- (4) clinical and economic impact of the PIs, and
- (5) involvement of physicians with respect to type and relevance of DRPs.

## 2. Methods

### 2.1. Study design

We conducted an intervention study in the ambulatory setting with a pre-post design and an observational period of approximately 6 months per patient. This design was chosen to capture the longitudinal and iterative nature of the intervention and to allow sufficient time for the proposed pharmaceutical interventions to be discussed, accepted, and implemented. Since the objective was not to assess clinical outcomes but to describe implementation-related processes and outcomes within patients over time, no control group was included. The intervention i.e., participation in the interprofessional medication management program ARMIN, consisting of an initial type 3 medication review (according to the Pharmaceutical Care Network Europe (PCNE) nomenclature,<sup>1</sup> i.e. a structured evaluation and optimization of a patient's medication including information on the medication history, a patient interview and clinical data) and follow up-interventions during every visit at the pharmacy or physician's practice. This required that patients agreed to sign up with one pharmacy and one physician practice, each that took over responsibility for the medication.

### 2.2. Ethics

The study was conducted in accordance with the Declaration of

Helsinki. The participants gave their written informed consent. All data were collected, processed, and stored in compliance with the European General Data Protection Regulation (GDPR, Regulation (EU) 2016/679). Ethical committee approval was not required under national regulations as only anonymized data were analyzed.

### 2.3. Patients

Patients were approached by community pharmacies participating in ARMIN. Only patients newly signing up for the program were eligible. Further inclusion criteria were:  $\geq 5$  long-term medications,  $\geq 18$  years of age, living at home, understanding and speaking German, and written informed consent.

To include a convenience sample of at least  $n = 60$  patients, we aimed at inviting a minimum of 12 community pharmacies that were approached by the Pharmacist Associations of two federal states, Saxony and Thuringia, where the program ARMIN was implemented. Patients were recruited by the pharmacists during regular visits or contacted by phone. If patients were interested in participating, a meeting was scheduled in the pharmacy for a brown-bag review. Patients were requested to bring their entire current medication including self-medication/OTC-drugs along to this meeting.

### 2.4. Data collection and classification

The patients' medication was documented by the CPs at four different times (Fig. 1: Data collection during the medication management process (MP: medication plan)): (1) initially during the brown-bag review, (2) the provisional medication plan (MP) prepared by the pharmacist after the pharmaceutical review, (3) the consolidated MP issued by the physician, and (4) the MP at the end of the observational period of approximately 6 months. CPs also documented all DRPs detected including the category as well as a short description of the DRPs and the resulting PIs.

Medication at time point (1) as well as all DRPs and PIs were documented handwritten on paper report forms. Medication at time points (2) to (4) was documented electronically in the primary software system of the individual pharmacy. All documentation was either copied or printed out, anonymized and handed to the study team. All data was entered into a Microsoft™ Access database, version 2016, that was set up for this project.

Medication was classified using the Anatomical Therapeutic Chemical (ATC) classification system.<sup>23</sup> Complexity of the medication was assessed with the German version of the medication regimen complexity index (MRCI-D) for both MPs at baseline (3) and after 6 months (4).<sup>24,25</sup>

### 2.5. Association of pharmaceutical interventions with changes in the medication

Based on the pharmacists' description of the DRP and the documented medication at the different times, associations of the interventions with changes in the medication were explored. Only DRPs detected during the initial brown-bag review were included in this part of the evaluation, since changes in the prescribed medication relating to DRPs normally involved patients' visiting their general practitioner or specialist and, therefore, took some time to be implemented.

All changes in the medication associated with DRPs were identified. These associations were retrospectively rated by the study team taking the complete documentation into account – that is, the medication over the complete observational period, the classification and the description of the DRPs and applied PIs documented by the CPs. Based on this documentation, the associations were grouped either as (i) valid i.e., plausible, (ii) unclear, or (iii) no association.

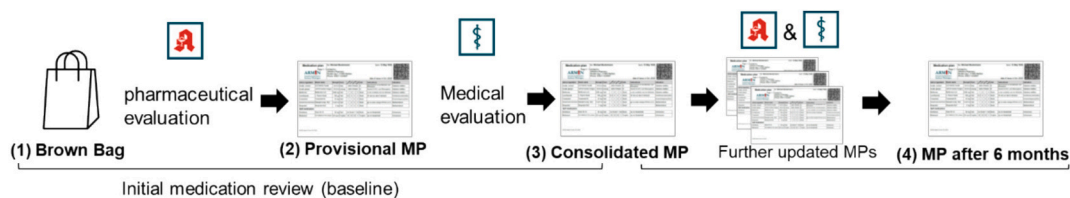


Fig. 1. Data collection during the medication management process (MP: medication plan).

