Feasibility and Efficacy of a Collaborative Medication Management for Elderly, Multimorbid Patients

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Content

Gender disclaimer:

For the purpose of easier legibility, references to persons in this dissertation are not gender-specific. Unless otherwise stated, whenever the masculine gender is used, both men and women are included.

Abbreviations:

AACP	American Association of Colleges of Pharmacy
AACP	Australian Association of Consultant Pharmacy
ACCP	American College of Clinical Pharmacy
ABDA	Bundesvereinigung deutscher Apothekerverbände
ADE	Adverse drug event
ADL	Activities of daily living
AMTS	Arzneimitteltherapiesicherheit (medication safety)
ASHP	American Society of Health-System Pharmacists
b.i.d.	Bis in die, twice daily
BMI	Body mass index
ARB	Angiotensin receptor blocker (Sartan)
CDTM	Collaborative drug therapy management
CMM	Comprehensive medication management
CRF	Case report form
CV	Cardiovascular
CYP	Cytochrome-P (-450-isoenzymes)
DIADEMA study	Diabetes in Adoleszenz: Einsatz und Monitoring in Apotheken-study
DMARD	Disease-modifying antirheumatic drug
DOI	Digital Object Identifier, digitaler Objektbezeichner
DRE	Drug-related event
DRP	Drug-related problem
eGFR	Estimated glomerular filtration rate
et al.	Et alii respectively et aliae

FINDRISC	Finnish diabetes risk score
FIP	International Pharmaceutical Federation
FSozu K-14	Questionnaire social support, shortform 14 Items (Fragebogen soziale Unterstützung, Kurzform 14 Items)
GFR	Glomerular filtration rate
GP	General practitioner
HbA_{1c}	Glycated hemoglobin A_{1c}
HDL-C	High density lipoprotein-cholesterol
HEDIS	Healthcare effectiveness data and information set
HMR	Home Medicines Review
IADL	instrumental activities of daily living
ICC	Intraclass correlation coefficient
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	Intention to treat
LBM	Lean body mass
LDL-C	Low density lipoprotein-cholesterol
LOCF	Last-Objective-Carried-Forward method
MA	Medikationsanalyse (Medication review)
MAI	Medication appropriateness index
Medicare Part D	Medicare prescription drug, improvement, and modernization act of 2003, part D
MM	Medication Management
MMSE	Mini mental status examination
MR	Medication review
MRCI	Medication regimen complexity index
NCEP	National cholesterol education program

Nr.	Number
NSAID	Non-steroidal anti inflammatory drug
NHS	National Health Service
OLS	Ordinary least squares
OTC	Over The Counter
PCNE	Pharmaceutical Care Network Europe
PCP	Primary care provider
PI-Doc®	Problem-intervention-documentation
PIM	Potentially inappropriate medication
PP	Per protocol
p.r.n.	Pro re nata = when required
PZN	Pharmazentralnummer, German drug code
q.d.	Quaque die, daily
RCT	Randomized controlled trial
SEE	Standard error of the estimate
SOAP	Professional note based on subjective, objectives, assessment and plan
t.i.d.	Ter in die, three times a day
UK	United Kingdom
USA	United States of America
VAS	Visual analog scale
WHO	World Health Organization

1. INTRODUCTION

1.1. PHARMACEUTICAL CARE AND PROFESSIONAL DEVELOPMENT

Pharmaceutical Care was defined by Hepler and Strand in 1990 as the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve patient's quality of life [1]. Providing pharmaceutical care was soon found to be beneficial to the patient, the society and other health care professions and was promoted among pharmacists in Germany a few years later by Derendorf and others [2]. Along with the professional changes the World Health Organization (WHO) and the International Pharmaceutical Federation (FIP) have published a handbook on developing pharmacy practice with a strong focus on patient care in 2006, which was used as a blueprint for many countries worldwide [3]. The definition of pharmaceutical care was updated by the Pharmaceutical Care Network Europe in 2013 as [4]:

"Pharmaceutical Care is the pharmacist's contribution to the care of individuals in order to optimize medicines use and improve health outcomes"

New tools like Medication Review and Medication Management with its underlying clinical sciences are new services to serve the patient. They might as well have a strong impact on positioning the pharmaceutical profession in a future healthcare system, as the pharmacist is involved as an active player in therapy and is enhancing

the therapeutic outcomes. Evolving and transforming pharmacy as a science and profession faces several challenges, as described by van Mil at al. in a review in 2004 [5]. Ten years later, in 2014, German pharmacists voted for a new orientation towards patient services [6]. Providing the profession with basic research results was the driving force behind these elaborations and this dissertation.

1.1.1. RESEARCH IN PHARMACEUTICAL CARE

During the last two and a half decades several pharmaceutical care studies were conducted to demonstrate the effects of pharmaceutical interventions on outcomes like adherence, costs, laboratory and surrogate parameters or other definite clinical endpoints [7–10].

Initially, many pharmaceutical care studies focused on patient education provided by a pharmacist. Patient education by pharmacists increased the quality of life of patients with diabetes [11]. The DIADEMA-study reached a significant change in glycated hemoglobin A_{1c} (HbA_{1c}) in type-1 diabetic patients after 6 months of motivational interviews by community pharmacists [12]. Patient education by pharmacists within the GLICEMIA program led to a significant reduction in the FINDRISC score [13], a type-2 diabetes mellitus risk score [14]. Benefits of pharmaceutical care have been reported in breast and ovarian cancer with a focus on patient counseling [15] as well as in palliative care by Needham et al. [16]. Patient education of pharmacists was effective in optimizing the handling of asthma-inhalation devices [17, 18]. In a recent systematic review Jalal et al. found that

pharmaceutical patient education has a good level of evidence to be beneficial on cardiovascular outcomes in increasing medication adherence [19].

Increasing medication adherence is another typical pharmaceutical care activity that can be affected by pharmacists [20]. A meta-analysis by Carter et al. showed a reduction in systolic blood pressure by pharmaceutical interventions in the hospital and community setting of 7.76 respectively 9.31 mm Hg [21].

Other examples of pharmaceutical care services are screening for interactions or use of inappropriate drugs [22–25] searching for prescription errors or any kind of drug-related problem (DRP) [26–28], supporting disease screenings or to perform a Medication Review or Medication Management. Cai et al. concluded that pharmaceutical interventions have a positive impact on adherence, blood pressure or lipid management but failed to reduce mortality, cardiac events or hospitalization in a systematic review on coronary heart disease [29]. A systematic Cochrane review in 2010 tried to evaluate the benefits of pharmaceutical patient services but complained that current studies are too heterogeneous to be pooled and that pharmaceutical services can hardly be compared to care services, delivered by other health care professionals [30]. In summary, many pharmaceutical care studies have been published in several specific settings and the benefits could be demonstrated, but the heterogeneity of the studies makes it difficult to draw a final evidence-based conclusion.

1.2. MEDICATION REVIEW AND MEDICATION MANAGEMENT

Medication Therapy Management (MTM) as a new tool in pharmaceutical care was implemented first in the Medicare Prescription Drug, Improvement, and Modernization Act of the United States of America, where Part D regulates access to a Medication Therapy Management for certain patients [31]. Medication Therapy Management or Medication Management as well as Medication Review are used synonymously in many countries and are current international trends with the potential to have a profound impact on patient outcomes and on pharmaceutical practice. Both approaches are based on a patient-oriented view on medication safety and pharmacotherapy and require clinical knowledge as well as clinical experience. A Medication Review was defined by the Pharmaceutical Care Network Europe (PCNE) [32]. Amendments of the current definition were suggested at the PCNE working symposium in Hillerød in 2016 and are published as [33]:

"Medication review is a structured evaluation of patients' medicines with the aim of optimizing medicine use and improving health outcomes. This entails detecting drug-related problems and recommending interventions"

In the United Kingdom a Medication Review is called Medicines Use Review by the Royal Pharmaceutical Society and the National Health Service whereas the American College of Clinical Pharmacy (ACCP) favors the terms Comprehensive Medication Management (CMM) and Collaborative Drug Therapy Management

(CDTM) [34, 35]. A Medication Review as a pharmaceutical service is called “Polymedikations-Check” in Switzerland [36]. In Australia, the Australian Association of Consultant Pharmacy (AACP) established the "Home Medicines Review (HMR)" [37]. In a Medication Management pharmacotherapy and medication safety are considered. Aspects for an assessment are potential contraindications, dosage errors, wrong dosage intervals, handling problems, non-adherence, potential therapeutic or drug doublets, prescribed drugs without an indication or detected indications without a drug. In addition to increasing medication safety, therapeutic as well as patient goals should be expressed and options to reach these goals should be suggested and wherever possible implemented. In a so called "Brown Bag Review" the drug use of the patient (supplied to the pharmacist in a “brown bag”) is compared to the medication plan of the prescriber and discrepancies are analyzed. Medication Reconciliation is regarded as a typical first step in a Medication Review. Discrepancies in dosages are examined. A patient interview, data collection and an analysis and assessment of the therapy is the second step, followed by documentation and further action. The implementation of a Medication Review and a Medication Management in community pharmacies as well as on the ward, is based on expanded skills in clinical pharmacy and pharmacotherapy, all efforts should be patient-oriented. Medication Review is the preferred wording by the PCNE. A Medication Review is the structured approach to assess a patient’s drug therapy. The PCNE defines four types of Medication Reviews based on the origin of the data sources (table 1) [38]:

Tab. 1: Different types of a Medication Review, based on the data sources, according to the PCNE definition [38]

Data source	Type 1	Type 2A	Type 2B	Type 3
pharmacy record	yes	yes	yes	yes
patient information	no	yes	no	yes
medical records/lab data	no	no	yes	yes

These 3 types of Medication Review were adopted by the Federal Union of German Associations of Pharmacists (Bundesvereinigung deutscher Apothekerverbände, ABDA), which calls a Medication Review “Medikationsanalyse” in German language. Medication Management or Medication Therapy Management is a term mainly used in the USA in an equivalent way to Medication Review [31]. In German language the term Medication Management, translated as "Medikationsmanagement", was defined by the German Pharmaceutical Society (DPhG) and was developed as longitudinal and interprofessional patient care by the ABDA in 2014 [39, 40]. According to the ABDA definition, Medication Management (Medikationsmanagement) requires further action after a Medication Review (Medikationsanalyse) is done, which could be a repeated review, the initiation of therapeutic changes, or any kind of activity that is undertaken to solve detected DRPs. Interprofessional cooperation is another crucial aspect mentioned by the ABDA definition of "Medikationsmanagement". As pharmacists in Germany cannot change any medication without a prescriber, a physician needs to be involved in most interventions. Cooperation with other health care providers (like home care experts or nurses) can be required as well and is another example for interprofessional collaboration.

Medication Management services gradually have evolved from patient education and medication-safety aspects to therapy consultations [41]. Pharmacists tend to play a more active role in several settings nowadays. A Medication Management is available for eligible patients in the USA, the UK, Switzerland, Poland, Slowenia and many other countries [42]. In the USA Medication Management is offered as the most prevalent patient oriented service by 60% of the pharmacists, according to the national pharmacist workforce survey 2014 by the American Association of Colleges of Pharmacy (AACP) [43].

Case reports in the Medizinische Monatsschrift für Pharmazeuten and in the Deutsche Apotheker Zeitung demonstrated Medication Management during the last decade in Germany [44–47]. In 2013 a Medication Management was defined by the “Apothekenbetriebsordnung” in §1a and §3. A Medication Management in Germany has been introduced as a pharmaceutical service, which has to be done personally by a pharmacist. Along with the omitting implementation in standard care, research on Medication Management in Germany is still scarce.

1.2.1. RESEARCH IN MEDICATION MANAGEMENT

During the past two decades, several remarkable studies and reviews on Medication Review and Medication Management have been conducted. In an early study by Hanlon et al. in 1996 the prescription of inappropriate drugs declined by 24% (versus 6% in the control group) by Medication Management ($p=0.0002$) [48]. Machado et al. found in a review that patient education and Medication Management can significantly reduce LDL-cholesterol by up to 32.6 mg/dl ($p < 0.001$) [49]. Chisholm-

Burns et al. reviewed significant improvements by a Medication Management focusing on LDL-cholesterol, blood pressure, HbA_{1c} and the reduction of adverse drug events ($p<0.05$) [50]. Planas et al. found provided Medication Managements helpful in reducing blood pressure by 17.32 mm Hg in a small study in 2003 [51]. Ramalho de Oliveira et al. determined in a large review article in 2010, based on Medicare Part-D data, that Medication Management programs have shown to improve clinical outcomes and to reduce costs [52]. A systematic review for the Cochrane Database on the effects of a Medication Management for elderly patients in care homes stated that the considered studies were too different in design and baselines to draw a final conclusion [53]. A meta-analysis came to the result that there is little evidence to show that Medication Management interventions can improve health outcomes, whereas they might help to solve some drug-related problems, including nonadherence, and might lower health-care costs [54]. Further studies are still desired and there is a strong demand to add evidence to the positive outcomes that could be reached by pharmacists' interventions for the patient. The efficacy of a Medication Management is particularly depending on the setting and grade of collaboration of the health care provider team. The acceptance of the pharmacist`s recommendation by the physician (and other health care providers) is another crucial point in providing patient-oriented services. Obviously, an intense pharmaceutical work-up cannot lead to any improvement, if the interventions do not reach the patient. Interprofessional collaboration as a potential confounder hence needs to be addressed in any Medication Management. The acceptance of the suggestions provided by pharmacists through a Medication Management was analyzed in 2005 by Doucette et al., who implemented a Medication Management in

community pharmacies and followed the outcomes of the interventions. Drug-related problems were addressed and almost 50% of the interventions were accepted by the physicians in charge [55]. A smaller study in community pharmacies rated the acceptance of pharmaceutical suggestions between 42 and 60% [56]. Professional collaboration and acceptance are the bottleneck in performance of any Medication Management.

1.2.2. ENDPOINTS IN MEDICATION MANAGEMENT STUDIES

Several endpoints have been used in previous studies to evaluate the effects of a Medication Management on drug therapy. Implicit or explicit endpoints can be chosen to assess the efficacy of a Medication Management. Explicit parameters are single laboratory data or vital signs, which can be obtained objectively [57]. Complex changes induced by a Medication Management, like the quality of therapy, can be formulated much better by implicit scales that consist of more than just one parameter and need further analysis to be done. Changes in the quality of therapy, DRP, quality of life or adherence need further evaluation to be rated and thus are regarded as implicit parameters.

1.2.3. QUALITY OF THERAPY

A meaningful approach to evaluate the effects of a Medication Management is to measure the quality of therapy. The Health Plan Employer Data and Information Set, the so called HEDIS goals are a tool to measure, rate and score changes in

medication [58]. HEDIS goals consist of surrogate endpoints and vital-sign goals, to meet targets in HbA_{1c}, LDL-cholesterol or blood pressure. HEDIS goals were the primary endpoint in a landmark study that was among the first studies to show a defined benefit from a Medication Management under controlled trial terms [59, 60]. The Medication Appropriateness Index (MAI), developed by Hanlon et al. in 1992 is another tool to rate the quality of therapy [61]. It has been evaluated to correspond to hospital admissions and for the prediction of adverse drug events and was modified by Samsa et al. as a weighted measure for the quality of therapy in pharmaceutical care [62–64]. The MAI consists of 10 questions per drug to identify potential medication safety or therapeutic issues. Higher MAI scores indicate a low quality of drug therapy. A more detailed explanation of the MAI can be found in the methods chapter (3.1.5.). A Cochrane review in 2011 revealed that the majority of studies of high quality rely on the MAI, seven out of eleven randomized controlled trials were based on the MAI as the primary endpoint [65]. The MAI has been tested and evaluated in various settings [66–69]. An article by Hanlon and Schmader in 2013 compared all RCTs that used the MAI and competing scores during the last 20 years [70]. They came to the conclusion that the MAI is “best at detecting prescribing improvement over time” but “most time consuming to apply” [70]. Besides for patients with polymedication and with widespread diseases the MAI was successfully used in special indications like in psychiatry in a study by Wolf et al. in 2015, even though the baseline MAI of 2.3 was extremely low, indicating an already high quality of drug therapy at baseline [71]. A higher absolute reduction in the MAI obviously could be reached with a higher baseline MAI. Castelino et al. reached a 9.3 MAI

reduction in patients with a MAI of 18.6 at baseline, indicating a low quality of therapy at study entry [72].

1.2.4. MEDICATION SAFETY AND DRUG-RELATED PROBLEMS

Another aspect of a Medication Management is to address medication safety, which seamlessly overlaps with the quality of therapy. DRP classification systems usually cover both aspects. Various systems have been developed during the past two decades. Van Mil et al. identified 14 different systems already in 2004 [73].The probably first approach on classification was developed by Hepler and Strand. They defined 8 categories of DRPs, which were initially used at the University of Florida in teaching and practice and have been published later in a statement by the American Society of Health-System Pharmacists (ASHP) in 1993 [74]. DRP categories according to Hepler and Strand are:

1. Untreated indications
2. Inproper drug selection
3. Subtherapeutic dosage
4. Failure to receive medication
5. Overdosage
6. Adverse drug reactions
7. Drug interactions
8. Medication use without indication

The Hepler and Strand criteria are still used in the USA to date. Several alternative classification systems were developed with regard to the specific setting and use. Classification systems for use in a community pharmacy show fewer categories compared to the hospital setting. The Westerlund classification is an example of a practical structured system [75, 76]. It consists of 11 kinds of DRPs: uncertainty about the aim of the drug, insufficient or no therapeutic effect (therapy failure), underuse of drug, overuse of drug, drug duplication, adverse reaction/side effect, interaction, contraindication, inappropriate time for drug intake/wrong dosage interval, practical problems and other DRPs.

The classification system of the PCNE is in contrast to the Westerlund system very detailed. The current version used during these studies was 6.2 [77]. Version 7 was published in 2016 [78]. The PCNE classification is structured into problems, causes, interventions and outcomes with several domains and subdomains. It might be most widely established in recent research as it has been tested for validity and reproducibility [79]. The Swiss Society of Public Health Administration and Hospital Pharmacists (GSASA) developed an evolution, with a focus on easy handling [80]. The DOCUMENT classification has a similar approach as the GSASA [81]. Several other classification systems were developed with regard to specific settings. In various settings significant effects of pharmaceutical interventions in reducing DRPs could be demonstrated [55], [82–85].

A more confined approach to increase medication safety is a focus on the use of potential inappropriate medications (PIM) for the elderly. Gustafsson et al. reached a significant reduction of PIM through a pharmaceutical intervention in Swedish nursing homes [86]. Further insight into the approaches of PIM reduction was provided by a

review article and a detailed description on their implementation, which became a natural part of any Medication Management in elderly patients [87, 88].

1.2.5. DRUG-DRUG INTERACTIONS

Drug-drug interactions, as one category of DRPs can be identified with numerous software programs. In the meantime, several attempts have been undertaken to compare these tools. There are some differences in severity staging or in the number of less relevant interactions. Furthermore, international tools can hardly be compared, due to a difference in nationally registered drugs, but most studied databases provide a helpful assistance in detecting interactions [89]. Roblek et al. in contrast found little accordance between international databases with an overlap as low as 11% in some cases [90]. In these comparative studies, less attention is paid on the clinical relevance of the interactions but rather on the mere number of interactions. The relevance of interactions can hardly be defined or classified but rather depends on clinical experience and the specific setting. Furthermore, drug-drug interaction software does not take interactions of more than 2 drugs into account. An important aspect is to avoid a so called “alert fatigue” with too many reported interactions to the prescriber [91].

1.2.6. QUALITY OF LIFE

A patient-oriented approach to measure outcomes of a Medication Management is to study the quality of life, measured by the SF12 or SF36 score [92], by the WHO-5

well being index or various other scores [93]. Changes in the quality of life by a Medication Management were challenged by several studies. Surprisingly, results are controversy [94, 95]. This might be due to the short observation period in most pharmaceutical care studies or to the limited relevance of drug therapy to the quality of life.

1.2.7. COMPLIANCE AND ADHERENCE

Adherence is defined by the WHO as "the extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider" [96]. The patient`s agreement is a crucial aspect of the definition and the main distinction between the terms adherence and compliance [97, 98]. Medical societies like the American Heart Association (AHA) and the American Diabetes Association (ADA) recognize the relevance of non-adherence on therapeutic outcomes in their standards and guidelines [99, 100]. The AHA emphasizes the importance to evaluate measurement of adherence and establish standards. A circulation report in 2009 helped to define adherence problems for cardiovascular indications [100]. Improvement in compliance and adherence is an original task for pharmacists [101]. A standard method to improve adherence is the motivational interview. Pharmacists educate the patients about drugs under various aspects and help to understand the drugs, their indications, its effects and its handling. Several studies could show a positive outcome of a pharmaceutical intervention on adherence in diverse settings, underlining the importance of a pharmacist in the therapeutic team [102–105].

1.2.8. COSTS

Reducing costs might be a major point of interest for health care stakeholders like national, public and private health insurances. Costs could be regarded as drug costs, the wider field of therapeutic costs, health costs (covering any type of intervention) or even overall costs for the society, including loss of labor days. Regarding a Medication Management only few studies on its cost efficacy are available. Costs in asthma therapy dropped by pharmacists' interventions due to a decline in emergency department visits [106]. A study by Stuart et al. on Medicare Part D expenses concluded that low adherence leads to additional costs between 49 and 840 $ per month in patients with diabetes, which likely could be reduced by a Medication Management [107]. As falls account for tremendous costs [108], a reasonable target to measure savings could be the reduction of falls by watching out for potential inadequate medication (PIMs) in the elderly. In this context, eliminating anticholinergic drugs wherever possible or reducing drastic blood pressure lowering are typical pharmaceutical care activities. Ramalho de Oliveira et al. analyzed the data of 10 years of Medicare Part D services in Medication Management in the USA and reported a saving of 86 $ per encounter with a pharmacist [52]. The consideration on costs would need to take the costs of the intervention into account comprising of the reimbursement of all involved health care providers. In the study by Ramalho de Oliveira et al. these costs were calculated with 67 $ per encounter, which results in a 19 $ saving for the health insurance [52]. Isetts et al. found that total annual health expenditures decreased from 11965 $ to 8197 $ per patient and calculated that the costs of a Medication Management in relation to the savings is

1:12 [60]. Wittayanukorn et al. conducted an analysis in patients with cardiovascular diseases with significantly lower total, pharmacy and medical health care expenditures in the Medication Management group compared to the control group [109].

1.2.9. PATIENT SELECTION IN MEDICATION MANAGEMENT

Patient selection for a Medication Review or a Medication Management is done mainly by the pharmacist (“pull referral”) or by the health insurances (“push referral”) [41]. In Switzerland and Australia, a medication review is typically initiated by the pharmacist, whenever DRPs are detected [110–112]. The Australian Residential Medication Management Review on the other hand needs to be initiated by a physician for reimbursement [113, 114]. In the United States (US), patients are referred to a Medication Management mainly through insurance companies [115]. Medication Management programs in the US vary and health expenditure might be an unpretentious criterion for patient selection [115]. In Great Britain patients are eligible for a Medicines Use Review if they have been prescribed two or more medicines and are regular users of the pharmacy [116]. The variety of selection criteria indicates that no evidence-based criteria have been assessed so far. Rosenthal et al. published an article describing the Medication Regimen Complexity Index (MRCI) as a potential criterion to identify patients for Medication Management [117, 118]. The study didn`t test for any correlation between the outcomes though and doesn`t provide new insights.

1.3. IDENTIFYING HIGH-RISK GROUPS

As pharmacists worldwide are implementing pharmaceutical care services like Medication Reviews and Medication Management, they might be facing limited capabilities in time and manpower. As a consequence of a shortage in manpower, pharmacists might want to focus on certain patient populations to identify those, who carry the highest benefit from a Medication Management, as long as this service cannot be offered to every eligible patient. Limited resources should be used in the most effective and appropriate way. In a report of the chief pharmacist Giberson et al. to the U.S. Surgeon General, several examples on how medication services are restricted to the population in the US are mentioned [119]. At that time, in 2011, only 12% of all eligible patients in the US had access to a Medication Management. Health insurance companies restricted patients from these pharmaceutical services as they were limiting it to the elderly, handicapped or socially deprived patients. The criteria for these limitations do not seem to be based on ethics or evidence but rather on financial or arbitrary considerations. A consequent approach by some health insurance companies in the USA is to offer Medication Management services only to patients consuming drugs of more than 3000 US-Dollars per year [120]. A change to a diagnosis-related access is suggested by US pharmacists as a better criterion to identify eligible patients [121]. Momentous decisions should still be evidence-based. An age of ≥ 65 is commonly defined as being elderly [122]. Chronic use of 5 or more systemic relevant drugs is a common definition of polymedication [123]. All selection criteria still are not evaluated to identify patients with a higher benefit of a Medication Management but are rather arbitrary. In addition, such criteria might include far too

many patients, taken the number of pharmacists into account who can offer a comprehensive Medication Management in Germany.

1.3.1. THE EPHOR CRITERIA

Approaches have been done by the PCNE in a workshop to evaluate risk parameters for DRPs. The "Ephor criteria" or "Ephor filter" suggests several parameters relating to a high risk of drug therapy. The Ephor filter is a tool rating each presence or absence with certain multipliers and forming a score to express the level of risk [124]. The basic criteria of Ephor are intake of 5 or more drugs and a patient age of 65 years or older. The Ephor and PCNE affiliated researchers suggest further alert parameters, which might increase medication risk and work as a precondition to apply the Ephor score [124]:

- reduced renal function of <50 ml/min
- reduced cognition (dementia and pre-dementia)
- increased risk for falling defined as: patient fell once or several times in the preceding 12 months
- signals of reduced adherence to therapy
- not living independently (nursing home)
- unplanned hospital admissions

Criteria of being at high risk are shown and rated in table 2. These citeria are age, number of drugs taken, number of drugs with a small therapeutic index, certain indications and kidney function.

Tab. 2: The Ephor-score

Parameter	Specification	Score
Age (y)	<65 66-75 76-85	0 1 2
Number of drugs	<6 6-9 >9	0 2 4
Drugs with small therapeutic index (Warfarin, Digoxin, Lithium, MTX, etc.)	number	number=score value
Indications treated by pharmacotherapy	CV, diabetes, anticoagulation, neurologic/psychiatric, asthma/COPD, NSAIDs, opioids, corticosteroids	number of indications=score value
Kidney function, GFR (mL/min/1,73 m^2)	>50 31-50 <31	0 2 4

The Ephor score is rather a suggestion than an evaluated tool and can help in patient screening. There are several limitations. The score is based on experience and not

on data. The steps in grading kidney function differ from the staging of the guidelines. The broad field "pharmacotherapy for neurologic/psychiatric diseases" is not very specific. Little is known about how these multipliers were evaluated. Isaksen et al. have suggested and tested criteria for medication-risk screening. These criteria are five or more drugs, ≥ 12 doses per day, four or more recent changes to the medication regimen, three or more chronic diseases, history of noncompliance, and presence of a drug requiring therapeutic drug monitoring (TDM) [125].

1.3.2. CARDIOVASCULAR DISEASE AS A HIGH-RISK FACTOR

Dyslipidemia and atherosclerosis are the leading causes of most cardiovascular diseases and are known to be prevalent independent from modern lifestyle throughout history [126, 127]. Suitable markers for patients at risk for cardiovascular events within the subsequent 12 months were discussed in a working group for the US-American National Heart, Lung, and Blood Institute [128]. Established scores and risk calculators, such as the Framingham score, the PROCAM score, the risk calculator of the American Society of Cardiology and American Heart Association or the European Society of Cardiology favored Systematic COronary Risk Evaluation (SCORE) are mentioned in this study but were found not to be specific enough, as these tools were designed to calculate and predict the 10-year risk for cardiovascular events rather than the short-term risk [129–131]. Tools like the TIMI risk score (named after the Thrombolysis In Myocardial Infarction, TIMI group) are designed to calculate a more acute risk but are limited to certain indications like the acute coronary syndrom [132]. Diagnostic tools are another option. Measurement of

coronary artery calcification or carotis intima-media thickness sonography are options but are not available for pharmacists [133], neither are soluble markers like endothelin-1, von Willebrand factor, tissue-type plasminogen activator and soluble thrombomodulin, which are discussed in the mentioned survey [128]. A reduction of risk factors might not even correlate to a change in patient outcomes. For example even though high homocysteine levels are a certain risk factor for cardiovascular diseases, lowering homocysteine levels failed to show any clinical benefit in reducing cardiovascular events [134].

A familial susceptibility and a genetic predisposition are the most likely underlying causes of dyslipidemia. Dyslipidemia and atherosclerosis can be further triggered by lifestyle, certain drugs, alcohol consumption and diseases like diabetes mellitus, systemic lupus and kidney disease. Statistics for Germany estimated that about 11% of the population can be diagnosed with dyslipidemia [135]. The DETECT study surveyed patients in German primary care practices and found that every second patient presented with dyslipidemia [136]. About 50% of these patients were incorrectly diagnosed despite clear laboratory data and only 10% of the patients treated matched the NCEP-defined targets, indicating a low consciousness regarding blood lipids among physicians and patients alike [137]. LDL-cholesterol has proven to match best with atherosclerotic progression and clinical endpoints while other laboratory data such as homocysteine have shown to be risk markers but not a reasonable target of drug therapy [138]. Intensive LDL-cholesterol lowering with statins can reduce mortality and cardiovascular events [139–141]. This might be not only true for the highest risk patients (defined as >10% risk for a cardiovascular event over 10 years) but as well for patients with a lower risk [142]. Current guidelines

demand a LDL-cholesterol goal of <70 mg/dl [138, 143]. Results of the IMPROVE-IT study and studies with the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor evolocumab and alirocumab suggest, that an even lower LDL-cholesterol might correlate with better outcomes [144–147]. The reduction of the cardiovascular risk is independent of the patient's age as shown in a large study in 2009 [148]. Community pharmacists succeeded to reduce LDL-cholesterol by implementing a lipid management program [149]. Another study came to similar results in 2005 [150]. A meta analysis found a 17.5 mg/dl stronger reduction in LDL-cholesterol in the intervention groups after pharmaceutical interventions compared to the control groups with standard care [49].

1.3.3. RENAL FUNCTION AS A HIGH-RISK FACTOR

The renal function declines with age in a natural way [151]. Cohen et al. found that a reduction of 1,18 ml/min per year can be expected in patients with multiple diseases [152]. Decreased renal function has shown to correlate with cardiovascular events in several surveys, including the large HOT and HOPE studies [153–158]. As many drugs need to be adjusted to renal function, kidney disease is a frequent source of DRPs [159]. Serum creatinine and patient characteristics like age and weight are accessible in most settings and hence the estimated glomerular filtration rate (eGFR) can be calculated. The Cockcroft-Gault equation is an evaluated tool, but many other equations were found to be clinically useful, like the MDRD and the new CKD-Epi equations [160–163]. In case of obesity, defined as having a BMI >30 kg/m^2, the Cockcroft-Gault equation tends to overestimate the eGFR, as it increases

with body size to a much lower extent [164]. As the lean body mass (LBM) has shown to correlate much better with the real eGFR [165, 166], it was suggested to utilize the LBM in the Cockcroft-Gault equation instead of the actual body weight in such cases. The estimated LBM (eLBM) can be calculated using the James equations [167]:

Men: $eLBM = 1.1 \times weight(kg) - 128 \times (weight(kg)/height(cm))^2$

Women: $eLBM = 1.07 \times weight(kg) - 148 \times (weight(kg)/height(cm))^2$

The US-American National Kidney Foundation (NKF) program of Kidney Disease Outcomes Quality Initiative (KDOQI) defines 5 stages of kidney function [162]:

- stage 1, normal GFR with a eGFR of ≥ 90 mL/min/1,73m^2
- stage 2, mildly decreased eGFR at 60-89 mL/min/1,73m^2
- stage 3, moderately decreased eGFR at 30-59 mL/min/1,73m^2
- stage 4, severely decreased eGFR at 15-29 mL/min/1,73m^2)
- stage 5, kidney failure at eGFR <15 mL/min/1,73m^2

The Kidney Disease Improving Global Outcomes (KDIGO) classification has similar grades G1-G5, grade 3 being subdivided into 45-59 mL/min/1,73m^2 as G3a (mildly to moderately decreased) and 30-44 mL/min/1,73m^2 as G3b (moderately to severely decreased) [168]. Both staging systems are used in international studies.

1.3.4. AGE AS A HIGH-RISK FACTOR

Age is an independent risk factor in cardiovascular disease and is an Ephor criterion for high risk in polymedication as well. The elderly patient is defined here as a patient at an age of 65 years or older. The definition of being elderly differs widely and is related to biological aging more than to chronological aging. In many guidelines the term elderly is not even defined and differs [169]. Most industrial societies and the WHO simplify the definition by using the age of 65 or the retirement age [170]. Geriatric age in contrast is mainly defined as an age of >70 years in industrial societies, as e.g. per definition of the German Society of Geriatrics [171].

1.3.6. MULTIMORBIDITY AND POLYMEDICATION

Multimorbid patients with cardiovascular diseases are a major patient group in pharmaceutical practice. A study by van Bossche et al. found the diseases hypertension, lipid metabolism disorders, chronic low back pain, diabetes mellitus, osteoarthritis and chronic ischemic heart disease as typical patterns of diagnosis in multimorbid patients [172]. Cardiovascular diseases nowadays are major causes of death in Germany (table 3) [173, 174].

Tab. 3: Mortality by disease, according to data of the German Center of Gerontology 2009 [174]. Cardiovascular diseases are displayed in blue script

rank	male	female
1	*coronary artery disease*	*coronary artery disease*
2	*cerebrovascular diseases*	*cerebrovascular diseases*
3	lung cancer	*chronic heart failure*
4	*chronic heart failure*	*hypertension*
5	respiratory tract diseases	Alzheimer disease and dementia
6	prostate cancer	diabetes mellitus
7	colorectal cancer	breast cancer
8	influenza and pneumonia	*arrhythmia*
9	*hypertension*	influenza and pneumonia
10	diabetes mellitus	respiratory tract diseases

Polymedication or polypharmacy, as another inclusion criteria, is commonly defined as the permanent use of 5 or more systemic available drugs [175]. Polymedication is increasing in industrial societies. In an epidemiologic study Hovstadius et al. showed an increase of 8.2 % in the prevalence of polymedication during a 4-year period from 2005-2008, covering the entire population data for Sweden [176]. Polymedication is expected to be a major cause of DRPs [177]. With a higher number of drugs, the relevance of drug-drug interactions is increasing and prescription cascades, in which adverse drug reactions are treated with further drugs, are more likely [178]. Polymedication is associated with a higher risk of hospitalization [179]. On the other hand, polymedication might as well be indicated in case of multimorbidity. Payne et al.

showed for patients with a similar number of prescribed drugs, that the risk for hospitalization is relatively lower for those with a higher number of diagnoses, indicating that a high number of diagnoses makes polymedication more reasonable [180]. National regulations are believed to have a profound impact on polymedication. Facing the challenges of rising costs in the health care systems, different approaches were tried to reduce the economic burden. While the United States have implemented managed care to reduce the costs at an unchanged or even higher quality of care [181], Germany has established budgets for health services and medication, which led to a distinct drop in the number of drugs prescribed per patient [182]. Drug budgets may have certain disadvantages but make prescriptions of drugs without an indication more unlikely compared to other regulation systems.

1.4. INTERPROFESSIONAL COLLABORATION AND MEDICATION RECONCILIATION

Collaboration of physicians and pharmacists have become a major aspect in Pharmaceutical Care. Bringing pharmaceutical expertise into the medication process of the prescriber has shown to be beneficious for medication safety [183, 184]. Medication Reconciliation is a key activity to demonstrate the advantages of interprofessional cooperation. Numerous studies found discrepancies in up to 88% of participating patients [185–187]. The experience of many years of collaborative care clearly favors interprofessional approaches [30, 188–191]. The emphasis on interprofessional cooperation with the participation of physicians, pharmacists and other health-care specialists is expected to show a greater potential in improvement,

compared to medication safety and therapy management programs by a single profession alone. This assumption is supported by the German PRIMUM study [192], which was based on a Medication Management of general practitioners alone but failed to show a significant change in the MAI score, according to narrative information by the study's principal investigator Muth [192]. It is strongly believed that optimizing a patient's therapy as well as reducing a patient's medication risk can only be provided by a health care team consisting of different professions [193], albeit clear evidence for the benefits of interprofessional collaboration in a health care team is missing [30, 194].

1.4.1. ACCEPTANCE

Under most jurisdictions pharmacists are not permitted to prescribe new drugs to patients. Great Britain and most provinces in Canada implemented changes to these restrictions during the last decade and granted prescription rights to pharmacists in certain settings [195, 196]. In most other countries pharmacists need a close collaboration with physicians to implement the findings from a Medication Management. German pharmacists can perform patient counselling to cope with DRPs regarding adherence and handling, but any changes on starting, stopping or adjusting the dosage of a prescription drug needs to be approved by a physician to be implemented. Interprofessional collaboration is the bottleneck in Medication Management. Recommendations on therapeutic changes can only reach the patient if the physician accepts the intervention. Thus, for a meaningful Medication Management, a good communication between the health care providers is essential. A few studies have assessed the physician's acceptance of pharmaceutical

suggestions following a Medication Management. Chau et al. obtained an implementation rate of 46.2% of interprofessional recommendations in a recent study, undertaken in a community setting in the Netherlands [197]. In nursing home or hospital settings a higher implementation rate of 75.6% and 90.0%, respectively, could be reached [27, 198]. The interprofessional acceptance might be influenced by the health care system and the historical orientation of the professions. Potential professional barriers and obstacles can affect the collaboration between physicians and pharmacists in Germany as well as in any other country.