## 2.6. Rating pharmaceutical interventions with PharmDISC

DRPs and PIs were classified by using the PharmDISC system (Pharmacists' Documentation of Interventions in Seamless Care), that was adapted to the community pharmacy setting by Maes et al.<sup>26</sup> DRPs and PIs that were not covered by version 1.1 were discussed within the study team and if needed, new subcategories were amended. This resulted in a revised PharmDISC version 1.2 (Supplementary Material, Fig. S1, Table S1). All DRPs and PIs were classified by two independent raters and interrater reliability was calculated (see statistical analyses). To avoid a rater bias, all PIs were numbered and the classification of both raters, sorted by even and odd numbers, were included in equal parts in the evaluation. The involvement of the physicians was also evaluated with the PharmDISC system.

## 2.7. Assessing the impact of the pharmaceutical interventions with CLEO<sub>de</sub>

The impact of the PIs was estimated with the German version of the CLEO<sub>de</sub> tool.<sup>27</sup> This tool allows to assess the potential relevance of interventions in the following three dimensions: Clinical, Economical and Organizational. The organizational category was not rated since the required information was not available.

All successfully implemented PIs were assessed. PIs were considered as successful, if the PharmDISC rating was (i) "accepted and implemented (F1)" or (ii) "not applicable (F5)", i.e. no acceptance or implementation was needed by any other person than the pharmacist. If F1 or F5 was classified by one of the two raters, the PI was included in the assessment with CLEO<sub>de</sub>.

To estimate the clinical relevance of each DRP and PI, the most probable scenario was assumed. All DRPs and PIs classified with CLEO<sub>de</sub> were collected in a catalogue (Supplementary Material, Tables S2, S3, and S4). This estimation for the clinical relevance (Tables S2 and S3) was reached by consensus involving three pharmacists from the study team. Drug-drug interactions (DDI) were classified by the ABDATA database™, which is standard in all community pharmacies in Germany. The economic relevance (Table S4) was rated by comparing the costs of the drugs in question and calculating costs of unplanned physician visits and monitoring resulting from PIs. The cost for each drug was calculated within the MS-Access database based on the prices without any rebates as of November 2018 (Lauertaxe™).

Again, assessment was independently performed by two raters. Deviations in classifying the PIs by the two raters were discussed until consensus was reached.

## 2.8. Statistical analysis

Descriptive statistics were performed using MS-Excel™ 2016 for Windows and are presented as sums, means ( $\pm$ SD), medians, and range. Interrater reliability was determined with Fleiss-Kappa coefficients  $K$  and calculated with SPSS™, version 25. The calculated  $K$ -values were interpreted according to Landis and Koch<sup>28</sup> as "almost perfect" ( $K$ : 0.81–1.00), "substantial" ( $K$ : 0.61–0.80), "moderate" ( $K$ : 0.41–0.60), "fair" ( $K$ : 0.21–0.40), "slight" ( $K$ : 0.00–0.20), and "poor" ( $<$ 0.00). A  $K$  value greater than 0.40 was considered sufficient for relevant agreement.<sup>28</sup>

## 3. Results

### 3.1. Patient characteristics

Between May 2018 and September 2019  $N = 79$  patients (54%;  $n = 43$  female) participated; 37% ( $n = 29$ ) were  $<$  65 years, 32% ( $n = 25$ ) aged 66–75 years, and 29% ( $n = 23$ ) were  $>$  75 years; for 3% ( $n = 2$ ) age was not specified. 58% ( $n = 46$ ) of patients completed 8 to 10 years of school education, 11% ( $n = 9$ ) more than 10 years, and 3% ( $n = 2$ ) less than 8 years. For 28% ( $n = 22$ ) of patients, education grade was not specified.

### 3.2. Medication

The mean number of drugs at baseline on the consolidated MPs was 10.2 (median: 9; range 5–26). Overall, the 809 medications on the MPs consisted of 81.8% prescribed drugs and 18.2% non-prescription drugs. After a mean of  $7.5 \pm 1.4$  months participation in the medication management program (median: 7.3 months, range: 5.7–13.8 months), the mean number of drugs on the MP was 10.9 (median: 6; range 5–26). The complexity of the medication assessed with the MRCI-D did not change significantly: baseline: 22.1 (range 7–46.5) versus at 6 months: 23.4 (range 7–50.5).

### 3.3. Drug-related problems

Overall, 470 DRPs were documented by the pharmacists for 92% of the 79 patients (Table 1). The median number of DRPs per patient was 6 (mean: 5.9; range: 0–19). Nearly 90% of the DRPs were detected during the initial MR whereas 11% were documented during the continuous

Table 1

Types and numbers of drug-related problems (DRPs) documented by the pharmacists during the observational period (470 DRPs in  $N = 79$  patients).