2. AIM AND OBJECTIVES

As Medication Management is emerging as a future core activity of pharmacists, specific national data is required to demonstrate its potential benefits. Medication Management is based on enhanced clinical skills of the pharmacist. Currently, national data for Germany is scarce. A future implementation into standard care should be based on evidence. All research should serve the patient and meet the society`s requirements.

The aim of this investigation was to evaluate an interprofessional collaborative Medication Management in Germany. The following objectives were defined:

- to show the influence of Medication Management on the quality of drug therapy and the number of DRPs
- to develop an approach for evidence-based patient selection for Medication Management
- to assess the results of Medication Reconciliation regarding patient safety
- to examine the acceptance of the pharmaceutical interventions by the general practitioners

The results should allow an appraisal of the effects of a Medication Management in outpatient care, provide information on the extent of interprofessional collaboration and give a first impression on patient benefit. Criteria for an evidence-based patient selection might help to make Medication Management more effective. The outcomes of these analyses might permit to focus a Medication Management to meaningful

aspects and provide data to support an implementation into German health care and reimbursement systems. Data on Medication Reconciliation could provide an impression, whether the physician is missing relevant information and whether it can be provided through an interprofessional Medication Management.

3. METHODS

All analyses in this work are based on data of the “WESTphalian study on a medication therapy management and home care-based intervention under Gender specific aspects in Elderly Multimorbid patients” (WestGEM study [199]. The study was registered at the ISRCTN registry ISRCTN41595373/ DOI 10.1186 and funded by the European Union and the state of North Rhine-Westphalia by the “European Regional Development Fund” program (project number: GW 2076). The funders had no influence in study design, data collection and analysis, decision to publish, or preparation of publications. Written informed consent was obtained from all individual participants included in the study (Appendix 1). The written statement was obtained from the patient by the general practitioner. One copy was archived by the general practitioner, one copy was handed to the patient. Clinical research associates confirmed obtainment of the written informed consent during clinical on-site monitoring. Included patients carried a participation pass throughout the study (Appendix 2). The study protocol was approved by the responsible local Ethics Committee in the Westphalia-Lippe region (approval number AKZ-2013-292-f-s). The study was conducted according to the principles of the Declaration of Helsinki [200]. The development of the intervention was based on the Medical Research Council guideline for the development and evaluation of randomized controlled trials [201]. It was piloted with seven general practitioners, two pharmacists and two home-care specialists.

3.1. STUDY DESIGN

3.1.1. STUDY SETTING

The study was conducted in an outpatient primary care setting in two model regions in North Rhine-Westphalia, Germany. Both regions had a different network structure. Outpatient health care in region A was organized as a network including general practitioners (n ≈ 15) and specialists (n ≈ 18). Outpatient health care in region B did not present in any network structures (number of general practitioners ≈ 55). 7 GPs of region A and 5 general practitioners of region B participated as study physicians. Home-care specialists in region A were social workers engaged by the county of Steinfurt. Home-care specialists in region B were social workers of the “Verein Alter und Soziales e.V.”, which is in charge of home care counselling in the county of Warendorf. The team of study pharmacists comprised of a team leader and clinical experts, who were experienced in pharmacotherapy and Medication Management. The group collaborated and communicated via webinars, telephone and e-mail. Each SOAP form (professional, see Appendix 5) was controlled by a second reviewer and the team leader, before it was handed to the physician. The documentation of the WestGEM study was based barely on data of the general practitioner to be comparable to the control phase and to assess the implemented effects and not just the pharmacists’ impressions. The setting and the workflow are shown in fig.1.

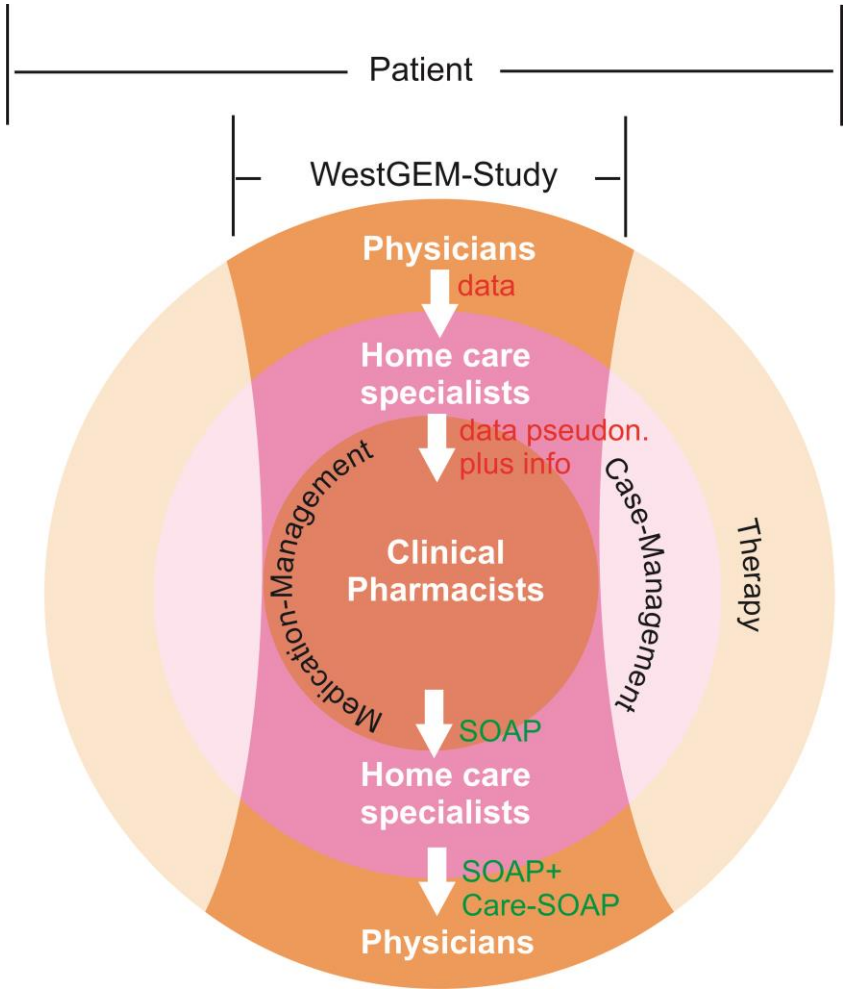


Fig. 1: Setting and workflow

A consensus between all health care providers was likely to support the therapy. Existing barriers between the professions needed to be identified and solutions to overcome these obstacles should be implemented [202–204]. The elaborations therefore had a strong focus on collaboration and interprofessional cooperation. The three health care professions physicians, pharmacists and home care specialists worked closely together. The interprofessional approach combined case management routines of home care specialists with information gained during the interprofessional Medication Management by the specialized study pharmacists. In

the WestGEM study the home care specialists provided their insights to the pharmacists. Pharmacists performed the Medication Reconciliation and Medication Management with a strong focus on medication safety and pharmacotherapy. The general practitioners could outweigh the suggestions and choose the best approach for the patient.

3.1.2. INCLUSION AND EXCLUSION CRITERIA

The study included elderly multimorbid outpatients with polymedication. Inclusion criteria of the WestGEM study were an age of 65 years or older, at least 3 chronic diseases in 2 organ systems with at least one being a cardiovascular disease and at least one being present for 9 months or longer, use of 5 or more systemic drugs, given formal consent on participation in the study and a history of at least one visit to the general practitioner during each the past 3 quarters. Exclusion criteria were an insufficient ability to speak or read German, participation in other studies and the existence of severe illnesses probably lethal within 12 months, according to the general practitioner’s estimation.

3.1.3. INTERVENTION

All patients received standard care at baseline and during the control phase. On the intervention group, pharmacists performed a PCNE type-3 comprehensive Medication Review [38]. Pharmacists received the patient data of the general practitioner in a case report form (CRF). The home care specialists, who visited the

patients at home, pseudonymized all patient data. At this encounter a brown bag review was performed as well as an intense patient interview, covering all the questions a pharmacist would ask the patient. The home care specialists followed a concise query developed in cooperation with the pharmacists (Appendix 4) and evaluated the demand of the patient for home care devices or products, social and financial support and identified tripping hazards and potential risks. The pharmacists transferred all provided data to a calculation sheet for statistical purposes and developed a message form to the general practitioner based on a SOAP note form (Appendix 5). In a first attempt, the data on drug therapy of the brown bag review was compared to the medication plan of the general practitioner (Medication Reconciliation). Deviations were registered and possible explanations were assumed and added. Based on the CRF-reported diagnoses, the laboratory data and the chief complaints, individual therapeutic goals were generated and the estimated glomerular filtration rate (eGFR) at baseline was calculated using the Cockroft Gault equation [160]:

$$eGFR_{Cockcroft} = \frac{(140\text{-age}) \times \text{mass (kg)} \; [\times 0.85 \text{ if female}]}{72 \times \text{serum creatinine (mg/dl)}}$$

For patients with a BMI of ≥ 30 kg/m², body weight was corrected and the lean body mass was used as described in chapter 1.3.3. [167].

The pharmacotherapy was assessed on:

- concordance between the prescribed and the taken medicines
- guideline concordance

- patient goals
- drug-drug interactions
- difficulties in handling the drugs
- intake and drug-food interactions
- duration of therapy
- therapeutic monitoring
- geriatric use
- indications without a drug
- drugs without an indication
- therapeutic doublets
- toxicity/dose
- adverse drug events
- potentially inappropriate medication according to the PRISCUS list [205]
- costs

Depending on the patient`s individual situation, further problems were assessed. The patient goals from the assessments were taken into account and were regarded with high priority in the Medication Review. Pharmacists discussed possible interventions in the assessment part of the SOAP note and generated a new medication plan. Suggestions for monitoring parameters and patient counseling were made. An

estimation on the patient`s individual falling risk was provided to the home care specialists, who used this information for their own intervention (prevention, recommendation of daily living aids, etc.).

3.1.4. MEDICATION RECONCILIATION

Medication Reconciliation leads to disclosure of otherwise unknown medication of the patient to all health care providers [206]. In this elaboration, the patient was assessed twice and a brown bag review was performed at each encounter. Drugs that were found but were not documented by the general practitioner were investigated further. Each drug that was not on the medication plan of the general practitioner was listed in a table. To get a deeper impression on the relevance of the drugs that were not documented, they were categorized under risk and indication aspects. In a first step it was rated whether the drugs were believed to be relevant to the general practitioner or less important. Relevance was given if drugs needed clinical monitoring or caused considerable effects on organ systems. Drugs were categorized less relevant if they had a limited systemic effect or seemed to be used only in acute situations (i.e. eye drops, topical or cold-relief medication). Sedative drugs were identified using pharmaceutical expertise. Potential inadequate medication for the elderly was identified by the PRISCUS list. Furthermore, all drugs were classified as carrying a high risk for hospitalization if they were related to the following groups: anticoagulation, cardiac glycosides, cytostatics, diuretics, antidiabetics with risk of hypoglycemia, salicylates or disease-modifying antirheumatic drugs (DMARDs). These categories were chosen according to previous studies [207, 208]. High-cost

drugs were defined by German law as a price of >1200 € per package [209]. All drugs were further screened for a relation to cardiovascular, pain-related, psychoactive, gastrointestinal or pneumologic medication (indication clusters). Drugs that were not documented by the prescriber were documented, to get an impression on the importance of the collaborative aspects in Medication Management. Drugs were not evaluated on the patient level, all data for this assessment was obtained only from the documentation of the general practitioner. Research on Medication Reconciliation was qualitative and descriptive. Cases of not documented drugs were counted, percentages were calculated.

3.1.5. PRIMARY ENDPOINT

One of the main objectives of the WestGEM study was to determine whether the complex intervention could change the quality of the medication. Therefore, the Medication Appropriateness Index (MAI) was chosen as the primary endpoint. It was measured at baseline (t_0/t_1, CRF 1&2), 3 months (t_2, CRF 3), 6 months (t_3, CRF 4), 9 months (t_4, CRF 5), 12 months (t_5, CRF 6) and 15 months (t_6, CRF 7) was compared by rating the 10 items indication, effectiveness, dose, correct directions, practical directions, drug-drug interactions, drug-disease interactions, duplication, duration, and costs.

The ratings resulted in a weighted score that served as a summary measure of prescribing appropriateness [48, 61, 62, 64, 210]. For each drug the 10 items were rated as appropriate, marginally appropriate or inappropriate. The item was rated with zero points for appropriate and marginally appropriate. Inappropriate items were

weighted with 1-3 points according to Samsa et al. (table 4) [64]. A maximum score of 18 could be achieved per drug. The score of each drug was summated as the patients individual MAI score.

Tab. 4: Weighting of inappropriate ratings per MAI item according to Samsa et al. [64]

item#	item criterion	weighted score
1	Is there an indication for the drug?	3
2	Is the medication effective for the condition?	3
3	Is the dosage correct?	2
4	Are the directions correct?	2
5	Are there clinically significant drug-drug interactions?	2
6	Are there clinically significant drug-disease interactions?	2
7	Are the directions practical?	1
8	Is this drug the least expensive alternative compared with others of equal utility?	1
9	Is there unnecessary duplication with other drugs?	1
10	Is the duration of the therapy acceptable?	1

For the study it was hypothesized that the pharmacists' intervention would improve the quality of medication by lowering the MAI score, as well as reducing DRPs. The choice for the MAI as the primary endpoint was done in consideration of a Cochrane review by Patterson et al., describing which interventions are effective in improving the appropriate use of polymedication, reducing drug-related problems in older people and avoiding hospital admissions [65]. The review reports that the majority of

the included high-quality studies (seven out of eleven) used the MAI as the primary endpoint.

3.1.6. SECONDARY ENDPOINTS

Additional information regarding the quality of drug therapy is obtained from assessment instruments used by the study pharmacists within their Medication Management:

- the number of DRPs, classified according to PCNE version 6.2
- the prevalence of inadequate medication, detected by the PRISCUS-list [205]

As discussed above the PCNE classification of DRPs was evaluated extensively and is frequently used in pharmaceutical care studies [77]. The PRISCUS list summarizes potentially inadequate medication (PIM) in the elderly and covers the drugs currently available in Germany [205]. It is well established in primary care medicine.

3.1.7. TIMELINE AND WORKFLOW

The WestGEM study was designed as a cluster-randomized controlled trial, incorporating qualitative analysis [199]. Qualitative analysis was performed during intervention development and piloting. Furthermore, qualitative methods were applied to perform a process evaluation of the randomized trial and to assess the acceptance of the interprofessional Medication Management approach. The study design was developed in line with the CONSORT statement extension to cluster RCT [211]. The

cluster design was chosen to avoid spillover effects among patients of a certain practice. The study protocol followed a stepped-wedge design (see 3.1.8.). All patients treated by one general practitioner switched from the control to the intervention group at the same time. Patients' recruiting process, randomization routines and the applied documentation forms and data collection procedures were reappraised by a study nurse.

All practices were initially assigned to the control group. After a 6-month observation period, general practitioners randomly entered one of the three clusters. Each cluster consisted of 4 practices. The interprofessional Medication Management approach was implemented sequentially in each cluster with a lag time of 3 months. During the Medication Management process, the general practitioners provided patient-specific data to the home-care specialists. The home-care specialists visited the patients and performed several patient interviews and assessments, including a brown bag review and a specifically developed standardized pharmaceutical questionnaire. They provided the pseudonymized results to the pharmacists. The pharmacists performed a comprehensive Medication Review (PCNE type-3) including Medication Reconciliation and supplied it to the home-care specialists, who allocated the Medication Review to the patient and handed it to the general practitioner. This procedure was repeated after 6 months. Each patient stayed in the intervention phase for 12 months. All primary and secondary endpoints were assessed at baseline and 6 months retrospectively as well as 3 months, 6 months, 9 months, 12 months and 15 months post baseline (fig.2).

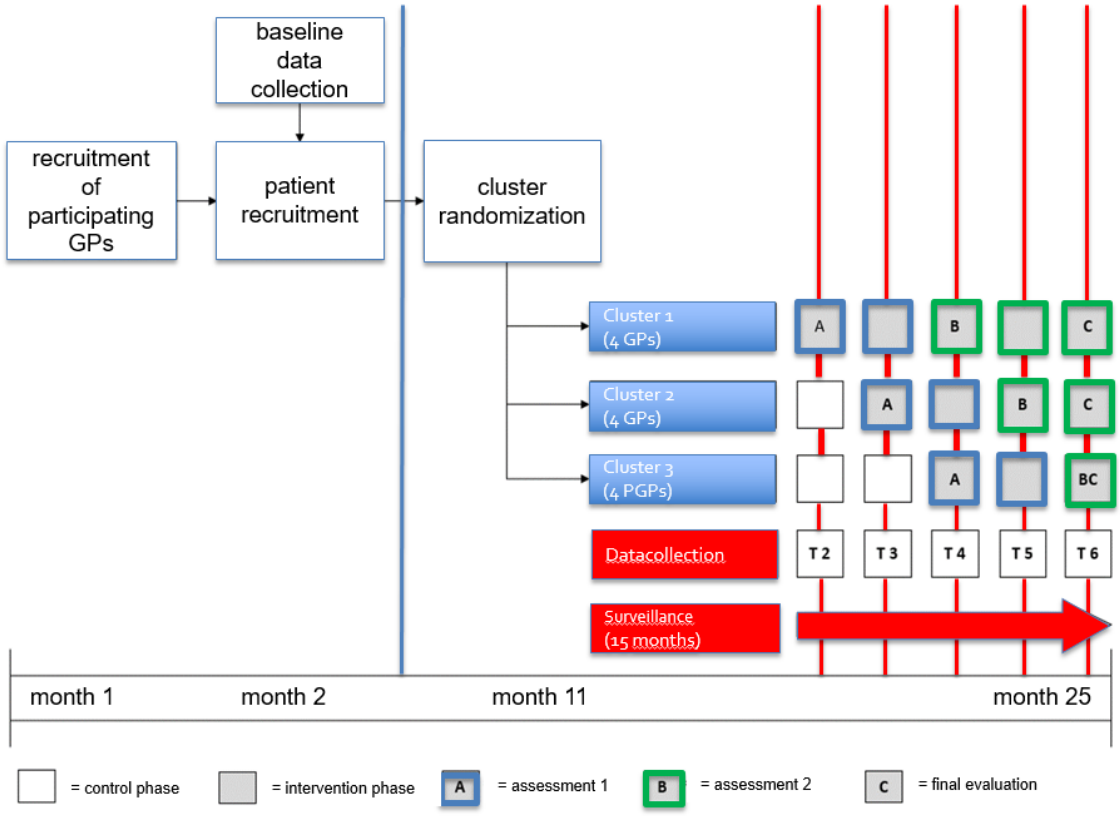


Fig. 2: Study timeline

Patients recruited by the general practitioners received standard treatment during the control phase. Patient information was documented in a Case Report Form (CRF) (Appendix 3) by the general practitioner. The general practitioner's documentation was chosen as the only source for all data to ensure a proper comparison with the control phase. This approach was done even if there were obvious discrepancies between the general practitioner`s and the home-care specialist`s documentation. The feasibility and acceptance of the workflow was tested in a pilot phase.