Category	Number of drug-related problems		
	Overall n (%)	Initial intervention n (%)	Continuous management n (%)
Dosage	130 (27.7)	126 (30.0)	4 (8.0)
Drug-drug interaction	104 (22.1)	84 (20.0)	20 (40.0)
Indication	80 (17.0)	79 (18.8)	1 (2.0)
Medication non-adherence	40 (8.5)	32 (7.6)	8 (16.0)
Adverse effects	38 (8.1)	33 (7.9)	5 (10.0)
Inappropriate medication use	21 (4.5)	16 (3.8)	5 (10.0)
Inappropriate effectiveness	13 (2.8)	13 (3.1)	–
Inappropriate drug form/ formulation	11 (2.3)	11 (2.6)	–
Inappropriate duplication	6 (1.3)	5 (1.2)	1 (2.0)
Inappropriate medication storage	6 (1.3)	5 (1.2)	1 (2.0)
Untreated symptom	3 (0.6)	3 (0.7)	–
Inappropriate self medication	2 (0.4)	2 (0.5)	–
Contraindication	1 (0.2)	1 (0.2)	–
Other	15 (3.2)	10 (2.4)	5 (10.0)
Total	470 (100.0)	420 (100.0)	50 (100.0)

medication management.

### 3.4. Pharmaceutical interventions classified with PharmDISC

#### 3.4.1. Adapting the PharmDISC system

The following 6 new subcategories were added to the PharmDISC version 1.1 to classify all DRPs and PIs detected:

- Patient information need (A6)
- Untreated indication/symptom (C1.8)
- Lack of knowledge of/awareness for lifestyle factors (C5.5)
- Patient motivation and awareness (D7.1)
- Accepted and implemented, but without success (F1.1)
- No priority (F6)

This resulted in PharmDISC version 1.2 (**Supplementary Material, Fig. S1**).

#### 3.4.2. Interrater reliability

The PharmDISC system version 1.2 reached a substantial user agreement for category C ( $K = 0.79$ ) and a moderate agreement for categories A ( $K = 0.66$ ), B ( $K = 0.51$ ), D ( $K = 0.65$ ), and F (0.52). For category E, no  $K$ -value was calculated since the agreement was almost perfect. Since all  $K$ -values were above the threshold of 0.40, this was considered a sufficient result for a reliable system to be used in practice.<sup>28</sup>

#### 3.4.3. Rating the pharmaceutical interventions with PharmDISC

All PIs were rated with the PharmDISC version 1.2 (detailed results: **Supplementary Material, Fig. S1, Table S1**). The number of PIs ( $n = 538$ ) exceeded the number of DRPs ( $n = 470$ ) since it was possible that a DRP resulted in more than one PI, which was the case for 68 DRPs. These were most often “DDI” ( $n = 21$ ; 30.9%), “medication non-adherence” ( $n = 16$ ; 23.5%), and “adverse effects” ( $n = 11$ , 16.2%). All PIs were classified with PharmDISC in the following 6 categories: (A) problem, (B) type of problem, (C) cause of intervention, (D) intervention, (E) communication, and (F) outcome of the intervention:

**(A) Problem:** The most frequently classified problem was “treatment effectiveness” ( $n = 200$ ; 37.2%), followed by “safety of treatment” ( $n = 147$ ; 27.3%), “patient information need” ( $n = 110$ ; 20.4%), and “patient dissatisfaction/problem” ( $n = 76$ ; 14.1%). “Untreated indication” ( $n = 4$ ; 0.7%) and “treatment costs” ( $n = 1$ ; 0.2%) were seldom the underlying problem of DRPs.

**(B) Type of problem:** The majority ( $n = 417$ ; 77.5%) were potential DRPs, i.e. problems that could still be prevented with an appropriate

intervention. DRPs classified as manifest ( $n = 121$ ; 22.5%) were most often “adverse effects” ( $n = 38$ , 31.4%), “medication non-adherence” ( $n = 20$ , 16.5%) and “inappropriate effectiveness” ( $n = 17$ , 14.0%).

**(C) Cause of intervention:** More than 75% of the causes for conducting a PI were within the following categories: “interaction” ( $n = 123$ ; 22.9%), “insufficient knowledge” ( $n = 113$ ; 21.0%), “inappropriate timing or frequency of administration” ( $n = 86$ ; 16.0%), “adverse effects” ( $n = 47$ ; 8.7%) or “insufficient medication adherence” ( $n = 46$ ; 8.6%).

#### **(D) Intervention:**

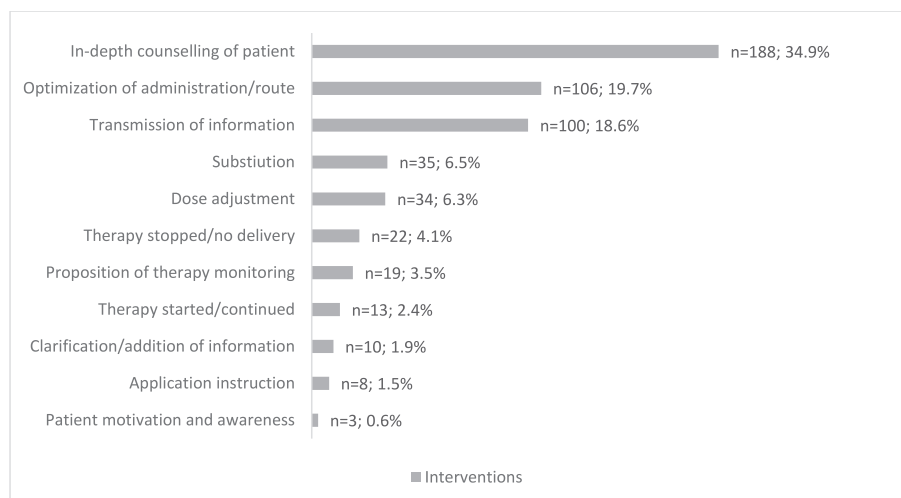
**Fig. 2** (Types and numbers of pharmaceutical interventions (PIs) classified with PharmDISC version 1.2 ( $n = 538$  PIs relating to 470 drug-related problems)) shows the number and frequency of the PIs conducted by the pharmacists with “in-depth counselling of patient”, “optimization of administration/route” and “transmission of information” accounting for almost 80% of all PIs being the most common interventions.

**(E) Communication:** All PIs involved the patient and the pharmacist ( $n = 538$ ). In 42.2% ( $n = 227$ ) of PIs, additional contact was made with the prescribing physician. Caregiver or home care was involved in two PIs.

**(F) Outcome of the intervention:** The majority of PIs were successful ( $n = 388$ ; 72.1%), i.e. either “accepted and implemented” ( $n = 174$ ; 32.3%) or no acceptance or implementation was needed ( $n = 214$ ; 39.8%) by any other person than the pharmacist (classified as “not applicable”), e.g. when the PI consisted of a “transmission of information”. Altogether, 34 (6.3%) PIs were not implemented since they were either “not accepted” by patients or physicians ( $n = 17$ ; 3.2%), “(partially) accepted without implementation” ( $n=14$ ; 2.6%), or had “no priority” ( $n = 3$ ; 0.6%). For nine (1.7%) PIs, the suggested interventions were “accepted and implemented, but without success” (e.g., continuous blood pressure fluctuations despite changes in the medication). For nearly 20% ( $n = 107$ ) of the PIs, the outcome was not known to the documenting pharmacist.

### 3.5. Pharmaceutical interventions resulting in changes on the medication plan

Of all DRPs detected during the initial MR ( $n = 420$ ), 79.8% ( $n = 335$ ) were associated with changes on the patient's MP. For those DRPs, 204 (60.9%) had plausible associations with changes in the medication. Therefore, it can be assumed that the changes in the patients' medication resulted from the PIs. For the remaining DRPs with changes in the medication, 117 (34.9%) DRPs had no association and for 14 (4.2%) the association was not clear.



**Fig. 2.** Types and numbers of pharmaceutical interventions (PIs) classified with PharmDISC version 1.2 ( $n = 538$  PIs relating to 470 drug-related problems).

The amount of valid changes in the medication related to DRPs highly varied depending on the category of DRP (Fig. 3: Drug-related problems (DRPs) detected during the initial medication review and their association to valid changes on the medication plan ( $n = 420$  DRPs)), ranging from 4.8 to 91.1% for the different DRP categories (mean: 35.0%; median: 27.3%).

Most valid changes on the MPs related to two DRP categories: 1) “Dosage” ( $n = 96$ ; 76.2% of all associations in this category), mainly resulting from wrong administration with respect to food ( $n = 47$ ). These DRPs were often solved by counselling the patient and amending the MP accordingly. 2) “Indication” ( $n = 72$ ; 91.1% of all associations in this category), mainly resulting from unknown indications ( $n = 66$ ), solved by adding the indication to the MP. The DRPs categories “medication non-adherence” and “adverse effects” resulted less often in changes on the MPs (28.1 and 27.3%, respectively). Although DDIs were detected frequently, they rarely resulted in changes on the MP ( $n = 4$ ; 4.8%). This is because, after pharmacist review and, when necessary, consultation with the physician, many interactions were deemed as not clinically relevant, and therefore no modification of therapy was indicated.

### 3.6. Impact of pharmaceutical interventions

Of the total number of 538 PIs conducted, the impact was assessed for the PIs ( $n = 404$ ; 76.0%) classified as successfully implemented by at least one of both raters. Those PIs are summarized in a catalogue including 68 different scenarios rated with CLEO<sub>de</sub> for clinical and economic impact (Supplementary Material, Tables S2, S3, and S4). The clinical and economic impact of the PIs is summarized in Table 2.

Overall, 394 (97.5%) of the successfully implemented PIs had a positive clinical impact, with the majority ( $n = 340$ ; 84.2%) classified as minor impact. 18.1% ( $n = 73$ ) of the PIs had an economic impact, with 50 (12.4%) PIs resulting in an increase and 23 (5.7%) in a reduction of drug and monitoring costs.