3.1.8. STEPPED WEDGE DESIGN AND SAMPLE SIZE CALCULATION

A stepped wedge design was chosen for this cluster-randomized control trial. The stepped wedge design can be described as a modified cross-over design and has certain advantages and disadvantages [212]. A clear advantage is that every patient and every general practitioner enters the intervention phase sooner or later. The total number of patients is reduced as every patient serves as member of the control and intervention group. A disadvantage is the limited flexibility of the intervention in time. Delays in provision of the patient assessment or the performance of the Medication Review might lead to biased results. The sample size calculation for the stepped wedge design was based on Woertman et al. [213]. As there were no comparable studies investigating the effect of collaborative Medication Management, an effect size of Cohen's d=0.25 was considered as clinically and socially relevant. Based on this assumption and using a two-tailed t-test with a statistical power of 80% and a significance level (α) of 0.05 a total unadjusted sample size of 502 was calculated. An assumption of 20 patients per practice and little correlation between the clusters (ICC = 0.05) led to a design factor of 0.383 in the present stepped wedge model. Adjusting the sample size with the design factor and considering a maximum drop-out rate of 20% the final sample size was calculated to be 240.

3.1.9. RANDOMIZATION AND PATIENT RECRUITEMENT

Participating practices were randomly allocated to one of the three study arms. A biometrician, not involved in the field work, randomly selected the practices. To avoid

changes in physician's prescription behavior, random lists remained concealed until each allocation date. The participating general practitioners carried out the recruitment of the patients. To avoid selection bias, patient's inclusion comprised of two steps. At first general practitioners systematically identified patients who were generally eligible for study inclusion by screening all patients for the defined in- and exclusion criteria. Potential study patients were listed in alphabetic order and were numbered consecutively (basic population). General practitioners then entered gender, age, and conditions in that list. In a second step, physicians forwarded a pseudonymous version of the recruitment list to the biometricians of the Institute of Medical Statistics, Informatics and Epidemiology (IMSIE, University of Cologne), who determined a random sample of 40 patients. The potential participants were informed about the study subsequently at routine-care appointments and asked to join the study, until a total of 20 patients per practice were listed. After giving informed consent, baseline documentations forms and questionnaires were completed. For every patient of the sample list who declined participation, a new patient was drawn from the basic population.

3.1.10. DATA COLLECTION

The WestGEM study was conducted from July 2012 till June 2015. The intervention phase started at January 1st, 2014. Patients were evaluated at baseline (t_0/t_1, CRF1/2), 3 months post-baseline (t_2, CRF3), 6 months post baseline (t_3, CRF4), 9 months post-baseline (t_4, CRF5), 12 months post-baseline (t_5, CRF6) and 15 months post-baseline (t_6, CRF7). Baseline documentation included a retrospective

assessment period over six months. Provided patient data was based on the general practitioner's patient record and on the generated information of the home-care specialists. The general practitioner's record included the anamnesis, laboratory data, medication and specific assessments done for the study, like the mini–mental state examination (MMSE) on cognitive state [214] and the Tinetti-test on mobilty [215]. Diagnoses were classified according to the International Statistical Classification of Diseases and Related Health Problems, version 10, German modification (ICD-10-GM) of the WHO [216].

The home-care specialists performed a brown bag review at the patients' home including name and registration number (Pharmazentralnummer) of the taken medicine, the origin of the prescription (general practitioner, specialist or in case of non-prescription drugs the pharmacist), the taken dose according to the patient, the dosage form, chronic or as needed use, whether the drug was taken with food or fasting and the indication stated by the patient. Home-care specialists conducted a patient interview, with 34 defined pharmaceutically relevant domains, like the Morisky-questions on adherence [217] or a visual analog scale (VAS) pain assessment [218] and did their own home-care assessment as well (Appendix 4). During the study the pharmacists gathered the data 7 times regarding the general practitioners' assessments and 2 times regarding the home-care specialists' information and transferred all data into a calculation sheet. Checklists of DRPs, drug-drug interactions, MAI and MRCI were added to the pharmaceutical workup. In these elaborations, an interaction was rated as clinical relevant if further action, like a proposed intervention, seemed to be necessary. Only severe and relevant

interactions were reported to the general practitioner and suggestions on a potential solution were provided along with each interaction.

3.1.11. QUALITY ASSURANCE

To ensure data quality and to reduce missing data or processes which are not adherent with the study protocol, clinical research associates visited the general practitioners for clinical monitoring. Furthermore, several routines were established to prevent or detect incorrect as well as inconsistent data entry and incomplete data. In case of missing documentation, the general practitioners were asked to complete the information subsequently. The data of the home-care specialists was consecutively compared with the pharmacists' data and thoroughly provided.

3.1.12. ETHICAL ASPECTS

The study protocol and all study forms were approved by the ethics committee of the Medical Association of Westphalia-Lippe (Aerztekammer Westfalen-Lippe), approval number AKZ-2013-292-f-s and conducted to the principles of the World Medical Association (WMA) Declaration of Helsinki. Written informed consent was obtained from all individual participants included in the study by the general practitioner. One copy was archived by the general practitioner; one copy was handed to the patient. Clinical research associates proved obtainment of the written informed consent statement during clinical on-site monitoring. The ethics committee of the Medical

Association of Westphalia-Lippe has approved this procedure. The study was registered at the ISRCTN registry.

3.2. STATISTICAL METHODS

For descriptive statistics, patient characteristics were described using mean ± standard deviation (SD) or count (percentages). Corresponding p-values are from Fisher's exact test (qualitative data) or Kruskal-Wallis test (quantitative data), respectively. The confirmatory calculations of the primary and secondary endpoints were based on the intention-to-treat (ITT) population (initial treatment assignment). A Mixed Model with a significance level of 5% was created with the summated MAI score per patient as the dependent variable.

The analysis on patients with a major benefit from the Medication Management was based on logistic regression. In a first step the association between possible predictor variables and a greater benefit status was analyzed using univariate logistic regression models. Variables with similar content were selected by taking the variable with lowest p-value in univariate logistic regression for further analysis into account. The univariate regression was done to assort the variables. In a second step a multiple logistic regression model with stepwise backward selection (likelihood ratio test, p-value for inclusion 0.05, p-value for exclusion 0.1) was performed. Additionally, possible cut-off values for quantitative variables were computed with Receiver Operating Characteristics (ROC). For logistic regression models Odds Ratios (OR) with corresponding 95% confidence interval (CI) and p-values were

computed. For ROC-curves area under the curve (AUC) and corresponding 95% CIs are presented. All reported p-values are two-sided and considered statistically significant if lower or equal than 0.05. Calculations were performed using SPSS Statistics 22 (IBM Corp., Amnok, NY, USA) and STATA 14 (StataCorp., College Station, Texas, USA).

3.2.1. EFFECT OF THE INTERVENTION ON MAI SCORE AND DRP

Confirmatory analysis on changes in the MAI score and the number of DRPs were based on the intention-to-treat (ITT) population. A Mixed Model with a significance level of 5% was created, containing the summated MAI score per patient at documentation date two to seven (T1-T6) as the depending variable. The MAI baseline score, the documentation dates and the treatment status (intervention or control group) were regarded as fixed factors and the cluster as random factor. To detect the mere effect of the intervention, measured as the patient switch from the control phase to the intervention phase and from the intervention phase with the first assessment to the intervention phase with the second assessment, only the point in time in the Mixed Model was regarded, to which a score was retrieved in the comparable phase. The Mixed Model hence was expanded by so called contrasts [219], adding a time effect. The MAI score was compared at:

- contrast 1 for the comparison of the control phase to intervention phase 1, resembling the principal switch into the intervention phase by the first assessment at documentation 4 and 5,

- contrast 2 for the comparison of intervention phase1 with intervention phase 2, resembling the transition to the second assessment.

The DRP analysis was performed in a similar way.

3.2.2. EFFECTS OF THE INTERVENTION ON LDL-CHOLESTEROL CONCENTRATIONS

In this study LDL-cholesterol levels were obtained by the physician according to standard practice. LDL-cholesterol was measured indirectly by the collaborating laboratories using the Friedewald equation [220]:

LDL-cholesterol = Total-cholesterol (TC) – HDL-cholesterol – Triglycerides (TG)/5 (mg/dL)

It is unknown whether the contract laboratories of the general practitioners used corrections of the Friedewald equation, which might not be accurate with increasing Triglyceride levels >150 mg/dl [221].

For the evaluation of changes in LDL-cholesterol under controlled conditions in the stepped wedge design, laboratory data at several points in time were necessary. The laboratory data of the WestGEM study on LDL-cholesterol did not support a controlled approach as the general practitioners had drawn laboratory data under routine care only at inconsistent times of the study. Some general practitioners did not even test for LDL-cholesterol at all. During the study, general practitioners were free to order laboratory data and could handle the patients unchanged from daily practice. LDL-cholesterol levels hence were only provided according to the practice

of the general practitioner. LDL-cholesterol reduction was initially tested in a comparison of the levels at study entry (T0) and of the levels after the intervention (T3-T7). In case more than one level was available, the latest one was used. The patient's LDL-cholesterol levels were summated and were tested for significance with a t-Test. In a second step, all patient data of each assessment (T0-T7) was analyzed in a Mixed Model. In case of missing data, the last obtainable level was carried forward, the so called Last Observation Carried Forward (LOCF) approach, missing LDL-cholesterol levels were filled with the previous level to have more consistent data [222]. In contrast to the before-after method, the Mixed Model considered the control and the intervention phase. In addition, the number of patients at target (<70 mg/dl) was counted before and after the intervention.

3.2.3. PATIENT SELECTION

To analyze whether certain patient groups had a major benefit from the medication review and hence might be prioritized in a future setting, several patient parameters were tested and suitable indicators were searched for. For statistical purpose a MAI cut-off, defining a major benefit from a Medication Review needed to be defined. The cut-off must not derive from the study data. Unfortunately, the achievable reduction of the MAI score is very much depending on the setting. To avoid a mere arbitrary MAI score cut-off number to define a major benefit, a Cochrane Review by Patterson et al. was regarded as a benchmark [65]. Patterson et al. identified 5 studies on Medication Management as being of better quality. The mean reduction in the MAI score in these studies was 3.88 points. As the included studies carry a high relevance and came to

significant results, patients of the study with a reduction of ≥3.88 points in the MAI score were defined as having a major benefit from the intervention.

In a first approach, explicit baseline characteristics that could be obtained early in the medication review process at the time of data collection and the initial patient interview were analyzed. These parameters were gender, age, eGFR, number of drugs in use at baseline, number of differences between the prescribed and used drugs, Cumulative Illness Rating Scale (CIRS-G) severity index [223, 224], number of diagnoses, number of responsible health care providers (specialists and hospitals) and the number of visits to the general practitioner. Results here could lead to a fast selection of eligible patients by the pharmacist or health care professional.

In a second approach, the implicit parameters baseline MAI score and the length of the Medication Management (length of the intervention) was tested along with gender, age, eGFR and the number of drugs at baseline as prediction factors. Data on the MAI score and the longitudinal service was generated later in the pharmaceutical work up during a medication review. The influence of these parameters on receiving a greater benefit status was analyzed in a multiple logistic regression model with backward selection (LR method) and the Odds Ratio was calculated. Possible cut-off values for quantitative parameters were computed with Receiver Operating Characteristics (ROC). The influence of these factors on developing a higher benefit status was analyzed in a multiple logistic regression model.

3.2.4. ACCEPTANCE ANALYSIS

The acceptance of the pharmaceutical recommendations in the Medication Management was analyzed based on the general practitioners appraisal on the feedback form, which included a table enabling the general practitioner to respond to every single recommendation made by the pharmacists. General practitioners could rate their acceptance in 3 categories of approval: partial/complete, no action/refusal or further information requested. In this analysis, forms without any feedback and requests for further information were excluded. The feedback was subsequently allocated to one of the three domains of stopping an existing drug, starting a new drug or changing an existing drug's dose. To identify covariates of the prescriber's acceptance of the recommendations, an ordinary least squares (OLS) regression with the approval rate as the dependent variable was conducted. In a first approach, univariate analyses were performed and then all influential factors were considered within one model. The standard error was clustered at the practice level to adjust for correlations within physicians. The analyzed influential factors were: demography, nutrition, morbidity, drug therapy, intensity of physician-patient relationship, patient-reported health, family support, cognitive impairment, mobility, patient's daily functioning, adherence and duration of the interprofessional collaboration.

To find out whether certain influential factors might lead to a higher or lower frequency in the physician's acceptance of a suggested intervention, 3 categories of starting a drug, stopping a drug or changing a drug`s dose were tested versus the patient's age, gender, education level, Body Mass Index (BMI), morbidity (CIRS-G), number of prescribed drugs, number of drug-related events, number of patient-

reported adverse events, number of potentially inadequate medications (PIM), number of patient visits to the general practitioner per quarter (3 months), patient-reported health (Visual Analog Scale, VAS), social support (Questionnaire Social Support, short form 14 Items / Fragebogen soziale Unterstützung, Kurzform 14 Items, FSozu14), cognitive impairment (MMSE), mobility (Tinetti test), daily functioning (activities of daily living, ADL and instrumental activities of daily living iADL), and adherence (Morisky score) in a multivariate ordinary least squares (OLS) regression.

4. RESULTS

4.1. STUDY POPULATION AND PATIENT BASELINES

In the area of the city of Steinfurt 92 patients out of 7 general practitioner practices were included, in the area of the city of Ahlen 73 patients from 5 practices. 33 patients could not finish the study and dropped out. Of these 33 patients, 7 patients died, 1 patient changed the general practitioner, 6 patients finished participation of the study due to moving to a nursing home, 17 for various reasons like worsening disease state, dementia or simply because of excessive involvement into the study (“annoying interviews”), in two cases the general practitioner stopped the participation of the patient in the study as the patients felt uncomfortable with the interviews. Data was sufficient for 142 patients, who comprised the ITT population for the MAI analysis. The most frequent diagnoses were related to the metabolic syndrome with hypertension, dyslipidemia, type 2 diabetes mellitus being among the most documented diseases (table 5).

Tab. 5: Pattern of diagnoses in the ITT population (N=142)

	Disease (ICD-10 Code)	Pat. (%)
1	Hypertension (I10)	109 (76.8)
2	Dyslipidemia (E78)	77 (54.2)
3	CHD (coronary heart disease) (I25)	57 (40.1)
4	Diabetes mellitus Type 2 (E11)	50 (35.2)
5	AFIB (atrial fibrillation) (I48)	29 (20.4)

Further patient characteristics are shown in table 6 separately for the ITT-population, the patients included in the LDL-cholesterol analysis and the patients included in the acceptance analysis. The baseline values of the 3 clusters are very similar.

Tab. 6: Further patient characteristics of the ITT-population and of the eligible patients for the LDL-cholesterol and acceptance analysis

Parameter	ITT population *n = 142*		LDL-C analysis *n = 92*		Acceptance analysis *n = 103*	
	Mean; N	SD; %	Mean; N	SD; %	Mean; N	SD; %
Age	76.7	6.3	76.2	6.0	77.0	620
Gender (% female)	76	53.5 %	45	49%	68	54.5%
Body Mass Index	28.4	4.3	28.6	3.8	28.4	4.3
Morbidity (CIRS-G)	1.6	0.4	1.6	0.4	1.6	0.4
No. of diagnoses	12.7	5.7	12.5	5.9	12.3	5.1
No. of prescribed drugs	9.4	3.1	9.9	3.3	9.5	3.3
No. of DRPs	7.3	3.4	7.3	3.2	7.3	3.5

The available data allowed an inclusion of 142 patients for the analysis of changes in the MAI, 92 patients for the LDL-cholesterol analysis and 103 patients for the acceptance analysis.

4.2. MEDICATION APPROPRIATENESS INDEX

The MAI score was defined as primary endpoint. Results for each of the 10 items of the MAI score are shown in table 7.

Tab. 7: Effect of the Medication Management on the MAI score per cluster and item

MAI item	Total				Cluster 1				Cluster 2				Cluster 3			
	T0 N=1261		T6 N=1283		T0 N=582		T6 N=585		T0 N=312		T6 N=311		T0 N=367		T6 N=387	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
1	197	16	96	8	87	15	30	5	61	20	34	11	49	13	32	8
2	261	21	131	10	102	18	39	7	88	28	45	15	71	19	47	12
3	353	28	203	16	133	23	63	11	124	40	70	23	96	26	70	18
4	358	28	201	16	138	24	61	10	117	38	71	23	103	28	69	18
5	322	26	154	12	132	23	42	7	99	32	57	18	91	25	55	14
6	251	20	170	13	118	20	74	13	71	23	45	15	62	17	51	13
7	87	7	52	4	32	6	18	3	33	11	17	6	22	6	17	4
8	82	7	43	3	40	7	20	3	29	9	13	4	13	4	10	3
9	218	17	114	9	84	14	28	5	77	25	43	14	57	16	43	11
10	118	9	86	7	46	8	32	6	39	13	27	9	33	9	27	7

N=Total summated MAI score and MAI score per item for all included patients,
%=Percentage of ratings per patient as not appropriate

As the intervention was done longitudinal over time and interprofessional action was required, the German definition of Medication Management was fulfilled. The Medication Review was repeated after 6 months, home-care specialists visited the patients two times at home and the patients had at least 7 documented visits to their general practitioners. Patients entered the study in 3 clusters with a lag time of 3 months between each. The MAI score was reduced (fig.3):

- for group 1 from a mean of 30.15 ± 24.14 at T0 to 14.09 ± 14,80 points at T6
- for group 2 from 43,28 ± 30,95 to 24,47 ± 16,17 points
- for group 3 from 26,07 ± 17,33 to 18,44 ± 14,67 points

Patients who had experienced the intervention at an earlier time and thus benefited from the Medication Management for a longer time had a more pronounced effect compared to those who entered the study later (fig.3). Overall, the difference in the MAI score between control phase and intervention phase was 4.27 points (95-%-CI: 2.36 – 6.18; $p < 0,001$) in the original study consideration. Hence a significant effect of the Medication Management in terms of a reduction of the MAI score was shown for the intervention-phase compared to the control-phase [225].