### 3.7. Contact with the physicians

Overall, the prescribing physician was contacted in 42.2% ( $n = 227$ )

**Table 2**

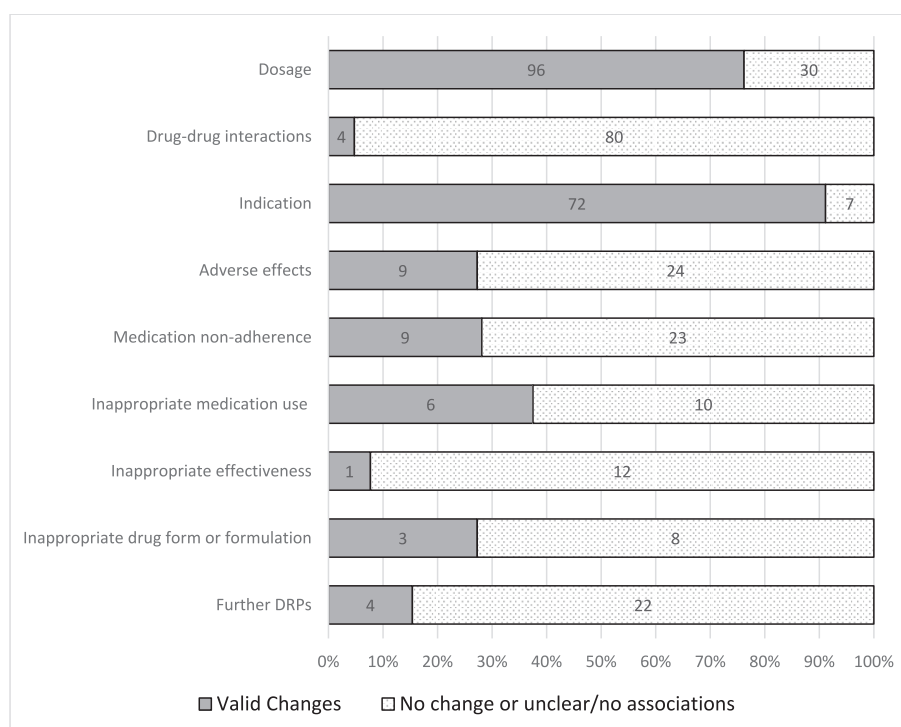
Evaluation of the impact of successfully implemented pharmaceutical interventions (PI), classified with the CLEO<sub>de</sub> tool ( $n = 404$  successfully implemented PIs).

Clinical impact according to the most likely case expected			
Score	Impact	Definition	n (%)
-1C	Harmful	The PI may lead to negative results in terms of e. g. clinical condition, knowledge or adherence	0 (0.0)
0C	Null	No impact	10 (2.5)
1C	Minor	The PI may improve the patient's knowledge, satisfaction, adherence and/or quality of life OR can prevent damage to the patient not requiring monitoring or treatment	340 (84.2)
2C	Moderate	The PI can prevent harm to the patient which requires surveillance or treatment but does not induce hospitalisation or prolong hospitalisation e.g., adverse effects such as diarrhoea	51 (12.6)
3C	Major	The PI can prevent damage that causes or prolongs hospitalisation of the patient OR the PI can prevent harm to the patient that causes permanent disability or impairment e.g., prolonged QT interval due to drug-drug interactions (DDI)	3 (0.7)
4C	Vital	The PI can prevent damage to the patient that results in intensive medical treatment or death	0 (0.0)

Economic impact on the costs of drug treatment (drug and monitoring costs)			
Score	Impact	Definition	n (%)
-1E	Higher costs	PI increases costs	50 (12.4)
0E	Null	No change in costs	331 (81.9)
1E	Lower costs	Decreased drug and monitoring costs	23 (5.7)

of all PIs ( $n = 538$ ). Most often (approximately 60%) physicians were contacted because of the following DRPs: DDIs ( $n = 66$ ; 12.3% of all PIs), followed by “adverse effects” ( $n = 34$ ; 6.3%), and “medication non-adherence” ( $n = 32$ ; 5.9%). Fig. 4 (Number of drug-related problems (DRPs) resulting in pharmaceutical interventions (PIs) with or without physicians' contacts ( $n = 538$  PIs:  $n = 227$  with and  $n = 311$  without



**Fig. 3.** Drug-related problems (DRPs) detected during the initial medication review and their association to valid changes on the medication plan ( $n = 420$  DRPs).

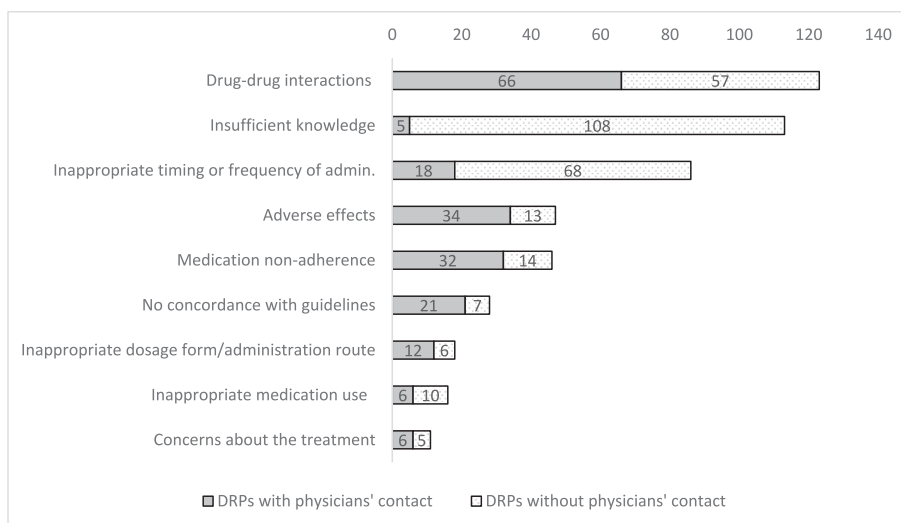


Fig. 4. Number of drug-related problems (DRPs) resulting in pharmaceutical interventions (PIs) with or without physicians' contacts ( $n = 538$  PIs:  $n = 227$  with and  $n = 311$  without physicians' contact).

physicians' contact)) shows the numbers of DRPs with and without physician contact for the different categories. The percentage solved without physician contact varied for the different types of DRPs ranging from >95% for “insufficient knowledge and inappropriate timing” or “frequency of administration” (79%) to “untreated symptom” (0%).

Fig. 5 (Number of pharmaceutical interventions (PIs) with and without physicians' contact ( $n = 538$  PIs:  $n = 227$  with and  $n = 311$  without physicians' contact)) shows the number of PIs with and without physicians' contact for the different categories. The three interventions conducted by pharmacists most often in absolute numbers when contacting a physician accounted for almost two thirds of all PIs were “transmission of information” (44.1%, although this required no action from the physician), “optimization of administration/route” (13.7%), and “substitution” (12.3%). Physicians were relatively often contacted if the PIs recommended a change in the pharmacotherapy treatment, e.g. “therapy stopped” (100% of all PIs of this category), followed by “substitution” (80%), “therapy started/continued” (62%), “proposition of therapy monitoring” (53%), and “dose adjustment” (50%). PIs concerning the administration were often solved without contacting the physician (“optimization of administration/route” 29% and “application instruction” 13%).

Of the 227 PIs with physician contact, 58.1% of PIs could be assessed

with CLEO<sub>de</sub>. Of these, 66.7% ( $n = 88$ ) were rated as having a minor clinical impact, 25.0% ( $n = 33$ ) as having a moderate clinical impact, and 2.3% ( $n = 3$ ) as having a major clinical impact.

Half ( $n = 18$ ) of the PIs with physician contact and a high or moderate clinical impact were related to DDI. More than half of the PIs with physician contact (58.3%;  $n = 77$ ) did not have an economic impact; costs increased up to 25.8% ( $n = 34$ ) and decreased by 15.9% ( $n = 21$ ) of these PIs. Again, PIs due to a DDI were most often responsible for the increase in costs ( $n = 12$ ; 35.3%).

#### 4. Discussion

We assessed 470 drug-related problems (DRPs) and the resulting 538 pharmaceutical interventions (PIs) in 79 multimorbid elderly patients for the first 6 months after signing up for the interprofessional medication management program ARMIN to provide mechanistic insights in the implemented interventions.

##### 4.1. Drug-related problems in the medication management process

In this study, the number of DRPs ranged from 0 to 19 (mean: 5.9; median 6) per patient. This is higher than reported in other studies in

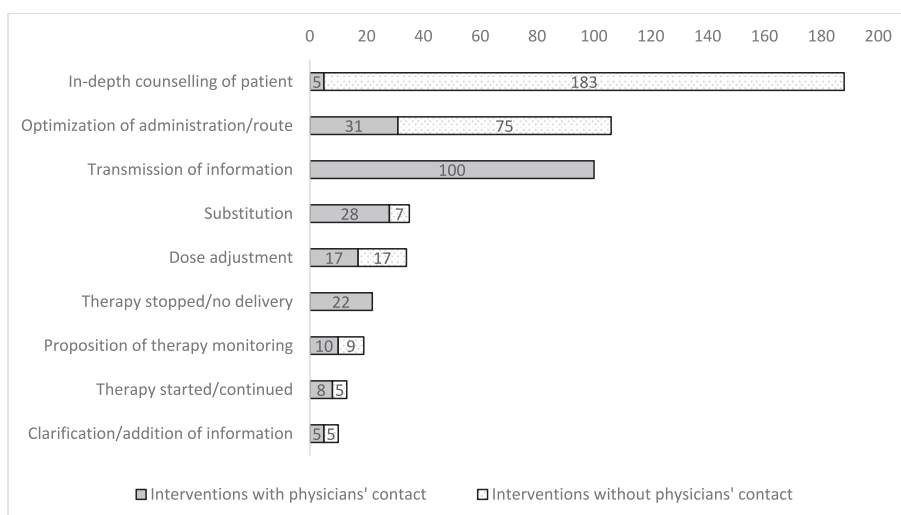


Fig. 5. Number of pharmaceutical interventions (PIs) with and without physicians' contact ( $n = 538$  PIs:  $n = 227$  with and  $n = 311$  without physicians' contact).

comparable settings (mean ranging from 1.1 to 4.2 DRPs per patient)<sup>29–33</sup>; this difference is probably due to the close and structured cooperation between CP and physician and the longitudinal evaluation.