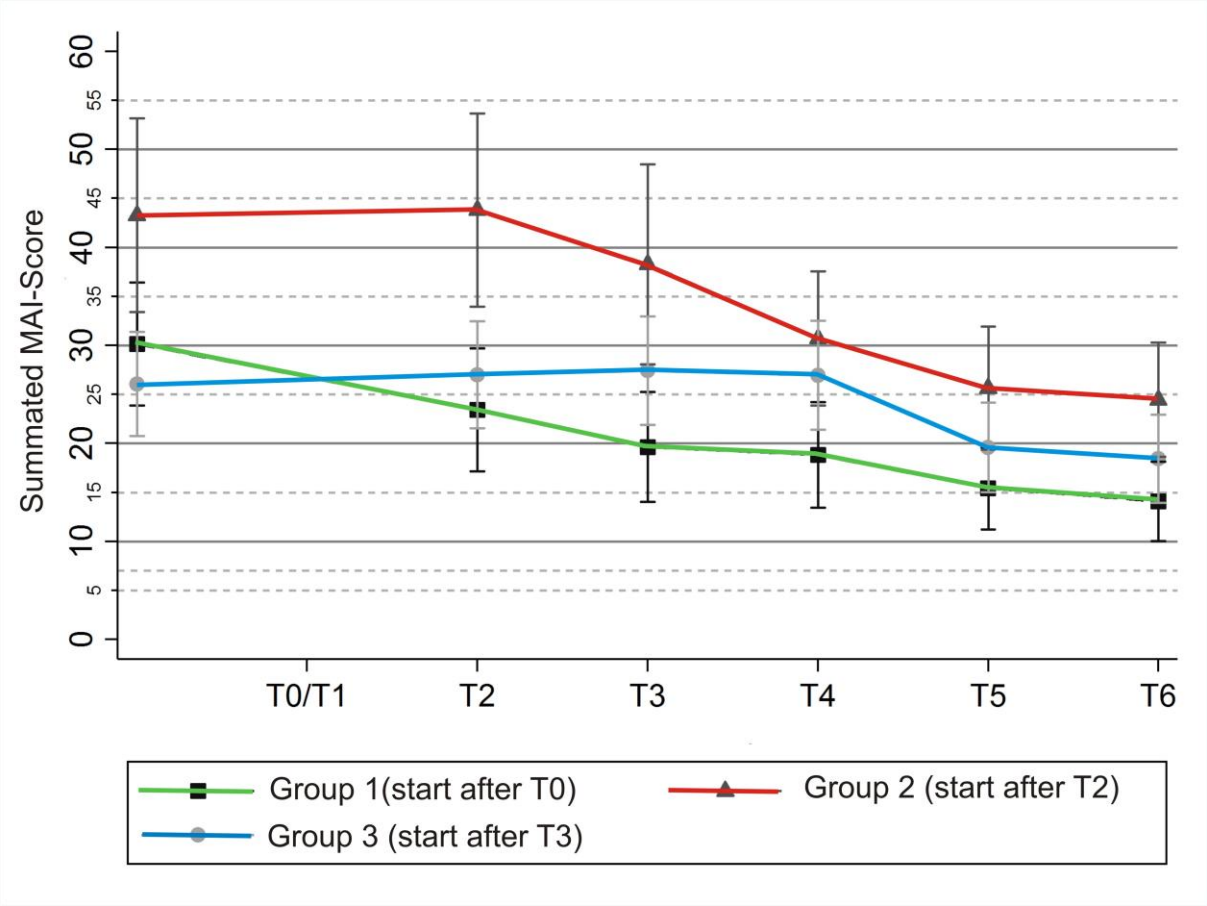


Fig. 3: Graphical presentation of the effect of Medication Management per cluster over time

4.3. DRUG-RELATED PROBLEMS AND POTENTIALLY INADEQUATE MEDICATION

A secondary endpoint of the WestGEM study was the reduction of DRPs. DRPs were classified according to PCNE version 6.2 and were another indicator of the quality of therapy and medication safety (as described in chapter 1.2.4.). A total of 1588 DRPs were detected in 142 patients (cluster 1: 688 DRPs, cluster 2: 425 DRPs; cluster 3: 475 DRPs). In the Mixed Model, a reduction of -0,45 DRPs could be shown in the intervention phase versus the control phase (p = 0,014). Comparable to the reduction

in the MAI score, the number of DRPs declined with a stronger effect over time. Reduction of DRPs again was more profound in cluster 1 with -2,63 DRPs compared to cluster 2 with -1,19 and cluster 3 with -1,02 (table 8).

Tab. 8: Effect of the Medication Management on the number of DRPs

Cluster	No. of GPs	No. of patients	Δ of DRPs*	p value
1	4	59	-2.63	<0.001
2	4	40	-1.19	0.009
3	4	43	-1.02	0.006

**Difference in no. of DRPs per patient at T_0-T_6*

DRPs were counted based on the documentation of the general practitioner, to be comparable to the control group. Hence, an initial increase of DRPs was expected with the general practitioner having more drugs on the list. In fig. 4 the increase of DRPs can be seen in cluster 2 and a slight increase in cluster 3.

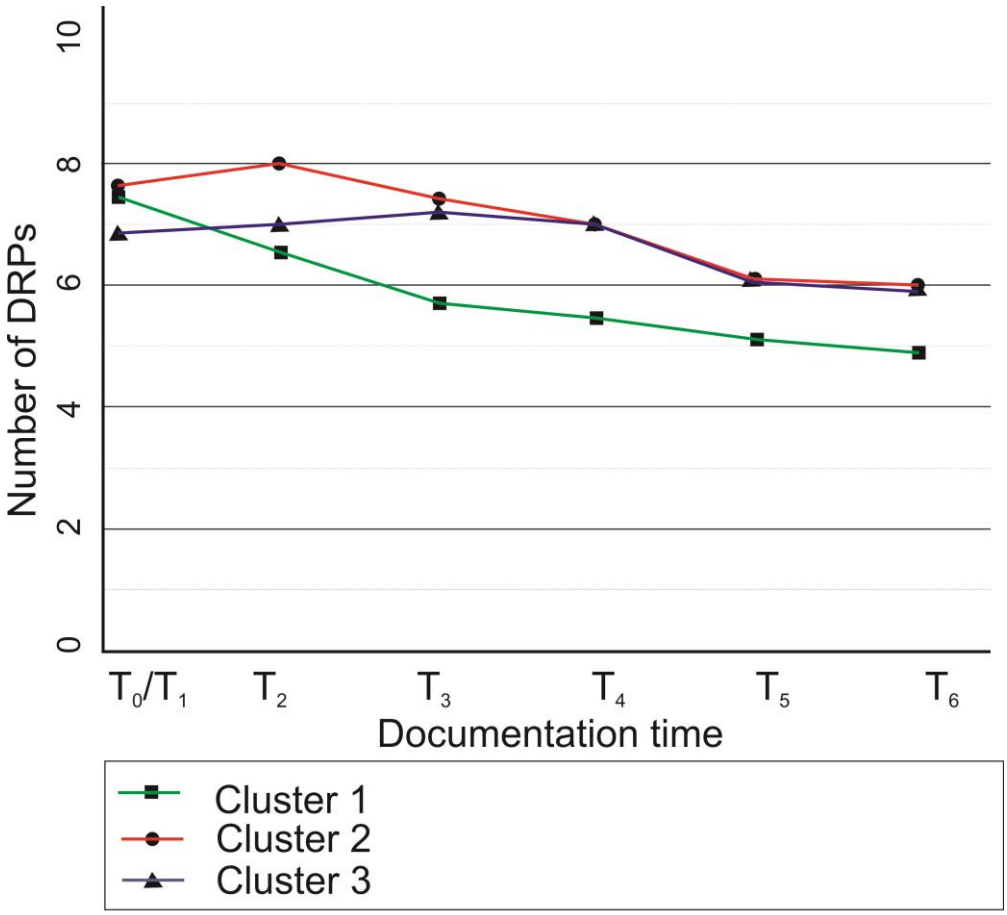


Fig. 4: Graphical presentation of the effect of Medication Management on the number of DRPs

In the same 142 patients the prevalence of inadequate medication, using the PRISCUS list was reduced from a total of 50 PIM drugs before (T_0) to 40 PIM drugs at the end of the study (T_6). The t-Test shows a p value of 0,347. The study revealed only a trend towards the reduction of PIM drugs but no significance.

4.4. LDL-CHOLESTEROL CONCENTRATIONS

The obtained data on LDL-cholesterol was fragmentary, as the general practitioners performed routine care during the study and drew LDL-cholesterol samples according to their own budgets and responsibilities. For a total of 92 patients LDL-cholesterol levels were available at baseline (before the study started) and at least once after the intervention. Individual patient data is shown in Appendix 9. Table 12 shows the characteristics of eligible patients for the analysis of LDL-cholesterol values. Even though only 92 of 142 patients were eligible for the test, the characteristics do not differ profoundly from the whole study cohort.

Tab. 12: Patient characteristics of eligible patients for the LDL-cholesterol analysis compared to the ITT population

Parameter	ITT population (SD,%)	LDL-C population (SD,%)
Age (years)	76.7 (6.3)	76.2 (6.0)
Gender (female) [N (%)]	76 (53.5)	45 (49.0)
BMI (kg/m²)	28.4 (4.3)	28.6 (3.8)
Morbidity (CIRS-G)	1.6 (0.4)	1.6 (0.4)
No. of diagnoses	12.7 (5.7)	12.5 (5.9)
No. of prescribed drugs	9.4 (3.1)	9.9 (3.3)
No. of DRPs	7.3 (3.4)	7.3 (3.2)

A stronger deviation can be found among the clusters, as shown in table 13.

Tab. 13: Patient characteristics of eligible patients for the LDL-cholesterol analysis per cluster

Variable (mean)	Cluster 1 N=51 (SD)	Cluster 2 N=10 (SD)	Cluster 3 N=31 (SD)	Total N=92 (SD)
Age (years)	75.7 (6.699)	79.4 (4.904)	76 (4.934)	76.2 (6.022)
BMI (kg/m^2)	28.9 (4.174)	29.6 (2.749)	27.8 (3.502)	28.6 (3.843)
Morbidity (CIRS-G)	1.8 (0.421)	1.6 (0.401)	1.4 (0.241)	1.6 (0.398)
No. of diagnoses*	12.2 (6.232)	11 (4.570)	13.4 (5.795)	12.5 (5.920)
No. of drugs*	10.3 (3.559)	10.4 (3.596)	8.9 (2.435)	9.9 (3.262)
No. of DRPs	7.3 (3.142)	8.2 (3.765)	7 (3.027)	7.3 (3.156)

**according to the GP's documentation. cluster 1: intervention after Jan.1st, 2014, cluster 2: intervention after April 1st, 2014, cluster 3: intervention after July 1st, 2014*

Fig. 6 presents clusterwise changes in mean LDL-cholesterol over time. The figure reveals that the LDL-cholesterol reduction happened between T3 and T4 in all 3 clusters, which is unexpected, as the intervention started with a lag-time of 3 months between the 3 clusters. LDL-cholesterol levels seemed to be rather depending on seasonal fluctuation than on the Medication Management. Each cluster shows lower mean LDL-cholesterol levels at the end of the study as compared with study entry.

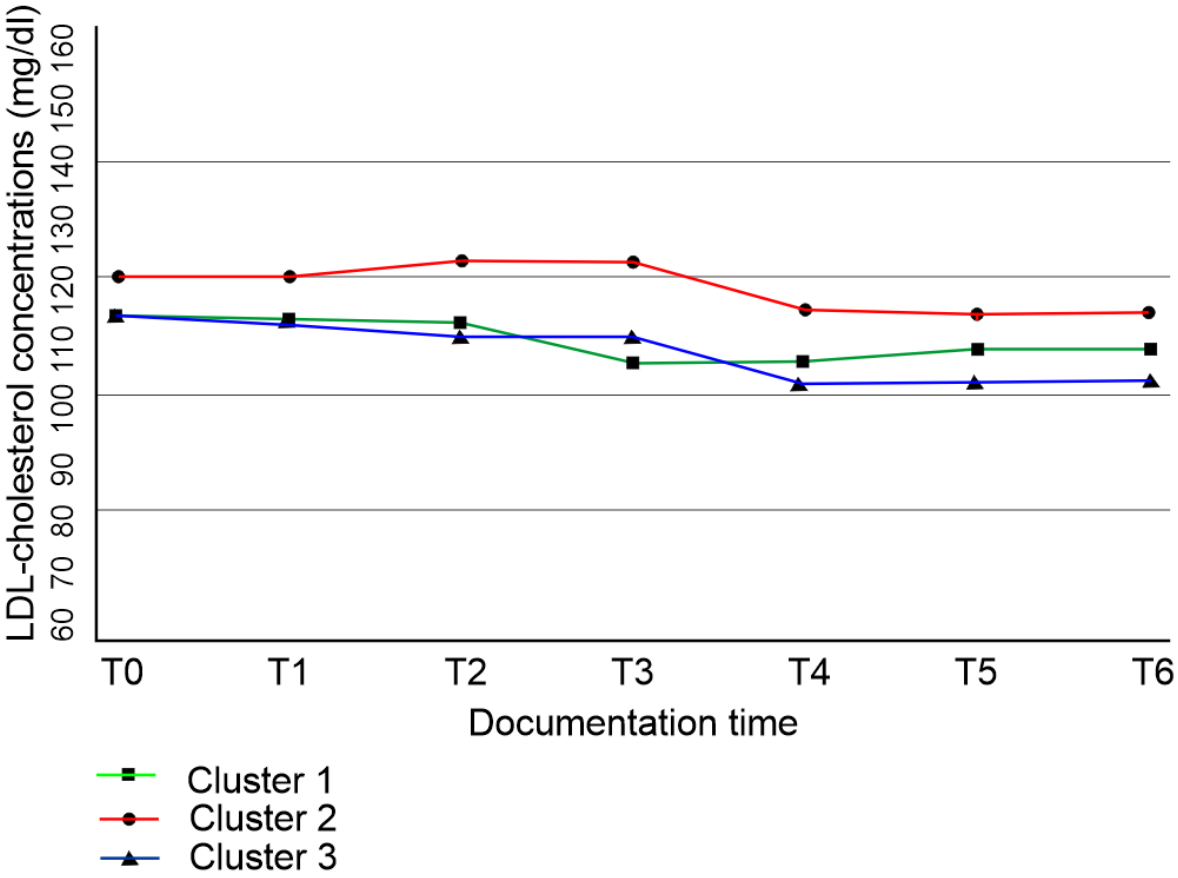


Fig. 6: Mean LDL-cholesterol concentrations (with LOCF) for the 3 clusters over time

Descriptive results demonstrate a decrease of LDL-cholesterol values. The paired t-test showed an overall significant LDL-cholesterol level reduction of -7.55 mg/dl (SD: 28.39) from 114.1 mg/dl (SD: 36.35) at T_1 (Baseline) to 106.5 mg/dl (SD: 35.8) at T_6 (after 15 months, with LOCF) ($p = 0.012$). The reduction in cluster 1 was 5.5 mg/dl (SD: 25.77), 5.8 mg/dl (SD: 25.28) in cluster 2 and 11.5 mg/dl (SD: 33.51) in cluster 3. Table 14 shows the mean LDL-cholesterol levels and the sample size during the study phase.

Tab. 14: Mean LDL-cholesterol reduction and sample size during the study phases (without LOCF)

Patient group	T1	T2	T3	T4	T5	T6	T7
LDL-C (mg/dl)	114.09	91.80	102.69	104.64	98.00	104.55	102.39
Patient N=	92	5	48	56	55	53	51

According to current guidelines, most study patients could be classified as cardiovascular high-risk patients and had a LDL-cholesterol goal of <70 mg/dl [226]. At T_1 only 5 of the 92 patients fell into the category of LDL-cholesterol <70 mg/dl whereas at T_6 a total of 10 patients showed LDL-cholesterol levels of <70 mg/dl (Appendix 9).

The Mixed Model calculations resulted in a greater reduction of LDL-cholesterol values for the intervention phase (-8.27 mg/dl, 95%-CI: -16.03 – -0.52) compared to the control phase (-4.81 mg/dl, 95%-CI: -14.1 – -4.5)). The mean difference between both groups in the Mixed Model was only -3.47 mg/dl and failed to reach statistical significance.

4.5. IDENTIFYING PATIENTS WITH A GREATER BENEFIT OF A MEDICATION MANAGEMENT

129 patients of the ITT population of the study met all criteria with a MAI score at the beginning (T_0) and at the end of the study (T_6) and were included in the analysis on patient selection criteria (table 10). 73 patients out of this group had a reduction in the MAI score of 3.88 or more and were considered as patients with a higher benefit

of a Medication Review, according to the chosen cut-off (as described in chapter 3.2.3.). The results of the final model are shown in table 10.

Tab. 10. Baseline characteristics of the studied patient group. Data is presented as mean ± SD unless otherwise indicated

Parameter		Total	Minor benefit	Major benefit	p value
Collective		129	56	73	
Female Gender (%)		69 (53.5%)	30 (53.6%)	39 (53.4%)	1.000
Length of the intervention	12 months[1] 9 months[2] 6 months[3]	54 (41.9%) 32 (24.8%) 43 (33.3%)	17 (30.4%) 13 (23.2%) 26 (46.4%)	37 (50.7%) 19 (26%) 17 (23.3%)	0.017
Age		76.4 ± 6.3	76.1 ± 6.4	76.7 ± 6.2	0.694
eGFR		55.6 ± 21.5	59.6 ± 21.3	52.6 ± 21.3	0.071
MAI*		31.3 ± 24.8	19.9 ± 16.0	40.0 ± 26.8	<0.001
Nr. of drugs		9.4 ± 3.2	8.1 ± 2.3	10.5 ± 3.4	<0.001
Nr. of discrepancies**		4.5 ± 3.5	3.3 ± 2.8	5.4 ± 3.7	0.001
CIRS-G severity index		1.6 ± 0.4	1.6 ± 0.4	1.7 ± 0.4	0.090
Nr. of diagnoses		13.1 ± 5.8	12.6 ± 5.1	13.5 ± 6.3	0.526
Nr. of health care providers***		3.0 ± 2.1	2.6 ± 1.7	3.2 ± 2.3	0.167
Nr. of GP visits****		12.3 ± 8.4	12.7 ± 7.7	12.0 ± 8.9	0.396

*[1]cluster 1, [2]cluster 2, [3]cluster3, * Mean summated baseline MAI score per patient, **between GP-prescribed and used drugs, ***specialists and hospitals, ****(during past 6 months)*

Based on this analysis, 4 influence factors on the status of having a high benefit from the Medication Review could be identified. These are the number of drugs in use ($p<0.001$), the number of differences between the prescribed and the used medicines ($p=0.014$), the baseline MAI score ($p<0.001$) and the time of change from the control to the intervention group ($p=0.001$). For each additional drug in use the chance of having a major benefit from a medication review increases 1.28 times and for each discrepancy between a prescribed drug and what is actually taken at home 1.18 times.