That patients benefit from a continuous care process is supported by other studies discussing that implementing PIs can take time and additionally new DRPs are detected e.g. with new medications added to the regimen. This was reported by Seidling et al.<sup>20</sup> that followed 115 patients after an initial MR over 3 to 6 months and reported that after 2 to 4 weeks about half (46.2%) of all DPRs were solved; after 3 to 6 months additionally 50.7% of the remaining DRPs were solved. Rose et al.<sup>34</sup> identified longitudinal patient care with repeated interventions following a medication review as one factor that predetermines superior patient benefit.

## 4.2. Pharmaceutical interventions

### 4.2.1. Refining the PharmDISC tool

All 538 PIs resulting from the 470 DRPs were classified with PharmDISC, an intervention-oriented classification system. Originally developed in Switzerland for the hospital setting, Maes et al.<sup>26</sup> adapted and validated PharmDISC for the community pharmacy setting. While Maes et al. trained pharmacy students to directly classify interventions in the community pharmacies, all DRPs in this study were retrospectively classified by the study team to reduce the workload for the participating CPs. In our setting and with the documentation available, PharmDISC proved to be useful and showed a sufficient interrater reliability in all categories.<sup>28</sup> Some categories were added in accordance with the authors of the previous version to classify all interventions documented; this resulted in a refined version PharmDISC 1.2 (**Supplementary Material, Fig. 1S**).

### 4.2.2. Types of pharmaceutical interventions

About one third of all interventions were “in-depth counselling of patient” followed by “optimization of administration/route” and “transmission of information” mainly to physicians (each approximately 20% of all PIs). Szilvay et al.<sup>29</sup> reported “education” with 25% as the most common intervention by CPs conducting MRs in Hungarian pharmacies followed by “replacement of drugs” with 20% reported as the second most common intervention. In a study conducted in an outpatient clinic in Iran,<sup>35</sup> clinical pharmacists conducted comprehensive MRs for 200 patients. 874 DRPs resulted in 912 interventions; again, the most frequently conducted PI was “patient education” (41.3%). This was followed by “medication initiation or discontinuation” (24.5%), and non-pharmacological interventions (12.9%). While education seems to be a comparable intervention to the “in-depth counselling” reported in our study also as the most frequent intervention, replacing (or as we classified it: substituting) a drug was less frequent in our study with only 6.5%.

### 4.2.3. Rate of successfully implemented PIs

In our study, 72% of all PIs were successfully implemented and solved, in almost half of these cases with the involvement of the physicians that followed the pharmacists' recommendations. This finding is consistent with previous evidence showing that acceptance of pharmacists' recommendations is strongly associated with the degree of inter-professional collaboration. In the review of Kwint et al.<sup>18</sup> implementation rates ranged from 17 to 86% (mean 50%) with higher rates observed in settings with closer pharmacist-physician cooperation. Similar conclusions were drawn by Tan et al.<sup>36</sup> and Peled et al.<sup>37</sup> who both demonstrated increasing acceptance rates as pharmacists became more integrated into the interprofessional team. In the WestGem-study,<sup>34</sup> the acceptance rate also increased over time indicating that the service could be more effective with confidence growing between the professions.

The exceptionally high acceptance rate in our study, with only 3.2% of all recommendations rejected, might be due to the defined processes

and roles of both professions as well as their personal contact in the continuous process of care. The acceptance of task sharing in the interprofessional medication management program ARMIN was shown by Moecker et al.<sup>38</sup>

In contrast, other studies evaluating MRs in the ambulatory setting showed lower acceptance rates, particularly when physicians were less involved or unfamiliar with the service. In the DIATHEM-Study,<sup>39</sup> 17.4% of the PIs were not accepted. This might be explained by the study design. Physicians were not involved regularly or informed about the study but only contacted if a DRP required their feedback. In the above cited Iranian study,<sup>35</sup> the acceptance rates of 912 PIs in community pharmacies were evaluated after a two-week follow-up for patients' dependent PIs as well as interventions involving physicians ( $n = 228$ ). While patients accepted 81.2% of the recommendations, the physicians' acceptance rate was only 44.1%. In contrast to our study, physicians were not familiar with the service provided by clinical pharmacists.

Two studies in the hospital setting showed similar or higher acceptance rates, likely reflecting a closer interprofessional collaboration. Nielsen et al.<sup>40</sup> found an acceptance rate of 71% using an electronic prescription template to communicate the proposed PIs. In the study of Zaal et al.,<sup>41</sup> hospital pharmacists communicated interventions to the physicians over the phone with an overall acceptance rate of 76% that was associated with the severity of DRP and number of drugs prescribed.