Multivariate regression on the parameters that are detectable at initiation of a Medication Review (approach 1) was significant for the number of drugs per patient ($p=0.001$) and the number of differences in drugs documented by the general practitioner and taken by the patient at home ($p=0.014$).

Multivariate regression on the parameters that are typically generated later in a Medication Review (approach 2) was significant for the baseline MAI score ($p<0.001$), the time of change from the control to the intervention group (overall $p=0.006$) and again the discrepancy between prescribed and used drugs ($p=0.009$) (table 11). The chance of benefiting from a medication review rises by 1.06 per 1-point increase in the baseline MAI score. Patients who entered the medication review service 3 months later than the first group and hence experienced a 3-month shorter intervention, had a fourfold reduced chance of having a major benefit from the medication review. Patients who entered the medication review 6 months later and experienced a 6-month shorter intervention had a 4.7 times lower chance of having a major benefit. Per each discrepancy between prescribed and used drugs the chance to have a major benefit from the medication review increases 1.21 times.

Tab. 11: Multiple logistic regression analyses after automatic selection, early detectable parameters (approach 1) and later detectable parameters (approach 2)

Variable	Comparison	OR	95%-CI	p-value
Approach 1, early detectable parameters				
Number of drugs per patient	1 diff.	1.282	(1.109 to 1.1482)	0.001
Number of differences in drugs between GP and patient	1 diff.	1.181	(1.034 to 1.350)	0.014
Approach 2, later detectable parameters				
Mean summated baseline MAI-score per patient	1-point higher score	1.061	(1.031 to 1.093)	< 0.001
Length of the intervention				0.006 (overall)
	9 vs. 12 months	0.248	(0.078 to 0.791)	0.018
	6 vs. 12 months	0.211	(0.077 to 0.578)	0.002
Number of differences in drugs between GP and patient	1 diff.	1.206	(1.048 to 1.387)	0.009

A receiver operating characteristic curve (ROC curve) was plotted to search for a MAI score, which could be a useful threshold in patient selection (fig. 5). The true positive (sensitivity) is plotted against the false positive rate (1-specifity), the value with the highest specificity and highest sensitivity (closest point in the graph to the

top left) corresponds to a potential cut-off number. The ROC analysis suggests that a potential cut-off for patients experiencing a major effect from a Medication Management could be a MAI score of ≥ 24 (AUC = 0.823, s.e. = 0.037). However, this cut-off level is only valid for the analyzed patient cohort of elderly multimorbid patients with polymedication and a similar patient baseline.

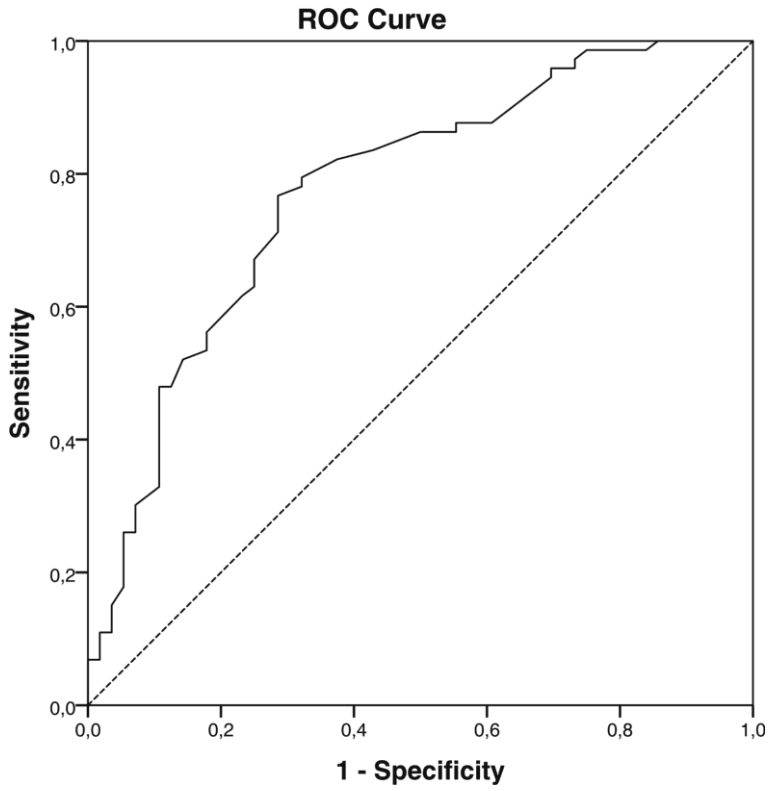


Fig. 5: ROC curve on the MAI-score

4.6. MEDICATION RECONCILIATION

Medication Reconciliation was the first step at performing the Medication Reviews in this study. It was soon realized that a high number of drugs was not documented by to the general practitioners. In total 1749 discrepancies in 142 patients were reported the general practitioners after the two patient assessments, with a total of 179 different drugs. 125 (69,8%) of these drugs were rated as highly relevant to the general practitioner, 54 drugs were less relevant. Examples of relevant drugs were apixaban, candesartan, oxycodon, ticagrelor, or metformin. Drugs rated less relevant were for example algedrat, ambroxol, cetirizine, external nonsteroidal anti-inflammatory drugs or nepafenac eyedrops. The rating was based solely on pharmaceutical expertise. 15 drugs had sedating effects and might increase fall risk, 12 were listed in the PRISCUS list of potential inappropriate medication for elderly patients and 33 of the 179 drugs were associated to a high risk for hospitalization. 99 drugs were classified as having a high potential for drug-drug interactions. Among these drugs for example were omeprazol but not pantoprazol and NSAIDs but not metamizol. With adalimumab, etanercept and imatinib three medications belonged to the high-cost group (>1200 €).

To get a more defined impression, the 179 drugs were related to 5 clusters of indication. As a result, 58 cardiovascular drugs, 45 pain relievers, 48 psychoactive drugs, 57 gastrointestinal drugs and 42 respiratory drugs were found. Table 9 shows the 30 most frequently registered drugs that were taken by the patients but were not documented by the general practitioner, assorted by total frequency and with the correlating cluster of indication. There were no sedative and no PRISCUS drugs

among the 30 most frequently found discrepancies. Only 1 out of 142 patients showed no discrepancy between the prescribed and the actually taken medication.

Tab. 9. The 30 most frequently drugs used by the patients but not documented by the prescriber

Drug	Registered cases	Cluster of indication
Diclofenac*	123	pain medication
Magnesium	90	
Ibuprofen	78	pain medication
Acetylsalicylic acid	75	cardiovascular
Calcium	55	
Metamizole	55	pain medication
Colecalciferol	51	
Glycerol trinitrate	39	cardiovascular
Macrogol	39	gastrointestinal
Acetaminophen	35	pain medication
Pantoprazol	34	gastrointestinal
Tilidine	28	pain medication
Metoprolol	25	cardiovascular
Tamsulosin	25	
Spironolacton	22	cardiovascular
Hydrochlorothiazid	21	cardiovascular
Furosemide	20	cardiovascular
Sennosides	20	gastrointestinal

Drug	Registered cases	Cluster of indication
Potassium	18	cardiovascular
Loratadine	18	
Gentamicin (eye drops)	17	
Ginkgo biloba leaf extract	17	
Timolol (eye drops)	17	
Hyaluronic acid (eye drops)	16	
Rivaroxaban	16	cardiovascular
Candesartan	15	cardiovascular
Simvastatin	15	cardiovascular
Amlodipin	14	cardiovascular
Torasemide	14	cardiovascular
Loperamide	13	gastrointestinal

**systemic and topic*

4.7. ACCEPTANCE ANALYSIS

As a result of the Medication Reviews, 1705 recommendations for interventions were proposed by the pharmacists to the physicians on 142 patients during the *WestGEM study*., i.e. 12 recommendations per patient [227]. 1082 of these recommendations (63.5%) on 104 patients were rated by the physicians (Appendix 6) using the response form (Appendix 7). 667 of these feedbacks on 103 patients could be allocated to the 3 domains on stopping an existing drug treatment, starting a new drug treatment or changing the dose of an existing drug, whereas the other

interventions were not drug-related but for example on laboratory data, monitoring or patient education. Characteristics of patients eligible for acceptance analysis are shown in comparison to the ITT population in table 15.

Tab. 15: Patient characteristics of eligible patients for the acceptance analysis

Parameter	ITT population (SD,%)	Acceptance analysis population (SD,%)
Number of patients	142	103
Age (years)	76.7 (6.3)	76.6 (6.4)
Gender (female, %)	76 (53.5)	67 (55.3)
BMI (kg/m^2)	28.4 (4.3)	28.4 (4.3)
Morbidity (CIRS-G)	1.6 (0.4)	1.7 (0.4)
No. of diagnoses	12.7 (5.7)	13.7 (6.1)
No. of prescribed drugs	9.4 (3.1)	9.7 (3.3)
No. of DRPs	7.3 (3.4)	7.1 (3.4)

The results of the acceptance analysis are summarized in table 16 (detailed data in Appendix 8).

Tab. 16: Acceptance analysis per category

Category	accepted	refused	total
start a drug	129 (51.8%)	120 (48.2%)	249
stop a drug	133 (53.4%)	121 (47.6%)	254
change a drug`s dose	104 (63.4%)	60 (36.6%)	164
total	366 (54.9%)	301 (45.1%)	667 (100%)

Reasons for refusal were the necessity of further information (18%), medical reasons (9%), budgetary reasons (5%) or special aspects in the patient's treatment history (68%) that were unknown to the pharmacist.

To find out whether certain influence factors might lead to a higher or lower frequency in accepting a suggested intervention, the 3 categories to start a drug treatment, to stop a drug treatment or to change a drug`s dose were tested versus the patient`s age, gender, education level, body mass index (BMI), morbidity (CIRS-G), number of prescribed drugs, number of drug-related problems, number of patient-reported adverse events, number of PRISCUS-PIMs, number of patient visits to the general practitioner per quarter (3 months), patient reported health (VAS), social support (FSozu14), cognitive impairment (MMSE), mobility (Tinetti test), everyday expertise (ADL and iADL) and adherence (Morisky score). The time effect of the acceptance over the trial period was assessed as well. The bivariate analyses demonstrated that interventions on stopping a prescribed drug were implemented significantly more often in patients with lower education level, cognitive impaired participants and in patients with good mobility. Suggestions to start a new drug treatment were implemented more frequently if the patient was female and less

frequently the more often the patient visited the general practitioner. Starting a new drug treatment based on the pharmacists' suggestions was more frequent, the longer the patients stayed in the Medication Management process. General practitioners implemented more recommendations on changing a dose if the patient had a high BMI, manifold DRPs, good social support, performed well at everyday expertise and had cognitive impairment. General practitioners implemented fewer recommendations on dosage changes with increasing age of the patient and a good self-reported health status ($p = 0.05$).

Influence factors gaining significance in the multivariate OLS regression analysis are shown in table 17. The multivariate model has shown no significant influence on the acceptance on stopping a prescribed drug.

Tab. 17: Influence factors on prescribers' approval per category as analyzed by multivariate ordinary least squares (OLS) regression

	Recommendations to		
Influence factors	stop an existing drug Coefficient (SEE)	start a new drug Coefficient (SEE)	change the dose of an existing drug Coefficient (SEE)
Demographic variables			
Age	0.0199 (0.1289)	-0.2303 (0.1428)	-0.4506* (0.1915)
Gender female	0.0719 (0.0993)	0.2062** (0.0605)	0.0164 (0.1183)
Education level	-0.0326 (0.0993)	0.0152 (0.0443)	-0.0399 (0.0391)
Nutrition			
BMI	-0.0035 (0.0181)	-0.0201 (0.0128)	0.0188 (0.0117)
Morbidity			
CIRS-G	-0.1133 (0.1084)	0.0886 (0.0932)	-0.2032 (0.1485)
Characteristics of medication			
No. of medication prescribed	0.0169 (0.0166)	0.0138 (0.0186)	-0.0116 (0.0184)
No. of DRPs	0.0003 (0.0246)	0.0121 (0.0260)	-0.0004 (0.0101)
No. of patient-reported ADEs	0.0762 (0.0650)	0.0430 (0.1279)	-0.0012 (0.0827)
No. of PIM drugs	-0.0098 (0.0502)	0.1113 (0.0747)	-0.0137 (0.1005)
Physician-patient relationship			
No. of contacts per quarter	-0.0123 (0.0080)	-0.0299** (0.0049)	-0.0022 (0.0058)
Patient-reported health			
VAS	0.0044 (0.0028)	-0.0002 (0.0036)	-0.0030 (0.0019)

Social/family support			
FSozu K-14	0.0225 (0.0779)	0.0976 (0.0790)	0.1732** (0.0323)
Cognitive impairment			
MMSE	-0.0078 (0.0061)	-0.0071 (0.0066)	-0.0121* (0.0051)
Mobility			
Tinetti Test	-0.0186 (0.0107)	-0.0153 (0.0100)	-0.0014 (0.0110)
Patient's everyday expertise			
ADL	-0.0057 (0.0053)	0.0086 (0.0083)	-0.0176 (0.0102)
iADL	0.0363 (0.0233)	0.0176 (0.0296)	0.0921** (0.0228)
Patient-reported adherence			
Morisky-Score	0.0076 (0.0747)	0.0020 (0.0558)	0.0892 (0.0980)
Time effect	0.0236 (0.0759)	0.1827 (0.0861)	-0.0046 (0.0819)
Adjusted R^2	-0.025	0.14	0.33
N	74	68	65

*Note:*p<0.05, **p<0.001*

Abbreviations: ADE: adverse drug event, ADL: activities of daily living, iADL: instrumental activities of daily living, CIRS-G: Cumulative Illness Rating Scale for Geriatrics, DRPs: drug-related problems, FSozu K-14: Fragebogen zur sozialen Unterstützung, short form 14, MMSE: Mini-Mental State Examination, PIM: potentially inadequate medication, SEE: standard error of the estimate (standard error of the regression), VAS: visual analogue scale

5. DISCUSSION

5.1. DATA QUALITY AND LIMITATIONS

The underlying data has several limitations. Involvement, implementation and feedback varied between the physicians as well as the MAI score baseline between the clusters. Some data was inconsistent, as not all analyzed parameters were covered by standard care. The stepped wedge study design led to a higher acceptance to participate but made statistics complicated. The patient interviews and the brown bag reviews were performed by the home-care specialists but are typically done by pharmacists. This limitation might on the other hand be regarded as a strength, as the patient interviews were performed comprehensively by the home care specialists. Visiting the patients at home might increase the completeness of the medication, whereas the patient could easily forget or hide drugs at a pharmacy visit. The reason for blinding the pharmacists was the funding program, which did not permit any personal advantage to a local pharmacist. Personal contact and patient counseling by the pharmacists might have led to a stronger study effect, as it is an important part of all pharmaceutical care activities. In this study the effects were limited on the cognitive skills of the pharmacist. The patient population of the WestGEM-study included multimorbid patients with a focus on cardiovascular diseases aged 65 or older with 5 or more drugs in use (polymedication). The inclusion criteria might already have narrowed down the eligible patients for a Medication Management and all results must be seen in this context. The effects of a

Medication Management are dependent on the acceptance of the pharmaceutical suggestions by general practitioners.

Data on the analyses in LDL-cholesterol reduction was not sufficient. The study protocol should have emphasized the necessity of drawing quarterly LDL-cholesterol levels.

The cut-off level of a reduction in the MAI score of 3.88 for a major benefit from a medication review cannot be seen as a definite number and might vary with the setting. The inclusion of several influence factors into the multivariate regression might have reduced the power of our sample. Furthermore, there were some interactions between variables weakening the influence, which was shown if compared to the bivariate models.

The results of the acceptance of the collaborative Medication Management by the physicians derive from quantitative analyses only; a qualitative approach was only briefly analyzed here. All physicians had no previous experience with Medication Management. Some of the participating 12 physicians responded inertly on the feedback forms of the suggested interventions. Communication with the general practitioner was mainly based on the written SOAP form. A more intense communication could have helped to increase acceptance and to solve drug-related problems.

The study was conducted as a regional project in two model regions in North Rhine-Westphalia, Germany. The acceptance and effects of a collaborative Medication Management need to be repeated in different jurisdictions and settings.

5.2. EFFICACY OF THE MEDICATION MANAGEMENT

5.2.1. MAI SCORE

The reduction of the MAI score is significant in the three clusters as well as in the Mixed Model in the intervention group (-4.27, $p < 0{,}001$), hence the quality of drug therapy could be improved by the intervention of a Medication Management. This might be the first time that the effects of comprehensive Medication Management were demonstrated in a controlled study in a community setting in elderly multimorbid patients in Germany. The degree of MAI score reduction was in-line with other international studies [65]. It differs with the setting and the indication [54, 228]. A stronger effect can be expected with a higher MAI score baseline, characterizing a high potential for optimization [72]. The fact that the strongest effect correlated to the longest intervention time, indicates a time effect. During the study phase, it was noticed that physicians tended to implement medication changes stepwise over time. Careful and guarded changes seemed to be appropriate in patients with polymedication and high morbidity. Multiple changes could rather lead to adverse effects. Furthermore, all alterations must be communicated to the patients requiring effort and time. With regard to the German definition of a Medication Management as a longitudinal process, the findings support the thesis that patient care improves with time and is superior to individual Medication Reviews.

5.2.2. DRUG-RELATED PROBLEMS

A significantly higher reduction in DRPs by -0,45 DRPs per patient could be found in the intervention group compared to the control group (p = 0,014). An initial rise in the number of DRPs could be explained by changes in the documentation of the physician. As the physician realized more drugs in patient`s medication and added them to his documentation, consequentially more DRPs could be registered. DRP reductions through pharmacists' interventions could be shown in several other national and international studies [28, 71, 85, 229, 230]. Vinks et al. reported a reduction of the number of DRPs from 4.13 to 3.29 in the intervention group, which was a 0.69 higher reduction compared to the control group [28]. The community setting and the baseline number of taken drugs per patient (8.8) was similar to this study.

5.2.3. LDL-CHOLESTEROL CONCENTRATIONS

LDL-cholesterol is a relevant marker in cardiovascular diseases. A reduction might carry a patient benefit and reduce the risk for coronary heart disease, stroke and heart attack. The Medication Management led to a LDL-cholesterol reduction over time ($t_0 \rightarrow t_6$) of -7.5 mg/dl from 114.1 mg/dl to 106.54 mg/dl (p = 0.012). However, the Mixed Model analysis did not reach significance. Interestingly, Machado et al. found in a review that all studies on pharmaceutical interventions in dyslipidemia came to a similar result. Lipid lowering was significant only in before-after analysis but not if compared to a control group [49]. Rating the clinical effect of the Medication

Management with these results is difficult. A large meta analysis of the Cholesterol Treatment Trialists' Collaboration in 2010 comes to the conclusion that a LDL-cholesterol reduction of 39 mg/dl results in a reduction of cardiovascular events of 22% during a one-year period [139]. Results of another large analysis suggest that a LDL-cholesterol reduction by 10 mg/dl leads to a reduction of 6% of major cardiovascular events [140]. Baigent et al. found an 18 mg/dl LDL-cholesterol reduction equivalent to a 23% reduction in major cardiovascular events if sustained for 5 years [139]. Hence, the observed LDL-cholesterol reduction might as well be clinically meaningful and lead to a reduction in cardiovascular events in the studied population. The LDL-cholesterol levels in this population were far too high and did not meet current guideline targets, aiming at a LDL-cholesterol level of <70 mg/dl or <100 mg/dl in the elderly patient with high cardiovascular risk [138, 143]. As seen with the differences in the clusters, the awareness of LDL-cholesterol levels seems to differ among the participating 12 physicians. According to the guidelines and to evidence based medicine most of the study patients require an intense statin therapy, leading to a >50% reduction in LDL-cholesterol. The average level of 106.54 mg/dl after the Medication Management should be reduced further to meet at least the moderate geriatric goals of the ACC/AHA and ESC guideline on dyslipidemia of <100 mg/dl [143]. During the qualitative part of the study many general practitioners expressed their expectation that pharmacists should rather assist them in discontinuing drugs than in starting a new therapy with their provision of Medication Management. Even though this was not supported by the acceptance analysis of this study, general practitioners seemed quite reluctant to initiate statins. On the other hand, the reduction in LDL-cholesterol levels in the analyzed 92 patients indicates

that some general practitioners responded well to the pharmaceutical suggestions and might not have been aware of the therapeutic requirement at routine work before.

5.3. PATIENT SELECTION

In the search of parameters, that correlated to a major benefit from a Medication Management and can be obtained easily by health care professionals, patient age, gender, eGFR, CIRS-G severity index, number of diagnoses, number of health care providers and the number of visits to the general practitioner during the last 6 months were not identified as covariates. These parameters should hence not be considered as patient selection criteria for a Medication Management. The results were quite surprising as multimorbidity and kidney function were regarded as potential risk factors for DRPs in a recent qualitative study by Kaufmann et al. and thus could be expected to have a correlation to the outcome of a medication review [231]. In a study by Green et al. the number of prescribing physicians was described as an independent risk factor for adverse drug events and was expected to be a risk factor for DRPs as well [232].

Among the parameters that were initially available from the medical record or the laboratory data or that were obtainable by a patient interview, the number of drugs in use and a high discrepancy between drugs prescribed compared to the drugs actually taken at home could be identified as determining factors for having a special benefit from a Medication Management. Especially the number of drugs in use could serve as a valid and easily accessible criterion in selecting patients for a Medication Review. The HARM study identified polymedication of 5 or more drugs as a reason

for potentially preventable medication-related hospital admissions, supporting the findings presented here [233].

Medication Reconciliation, which is usually a first step at Medication Management, could be useful for patient selection as well since a high discrepancy could be another decision criterion to initiate pharmaceutical patient care. Further analyses on parameters that are obtained later in Medication Management demonstrated a major benefit if the quality of medication was very low at baseline (as indicated by a high baseline MAI score) or if patients received longitudinal care with repeated Medication Reviews. Unfortunately, the calculation of the MAI score is very time consuming, might be regarded as a Medication Management itself and hence is not useful for identifying eligible patients in routine care. Otherwise, a MAI score of ≥24 could be suggested for the selection of eligible elderly patients with cardiovascular disease and similar inclusion criteria as in this study for a Medication Management. The effect of the Management on the quality of therapy increased significantly with the duration of performing patient care. A repeated Medication Review has proven to be reasonable in our study. The impact of the duration of the intervention with a 4-fold higher chance to benefit from a Medication Management after 3 additional months and a 4.7-fold higher chance after 6 months is profound. Future Medication Managements should emphasize the aspects of longitudinal patient care with repeated rather than with confined pharmaceutical services. These findings are in contrast to a study of Chinthammit et al. which favors shorter and less comprehensive reviews regarding the cost-effectiveness of a Medication Management [234].

Some results of the analyses seem quite obvious but needed to be evaluated. It could be expected that patients with more drugs in use, a lower quality of therapy and a longitudinal care experience a larger benefit from the Medication Management. Furthermore, the results demonstrate that age and morbidity alone are no significant risk factors in the medication process.

5.4. MEDICATION RECONCILIATION RESULTS

The high deviation between the prescribed medicine and the intake at home was a surprising result of this study, with high discrepancies in virtually all regarded patients. The majority of discrepancies was related to clinically relevant prescription drugs and not limited to over-the-counter drugs. Medication Reconciliation clearly contributed to the findings in the Medication Management. Even though only descriptive research was done in Medication Reconciliation here, it is obvious that several high-risk medications were taken by the patients but were not documented and most likely unknown to the prescriber. There is no doubt that a medication with blood-pressure lowering drugs or anticoagulation drugs leads to a tremendous risk if it is not covered by a comprehensive care plan. With the upcoming obligation to provide a medication plan for patients from October 2016 on, a step towards reducing medication risks is done in Germany. According to the study results, the number of deviations was clearly related to the benefit of the Medication Management, indicating the need to revise therapy in these patients. The study advocates an interprofessional Medication Reconciliation.

5.5. ACCEPTANCE ANALYSIS

Acceptance of the collaboration is a crucial aspect in Medication Management as many intervention need to be approved in order to reach the patient [235]. As 1082 (63.5%) of 1705 suggestions for interventions to optimize the therapy at the Medication Management were rated by the general practitioner, a lot of data could be analyzed. The missing feedback on 36.5 % of the suggestions was caused by a minority of general practitioners, who responded inertly. The majority of 10 general practitioners cooperated fairly well. A feedback on almost two third of the questions (63.5%) demonstrates profound commitment of the general practitioners to the study. The in-depth analysis showed that about half of the suggestions of the pharmacists to stop a drug (53.4%) were accepted by the general practitioner. During the study some general practitioners expressed their expectation that more drugs should be discontinued and pharmacists should focus on a reduction of the number of drugs rather than on optimizing the therapy. Hence a high acceptance to stop a drug treatment could be expected. Some suggestions to discontinue a therapy might have been processed stepwise, as the general practitioners hesitated to implement too many recommendations at once. Benzodiazepines, zopiclone and zolpidem however were frequently suggested for discontinuation but hard for the general practitioner to realize, as the patient might have been addicted to the drug. In this context it is rather unexpected that more than half (51.8%) of the interventions by the pharmacists to start a drug treatment were accepted and processed by the general practitioners as well, indicating, that general practitioners followed the recommendations to start and to stop a drug treatment to a similar extent. Willingness to accept recommendations

on new drugs based on the pharmacist's suggestions showed a high level of collaboration and trust between the professions, which exceeded the expectations, as some general practitioners seemed rather skeptical about the effects. Some doubtful general practitioners on the other hand were deeply involved in the study and reflected their former regimens even more than others. Another group of general practitioners uttered that they respected the suggestions in optimizing pharmacotherapy without any emotional restrictions. They felt safe with another profession revising the therapy and followed most advices, according to their own statements.

General practitioners followed the suggestions to change a dose by almost two third (63.4%) and thus to an even higher extent than to start or stop a drug treatment. Optimizing a dose might be less effort and be more easy to communicate to the patient. The need to change a dose is sometimes overseen in daily practice and might be accepted well, as pharmacists frequently supported their suggestion by a calculation of the eGFR, by laboratory data or by vital signs. The low mean baseline eGFR of 55 ml/min, with 19% of the patients showing a eGFR of even 40 ml/min or below, indicates that in elderly patients with polymedication there is a clear need to revise drug dosages. Typical drugs that were adjusted to the renal function were statins, spironolactone and angiotensin-converting enzyme (ACE) inhibitors. Vital signs that were taken into account most frequently were the blood pressure, to adjust an antihypertensive regimen, and the pulse rate, to adjust the dose of beta-blocking agents. Typical laboratory data that led to changes in a drug's dose were uric acid, to change the dose of allopurinol, LDL-cholesterol to change the dose of a statin and potassium, to change dosages of NSAIDs, ACE inhibitors/ARBs, thiazides, loop

diuretics and inhalative β_2-agonists. Serum creatinine was compulsory for the pharmacists to calculate the eGFR.

Compared to international studies, the acceptance of interventions in this work was quite high. In a study in France in outpatients with renal impairment by Pourrat et al. about one third of the interprofessional recommendations were accepted [236]. A recent study of Chau et al. in the Netherlands, which was done in a comparable setting and with similar patient characteristics (mean age of 78 years, about 9 drugs in use), found 46.6% of the suggested interventions on stopping a drug treatment, 43.3% on adjusting a drug's dose and 36.3% on adding a new drug accepted [197].

The lower implementation rate in this Dutch study is surprising as the interprofessional collaboration in the Netherlands is well established, whereas there is no implemented communication between pharmacists and physicians in Germany. The implementation rate might on the other hand increase with the clinical expertise of the pharmacists. As a very large group of pharmacists contributed to the results in the Dutch study, there might have been some heterogeneity in the clinical skills of the participating pharmacists, which comes closer to a real-life setting. In a clinical setting and with close collaboration on the ward, higher acceptance rates of up to 92% could be reached [27, 198, 237].

The results of this study on the acceptance rate in an outpatient setting however, can send out an encouraging signal on interprofessional collaboration in Germany.

5.6. MEDICATION SAFETY IN THE STUDIED POPULATION

With a mean of 11 detected DRPs per patient on the general practitioner's level and additional DRPs at patient side, the study population was very susceptible to medication risks. In study meetings with the physicians, the relevance and severity of the reported DRPs was intensively discussed. Some DRPs, as the prescription of 2 beta-blocking agents in the same patient, were very obvious and helped to create susceptibility on the intervention. Obvious examples might have increased awareness of the potential risks of the medication in the studied population and furthermore in routine care. Reasons for hospitalization were not analyzed in our study so far. Hohl et al. found that 10% of all emergency room visits were drug-related [238]. A review by Patel et al. related 28% of all emergency department visits to DRPs with 70% of them being preventable [239]. Based on these findings, the relevance of medication safety can be assumed for the studied population.

1705 suggestions on optimizing the therapy were suggested to the physicians. Even though some of them could not be impliemented for several good reasons, a clear potential for improvement on medication safety (Arzneimitteltherapiesicherheit, AMTS) could be seen in the elderly, multimorbid patients with polymedication. The high acceptance of recommended interventions by the physicians proves that a collaborative approach improving drug therapy is highly desired and could lead to a patient benefit.

5.6.1. DRUG-DRUG INTERACTIONS

Drug-drug interactions were addressed as one step in the pharmaceutical assessment. A prevalent interaction was the combination of multiple drugs affecting potassium levels and kidney function, namely thiazides, NSAIDs, loop-diuretics and ACE inhibitors/ARBs. For estimating the severity of relevant interactions, multiple factors played a much larger role than pairwise interactions, which usually were of lower relevance in these patients. A frequently reported interaction was the combination of proton-pump inhibitors (PPI) with other magnesium-excretion enhancing drugs like thiazides or loop diuretics. Relevance was granted in this situation only if the patient reported a history of lower leg cramps. Cytochrom P-450 related interactions were detected frequently but were rated with low relevance in many cases. Amlodipine and simvastatin are an example of a more frequent CYP 3A4 interaction and led to a suggested dose reduction of the statin. Physicians were mainly grateful for notifications on drug-drug interactions, even though the relevance was discussed intensively. On the pharmacists' side, it was soon found out that the drug-drug interaction detecting tools (e.g. the ABDA database) were helpful only as a first screening tool but frequently did not reflect the clinical severity or relevance of the interaction sufficiently. Individual patient parameters and multiple interactions as well as the drug history played a distinguished role in estimating the severity of an interaction. The contribution of drug-drug interaction detection tools to medication safety hence seemed to be limited in elderly multimorbid patients and a patient-individual approach should be preferred. These findings were described by other studies before. Van Roon et al. and Bergk et al. came to the result that in general

practice several interactions require no further action or are easily manageable [240, 241].

5.6.2. UNDER- AND OVERTREATMENT

Part of each particular Medication Management is the determination of therapeutic goals, wherever possible in accordance with current guidelines. In case of interfering recommendations by guidelines, a weighting of the best approach was done in this study. An example for the necessity to weigh guideline recommendations was the prescription of a beta-blocking agent in coronary heart disease with a concomitant asthma therapy, where beta-sympathomimetic agents are recommended [242].

A prevalent conflict with guidelines was the undersupply of patients with certain drugs, specifically recommended in their disease state. In coronary heart disease the guidelines recommend the patient to be supplied with a short acting nitrate to have a fast relieve on symptoms [243]. Prescription of short acting nitrates was, however, hardly seen in the study patients and was frequently declined, probably due to the drug costs. As demonstrated before, LDL-cholesterol was addressed by many participating physicians inertly, leading to an undersupply in statins, which is in-line with international data [244]. Short-acting betasympathomimetic agents (SABA) are recommended to all patients with an asthma therapy by the guidelines but were not prescribed to some of the study patients for unknown reasons [245]. In summary, an underprescribing was noticed mainly in dyslipidemia, coronary heart disease and pain therapy.

On the other hand, some regimens were seen that are not consistent with current guidelines. Prescription of systemic steroids in asthma and COPD didn`t seem to be appropriate for the majority of patients seen here. Drugs from the PRISCUS list are a burden that cannot be avoided in some cases. Amitriptylin, in contrast, was still commonly prescribed but could easily be substituted. Prescription of too many drugs or excessive doses was seen frequently in antihypertensive and antidiabetic therapy regimens. In hypertension severe lowering of the blood pressure doesn`t carry any benefit and increases the risk of falling. The current European guideline for hypertension reflects these findings with higher blood pressure goals [246]. In antidiabetic therapy intensive lowering of blood glucose and HbA_{1c} levels carries the risk of hypoglycemia [247].

5.6.3. PATIENT GOALS

Patient goals in the studied population were related mainly to a better pain-management, to pruritus reduction and a higher resilience. Patient goals were obtained by the home care specialists as a part of the home care and pharmaceutical assessment and seemed to differ from the patient goals the physicians noted. An explanation for this discrepancy could be the different setting. In a physician’s practice the attention of the patient might be drawn to other, acute problems and the available time with the physician is limited. The assessment of the home care specialist, in contrast, was done without urgency and at home environment, furthermore the patient was implicitly assessed and asked for pain, excretion, vertigo and other aspects interfering with quality of life. Physicians were grateful for this

structured assessment, providing new information to them. In pain management and due to the high cardiovascular risk of the patients, NSAIDs were frequently suggested to the physician for discontinuation and acetaminophen or metamizol (despite the risk of agranulocytosis), or a combination of both was suggested as a replacement [248, 249]. For more severe pain a switch to opioids was the only approach left with a risk for dizziness and obstipation and hence probably causing a new prescription cascade [250]. As many patients reported severe pain in the assessment, pain medication was frequently suggested for alterations, underprescribing seemed to be prevalent.

5.7. CONCLUSIONS

Aspects of this elaborations were the effects of the Medication Management on the quality of drug therapy, the identification of risk groups, who might carry a major benefit from the intervention, an analysis of the efficacy at patient level and an assessment of the interprofessional collaboration.

Significant effects could be shown for the reduction of the MAI score and DRPs, indicating an improve in the quality of drug therapy. LDL-cholesterol reduction could show trends but no significant improvements versus the control group. Further research with specifically designed studies is needed to demonstrate positive results.

The analysis of eligible patient groups suggests that the number of drugs in use is a valid screening criterion. It is easily accessible and correlates to the outcomes of a Medication Management.

The acceptance of the recommendations is a measure of interprofessional collaboration, which is often the bottleneck in Medication Management. Health insurances might hesitate to implement Medication Management even if the right patients are selected and an efficacy is expected, if the structures in collaboration do not make the intervention likely to reach the patient. The acceptance rate was profound and could likely even be increased with direct physician-pharmacist communication, which was not a standard procedure in the approach here. A part of the medication was not documented and most probably unknown to the prescriber and could be taken into account by the interprofessional approach.

With positive results in all elaborated domains, the efficacy of a Medication Management could be shown from different perspectives. Each aspect contributes to the patient outcomes and only by covering all aspects a Medication Management can be momentous to the patient and the society. The results of this study suggest that selecting eligible patients, performing a comprehensive Medication Management and collaborating interprofessionally leads to a patient benefit.

6. FUTURE PROSPECTS

Summarizing the results of this thesis, it can be stated that the implementation of a Medication Management would contribute to patients' health and medication safety in Germany. It would be suggested that future patient selection should mainly be depending on the number of drugs in use. In case of a high discrepancy between the prescribed and the used medication at the point of Medication Reconciliation, which is an indispensable component of a Medication Management according to the study results, additional attention should be paid to the patient. The cut-off of the number of systemic drugs in use could be adjusted to the estimated capacities of German pharmacies and physicians. In case of a certain discrepancy between the prescribed and the used drugs it would be meaningful to take further measures, i.e. a more intense type 3 Medication Review or a repeated follow-up. An increase in the efficacy of a Medication Management can be expected with growing interprofessional trust. Results of this study support a longitudinal patient care, future implementations should focus on continuous pharmaceutical services.

To ensure a high level of collaboration, standard procedures should be developed, evaluated and implicated into daily routine. For a timesaving communication, special forms can be developed and certain times could be reserved for a case conference. As pharmacotherapy is just a small facet in patient care in daily medical practice, there is a great potential for interprofessional cooperation. With regard of the study results it could be assessed whether blood pressure and pulse rate, serum creatinine, LDL-cholesterol, uric acid and potassium should regularly be available to the pharmacist in order to facilitate the Medication Management. With regard to a more

effective interprofessional collaboration, efforts should be done to overcome existing barriers. New prospects of professional development should be explored, as it is done in different jurisdictions and settings [50, 251]. Findings of this work are in accordance with the outcomes of Medication Management seen in other countries and support the thesis that there is a strong potential for patient-oriented pharmaceutical and interprofessional services in Germany.

7. SUMMARY

Medication Review and Medication Management are new pharmaceutical care services with a strong potential to contribute to patients' health care outcomes. The aim of this work was to evaluate an interprofessional, collaborative Medication Management in an outpatient setting in Germany. Objectives were to assess the efficacy of the intervention, to identify risk groups, who might carry a higher benefit from a Medication Management, to assess the results of the Medication Reconciliation process and to examine the acceptance of the collaborative Medication Management.

165 elderly multimorbid patients from 12 primary care practices were included in this cluster-randomized controlled study, following a stepped wedge design. A comprehensive Medication Review was performed twice and interprofessional action was undertaken, leading to prospective data on 142 patients and covering a 15 months' span of life.