## 4.3. Pharmaceutical interventions resulting in changes in the medication

In about 60% of DRPs, the conducted PIs resulted in changes in the medication in particular resulting from interventions due to DRPs on dosage or unknown/wrong indications. There are only a few studies available that evaluated this aspect. Like our study, Maes et al.<sup>42</sup> reported that 56.5% of PIs conducted resulted in a change in the prescription. In contrast to our setting, the PIs were conducted while dispensing prescribed drugs. Zermansky et al.<sup>43,44</sup> reported that in patients who were counselled by a pharmacist more changes in their long-term prescriptions were observed with a mean number of 2.2 changes per patient.

## 4.4. Impact of pharmaceutical interventions

The impact of the PIs assessed with CLEO<sub>de</sub> demonstrated that most successfully implemented PIs had a clinical impact and three PIs (0.7%) might have prevented serious damage or hospitalisation. In the ambulatory setting the impact of PI is rarely assessed. Reinau et al.<sup>45</sup> used CLEO<sub>de</sub> in a Swiss university hospital to evaluate the clinical pharmacists' interventions. In 5441 patients, a total of 5024 DRPs were identified. For 2892 DRP (57.6%) the suggested PI was directly accepted and implemented by the attending physician. In contrast to our study, the percentage of PIs with minor impact (59.1%) was lower and the percentages of PIs with moderate and major impact were higher (27.6% moderate, 11.1% major impact). These differences might be explained by the different settings. Other studies from hospital settings show high numbers with minor clinical and low numbers with major clinical impact.<sup>46–50</sup> In addition, studies showed that clinical pharmacists contribute to an optimized treatment.<sup>51–53</sup> Our study confirms the positive impact from PIs suggested by CPs in different settings.

## 4.5. Contact with physicians

In approximately 40% of all PIs, physicians were contacted. Almost half of these contacts consisted of a transmission of information only. Referrals to physicians were mainly associated with changes in prescribed drug therapy with pharmacists' suggesting interventions like stopping or substituting a drug. Szilvay et al.<sup>29</sup> reported that pharmacists involved physicians less often: This was either by informing the physician (11.7%) and referring the patient to the physician (14.5%). In contrast to our setting, the pharmacists often preferred to send the

patient without consulting the physician, because there was no established interprofessional collaboration. In a post-hoc analysis of the ATHINA project, physicians' contact and referrals to physicians were also less often compared to our study (22.9%).<sup>8</sup> As in Svilvays' study, the ATHINA concept did not include a structured interprofessional collaboration with defined roles.

In our study, the physicians were contacted most often because of identified DDIs, medication non-adherence, and adverse effects. In the ATHINA project, the physician was less often contacted for an adherence problem.<sup>8</sup> This might be due to the closer communication in the continuous management process where communication channels were established routine practice.

#### 4.6. Limitations

The small cohort of 79 patients limits the generalizability of the results. Furthermore, due to the complex intervention and long observation period of approximately six months the pharmacists had a high documentation burden. This might have led to underreporting of DRPs identified and interventions conducted. On the other hand, the potential Hawthorne effect (with pharmacists potentially altering their behavior due to study participation) could have led to an overestimation of changes. To minimize this effect, only pharmacists with prior experience in implementing the ARMIN medication management were involved, and structured process descriptions and documentation guided all intervention steps, helping to ensure consistent application and reduce the impact of observation on behavior.

The possible relation of the changes in medication with the DRPs conducted was assessed retrospectively based on the complete documentation per patient and no validated tool was used. Due to the anonymized data, contacting pharmacies and/or physicians was not possible to verify or reject our assumptions. In case of doubt, we therefore rated associations as "unclear". Nevertheless, it cannot be fully ruled out that the association was not correct in all individual cases.

#### 5. Conclusion

Within this interprofessional medication management program it was possible to solve DRPs with PIs resulting in changes in the medication and having a potential clinical impact. The implementation rate in our study suggests that intensive collaboration with clear responsibilities between community pharmacies and primary care physicians/general practitioners, continuous rather than isolated interventions, established professional relationships, and established communication channels are important contributing factors. These elements may provide transferable guidance for other health systems seeking to implement interprofessional interventions.

#### CRediT authorship contribution statement

**Christiane Eickhoff:** Writing – original draft, Visualization, Validation, Supervision, Software, Methodology, Investigation, Formal analysis, Conceptualization. **Ann Kathrin Strunz:** Writing – review & editing, Validation, Investigation, Formal analysis, Data curation. **Maike Petersen:** Writing – original draft, Validation, Project administration, Investigation, Formal analysis, Data curation. **Meike Ruschkowski:** Writing – review & editing, Validation, Formal analysis. **Uta Müller:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Martin Schulz:** Writing – review & editing, Supervision, Conceptualization.

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#### Declaration of competing interest

The authors do not have any interest to declare.

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#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.rcsop.2026.100717>.

#### Data availability

The datasets generated and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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