With a greater reduction in the MAI score of 4.27 points ($p < 0.001$) in the intervention group, the efficacy of a Medication Management in improving the quality of drug therapy was demonstrated. DRPs were reduced significantly, supporting this result. The efficacy in terms of the reduction of LDL-cholesterol concentrations showed significance in the before-after analysis ($p = 0.012$). However, in a Mixed Model the effect of the intervention was not significant.

The results further suggest the number of drugs in use ($p=0.001$) and the number of discrepancies between prescribed and used drugs ($p=0.014$) as patient selection

criteria for a Medication Management. The baseline MAI score ($p<0.001$) and the length of the intervention ($p=0.006$) correlated with positive outcomes as well but are not feasible for patient selection.

Medication Reconciliation revealed that the majority of drugs, which were not documented by the prescriber, were prescription drugs with clinically significant effects and risks. Therefore, an individual medication plan is highly desired to increase patient safety.

The interprofessional acceptance of the study with 54.9% of the recommendations being implemented, shows an effective collaboration between physicians and pharmacists within the Medication Management process.

The demonstrated efficacy and a high interprofessional acceptance support the implementation of a Medication Management into German health care.

8. LITERATURE

1. Hepler CD, Strand LM. Opportunities and responsibilities in pharmaceutical care. Am J Hosp Pharm. 1990;47:533–43.
2. Hepler CD, Strand LM, Derendorf H. Der Apotheker und die Arzneimittelversorgung - Zukunftschancen und Verantwortung. Pharm Ztg. 1990;135:3087–92.
3. World Health Organization and International Pharmaceutical Federation. Developing pharmacy practice-A focus on patient care, Handbook 2006 Edition. Available at: http://www.who.int/mediacentre/news/new/2006/nw05/en/. Accessed 25 Mar 2015.
4. Allemann SS, van Mil JW, Botermann L, Berger K, Griese N, Hersberger KE. Pharmaceutical care: the PCNE definition 2013. Int J Clin Pharm. 2014;36:544–55.
5. van Mil JW, Schulz M, Tromp TF. Pharmaceutical care, European developments in concepts, implementation, teaching, and research: a review. Pharm World Sci. 2004;26:303–11.
6. ABDA, Bundesvereinigung Deutscher Apothekerverbände. Apotheke 2030, Perspektiven zur pharmazeutischen Versorgung in Deutschland. Available at: http://www.abda.de/themen/positionen-und-initiativen/leitbild/?id=leitbild. Accessed 25 Mar 2015.
7. Pringle JL, Boyer A, Conklin MH, McCullough JW, Aldridge A. The Pennsylvania Project: pharmacist intervention improved medication adherence and reduced health care costs. Health Aff (Millwood). 2014;33:1444–52.
8. Ramanath K, Balaji D, Nagakishore C, Kumar SM, Bhanuprakash M. A study on impact of clinical pharmacist interventions on medication adherence and quality of life in rural hypertensive patients. J Young Pharm. 2012;4:95–100.
9. Lee JK, Grace KA, Taylor AJ. Effect of a pharmacy care program on medication adherence and persistence, blood pressure, and low-density lipoprotein cholesterol: a randomized controlled trial. JAMA. 2006;296:2563–71.
10. Pauly A, Wolf C, Mayr A, Lenz B, Kornhuber J, Friedland K. Effect of a Multi-Dimensional and Inter-Sectoral Intervention on the Adherence of Psychiatric Patients. PLoS ONE. 2015;10:e0139302.

11. Kjeldsen LJ, Bjerrum L, Dam P, Larsen BO, Rossing C, Søndergaard B, Herborg H. Safe and effective use of medicines for patients with type 2 diabetes - A randomized controlled trial of two interventions delivered by local pharmacies. Res Social Adm Pharm. 2015;11:47–62.

12. Obarcanin E, Krüger M, Müller P, Nemitz V, Schwender H, Hasanbegovic S, et al. Pharmaceutical care of adolescents with diabetes mellitus type 1: the DIADEMA study, a randomized controlled trial. Int J Clin Pharm. 2015;37:790–8.

13. Li J, Bergmann A, Reimann M, Bornstein SR, Schwarz PEH. A more simplified Finnish diabetes risk score for opportunistic screening of undiagnosed type 2 diabetes in a German population with a family history of the metabolic syndrome. Horm Metab Res. 2009;41:98–103.

14. Schmiedel K, Mayr A, Fießler C, Schlager H, Friedland K. Effects of the lifestyle intervention program GLICEMIA in people at risk for type 2 diabetes: a cluster-randomized controlled trial. Diabetes Care. 2015;38:937–9.

15. Liekweg A, Westfeld M, Braun M, Zivanovic O, Schink T, Kuhn W, Jaehde U. Pharmaceutical care for patients with breast and ovarian cancer. Support Care Cancer. 2012;20:2669–77.

16. Needham DS, Wong ICK, Campion PD. Evaluation of the effectiveness of UK community pharmacists' interventions in community palliative care. Palliat Med. 2002;16:219–25.

17. Hämmerlein A, Müller U, Schulz M. Pharmacist-led intervention study to improve inhalation technique in asthma and COPD patients. J Eval Clin Pract. 2011;17:61–70.

18. Schulz M, Verheyen F, Mühlig S, Müller JM, Mühlbauer K, Knop-Schneickert E, et al. Pharmaceutical care services for asthma patients: a controlled intervention study. J Clin Pharmacol. 2001;41:668–76.

19. Jalal ZS, Smith F, Taylor D, Patel H, Finlay K, Antoniou S. Pharmacy care and adherence to primary and secondary prevention cardiovascular medication: a systematic review of studies. Eur J Hosp Pharm. 2014:238–44.

20. Kripalani S, Yao X, Haynes RB. Interventions to enhance medication adherence in chronic medical conditions: a systematic review. Arch Intern Med. 2007;167:540–50.

21. Carter BL, Rogers M, Daly J, Zheng S, James PA. The potency of team-based care interventions for hypertension: a meta-analysis. Arch Intern Med. 2009;169:1748–55.

22. Bregnhøj L, Thirstrup S, Kristensen MB, Bjerrum L, Sonne J. Combined intervention programme reduces inappropriate prescribing in elderly patients exposed to polypharmacy in primary care. Eur J Clin Pharmacol. 2009;65:199–207.

23. Clyne B, Bradley MC, Hughes CM, Clear D, McDonnell R, Williams D, et al. Addressing potentially inappropriate prescribing in older patients: development and pilot study of an intervention in primary care (the OPTI-SCRIPT study). BMC Health Serv Res. 2013;13:307.

24. Spinewine A, Swine C, Dhillon S, Lambert P, Nachega JB, Wilmotte L, Tulkens PM. Effect of a collaborative approach on the quality of prescribing for geriatric inpatients: a randomized, controlled trial. J Am Geriatr Soc. 2007;55:658–65.

25. Al-Amin M, Zinchenko A, Rana S, Uddin MN, Pervin S. Study on Polypharmacy in Patients with Cardiovascular Diseases. J Appl Pharm Sci. 2012;2:53–60.

26. Nicolas A, Eickhoff C, Griese N, Schulz M. Drug-related problems in prescribed medicines in Germany at the time of dispensing. Int J Clin Pharm. 2013;35:476–82.

27. Raimbault-Chupin M, Spiesser-Robelet L, Guir V, Annweiler C, Beauchet O, Clerc M-A, Moal F. Drug related problems and pharmacist interventions in a geriatric unit employing electronic prescribing. Int J Clin Pharm. 2013;35:847–53.

28. Vinks TH, Egberts TC, de Lange TM, de Koning FH. Pharmacist-based medication review reduces potential drug-related problems in the elderly: the SMOG controlled trial. Drugs Aging. 2009;26:123–33.

29. Cai H, Dai H, Hu Y, Yan X, Xu H. Pharmacist care and the management of coronary heart disease: a systematic review of randomized controlled trials. BMC Health Serv Res. 2013;13:461.

30. Nkansah N, Mostovetsky O, Yu C, Chheng T, Beney J, Bond CM, Bero L. Effect of outpatient pharmacists' non-dispensing roles on patient outcomes and prescribing patterns. Cochrane Database Syst Rev. 2010:CD000336.

31. U.S. Government publishing office. Medicare Prescription Drug, Improvement, and Modernization Act. Available at: http://www.gpo.gov/fdsys/pkg/PLAW-108publ173/content-detail.html. Accessed 4 Apr 2015.

32. Pharmaceutical Care Network Europe. PCNE statement on medication review. Available at: http://www.pcne.org/working-groups/1/medication-review. Accessed 3 Apr 2015.

33. Pharmaceutical Care Network Europe. Medication review definition approved. 2016. Available at: http://www.pcne.org/news/35/medication-review-definition-approved. Accessed 5 Apr 2016.

34. Royal Pharmaceutical Society. Medicines use review. Available at: http://www.rpharms.com/health-campaigns/medicines-use-review.asp. Accessed 9 Sep 2015.

35. McBane SE, Dopp AL, Abe A, Benavides S, Chester EA, Dixon DL, et al. Collaborative drug therapy management and comprehensive medication management-2015. Pharmacotherapy. 2015;35:e39-50.

36. pharmaSuisse. Dienstleistungen. Available at: http://www.pharmasuisse.org. Accessed 11 Nov 2015.

37. Australian Association of Consultant Pharmacy. Home Medicines Review. Available at: https://www.aacp.com.au/accreditation/mmr/hmr.html. Accessed 12 Jul 2015.

38. Pharmaceutical Care Network Europe. Workshop during 2013 Working Conference in Berlin. Available at: http://www.pcne.org/working-groups/1/medication-review. Accessed 10 Mar 2015.

39. Deutsche Pharmazeutische Gesellschaft. Statement der DPhG und der DPhG-FG Klinische Pharmazie-Implementierung des Medikationsmanagements als neue pharmazeutische Dienstleistung. Available at: http://www.dphg.de. Accessed 7 May 2015.

40. ABDA, Bundesvereinigung Deutscher Apothekerverbände. Grundsatzpapier zur Medikationsanalyse und zum Medikationsmanagement. Available at: http://www.abda.de/themen/positionen-und-initiativen/medikationsmanagement. Accessed 14 Apr 2015.

41. Barnett MJ, Frank J, Wehring H, Newland B, VonMuenster S, Kumbera P, et al. Analysis of pharmacist-provided medication therapy management (MTM) services in community pharmacies over 7 years. J Manag Care Pharm. 2009;15:18–31.

42. Bulajeva A, Labberton L, Leikola S, Pohjanoksa-Mäntylä M, Geurts MME, de Gier JJ, Airaksinen M. Medication review practices in European countries. Res Social Adm Pharm. 2014;10:731–40.

43. American Association of Colleges of Pharmacy Web site. National Pharmacist Workforce Study 2014. Available at: http://www.aacp.org. Accessed 28 Apr 2015.

44. Rose O, Derendorf H. Eine Cholesterin-Hyperlipidämie Patientin aus Sicht der klinischen Pharmazie. Dtsch Apoth Ztg. 2012;152:2004–12.

45. Klemmer JM, Schmitz S, Roth S, Simons S, Reineking N, Eisert A, et al. Pharmacotherapy of a geriatric patient with Parkinson's disease. Med Monatsschr Pharm. 2007;30:411–4.

46. Kraff S, Frisse S, Ringsdorf S, Zerres M, Braun U, Joeres R, Jaehde U. Pharmaceutical care for a multimorbid patient mainly suffering from chronic obstructive pulmonary disease. Med Monatsschr Pharm. 2009;32:97–101.

47. Möltgen S, Weber L, Kurth V, Pizarro C, Skowasch D, Jaehde U. Comprehensive medication analysis in a multi-morbid patient with chronic renal failure. Med Monatsschr Pharm. 2015;38:135–40.

48. Hanlon JT, Weinberger M, Samsa GP, Schmader KE, Uttech KM, Lewis IK, et al. A randomized, controlled trial of a clinical pharmacist intervention to improve inappropriate prescribing in elderly outpatients with polypharmacy. Am J Med. 1996;100:428–37.

49. Machado M, Nassor N, Bajcar JM, Guzzo GC, Einarson TR. Sensitivity of patient outcomes to pharmacist interventions. Part III: systematic review and meta-analysis in hyperlipidemia management. Ann Pharmacother. 2008;42:1195–207.

50. Chisholm-Burns MA, Kim Lee J, Spivey CA, Slack M, Herrier RN, Hall-Lipsy E, et al. US pharmacists' effect as team members on patient care: systematic review and meta-analyses. Med Care. 2010;48:923–33.

51. Planas LG, Crosby KM, Mitchell KD, Farmer KC. Evaluation of a hypertension medication therapy management program in patients with diabetes. J Am Pharm Assoc (2003). 2009;49:164–70.

52. Ramalho de Oliveira D, Brummel AR, Miller DB. Medication therapy management: 10 years of experience in a large integrated health care system. J Manag Care Pharm. 2010;16:185–95.

53. Alldred DP, Raynor DK, Hughes C, Barber N, Chen TF, Spoor P. Interventions to optimise prescribing for older people in care homes. Cochrane Database Syst Rev. 2013;2:CD009095.

54. Viswanathan M, Kahwati LC, Golin CE, Blalock SJ, Coker-Schwimmer E, Posey R, Lohr KN. Medication therapy management interventions in outpatient settings: a systematic review and meta-analysis. JAMA Intern Med. 2015;175:76–87.

55. Doucette WR, McDonough RP, Klepser D, McCarthy R. Comprehensive medication therapy management: identifying and resolving drug-related issues in a community pharmacy. Clin Ther. 2005;27:1104–11.

56. Michaels NM, Jenkins GF, Pruss DL, Heidrick JE, Ferreri SP. Retrospective analysis of community pharmacists' recommendations in the North Carolina Medicaid medication therapy management program. J Am Pharm Assoc (2003). 2010;50:347–53.

57. Page RL, Linnebur SA, Bryant LL, Ruscin JM. Inappropriate prescribing in the hospitalized elderly patient: defining the problem, evaluation tools, and possible solutions. Clin Interv Aging. 2010;5:75–87.

58. Pugh MJV, Hanlon JT, Zeber JE, Bierman A, Cornell J, Berlowitz DR. Assessing potentially inappropriate prescribing in the elderly Veterans Affairs population using the HEDIS 2006 quality measure. J Manag Care Pharm. 2006;12:537–45.

59. Isetts BJ, Brown LM, Schondelmeyer SW, Lenarz LA. Quality assessment of a collaborative approach for decreasing drug-related morbidity and achieving therapeutic goals. Arch Intern Med. 2003;163:1813–20.

60. Isetts BJ, Schondelmeyer SW, Artz MB, Lenarz LA, Heaton AH, Wadd WB, et al. Clinical and economic outcomes of medication therapy management services: the Minnesota experience. J Am Pharm Assoc (2003). 2008;48:203-11

61. Hanlon JT, Schmader KE, Samsa GP, Weinberger M, Uttech KM, Lewis IK, et al. A method for assessing drug therapy appropriateness. J Clin Epidemiol. 1992;45:1045–51.

62. Gillespie U, Alassaad A, Hammarlund-Udenaes M, Mörlin C, Henrohn D, Bertilsson M, Melhus H. Effects of pharmacists' interventions on appropriateness of prescribing and evaluation of the instruments' (MAI, STOPP and STARTs') ability to predict hospitalization--analyses from a randomized controlled trial. PLoS ONE. 2013;8:e62401.

63. Lund BC, Carnahan RM, Egge JA, Chrischilles EA, Kaboli PJ. Inappropriate prescribing predicts adverse drug events in older adults. Ann Pharmacother. 2010;44:957–63.

64. Samsa GP, Hanlon JT, Schmader KE, Weinberger M, Clipp EC, Uttech KM, et al. A summated score for the medication appropriateness index: development and assessment of clinimetric properties including content validity. J Clin Epidemiol. 1994;47:891–6.

65. Patterson SM, Hughes C, Kerse N, Cardwell CR, Bradley MC. Interventions to improve the appropriate use of polypharmacy for older people. Cochrane Database Syst Rev. 2012;5:CD008165.

66. Fitzgerald LS, Hanlon JT, Shelton PS, Landsman PB, Schmader KE, Pulliam CC, Williams ME. Reliability of a modified medication appropriateness index in ambulatory older persons. Ann Pharmacother. 1997;31:543–8.

67. Spinewine A, Dumont C, Mallet L, Swine C. Medication appropriateness index: reliability and recommendations for future use. J Am Geriatr Soc. 2006;54:720–2.

68. Schmader K, Hanlon JT, Weinberger M, Landsman PB, Samsa GP, Lewis I, et al. Appropriateness of medication prescribing in ambulatory elderly patients. J Am Geriatr Soc. 1994;42:1241–7.

69. Kassam R, Martin LG, Farris KB. Reliability of a modified medication appropriateness index in community pharmacies. Ann Pharmacother. 2003;37:40–6.

70. Hanlon JT, Schmader KE. The medication appropriateness index at 20: where it started, where it has been, and where it may be going. Drugs Aging. 2013;30:893–900.

71. Wolf C, Pauly A, Mayr A, Grömer T, Lenz B, Kornhuber J, Friedland K. Pharmacist-Led Medication Reviews to Identify and Collaboratively Resolve Drug-Related Problems in Psychiatry - A Controlled, Clinical Trial. PLoS ONE. 2015;10:e0142011.

72. Castelino RL, Bajorek BV, Chen TF. Retrospective evaluation of home medicines review by pharmacists in older Australian patients using the medication appropriateness index. Ann Pharmacother. 2010;44:1922–9.

73. van Mil JW, Westerlund LO, Hersberger KE, Schaefer MA. Drug-related problem classification systems. Ann Pharmacother. 2004;38:859–67.

74. American Society of Hospital Pharmacists. ASHP-Statement on pharmaceutical care. Available at: http://www.ashp.org/DocLibrary/BestPractices/OrgStPharmCare.aspx. Accessed 11 Feb 2014.

75. Westerlund T, Almarsdóttir AB, Melander A. Factors influencing the detection rate of drug-related problems in community pharmacy. Pharm World Sci. 1999;21:245–50.

76. Westerlund T, Gelin U, Pettersson E, Skärlund F, Wågström K, Ringbom C. A retrospective analysis of drug-related problems documented in a national database. Int J Clin Pharm. 2013;35:202–9.

77. Pharmaceutical Care Network Europe. Classification for Drug-related problems version 6.2. Available at: http://www.pcne.org/upload/files/11_PCNE_ classification_V6-2.pdf. Accessed 11 Aug 2016.

78. Pharmaceutical Care Network Europe. Classification for Drug related problems version 7. Available at: http://www.pcne.org/upload/files/145_PCNE_ classification_V7-0.pdf. Accessed 11 Aug 2016.

79. Horvat N, Kos M. Development and validation of the Slovenian drug-related problem classification system based on the PCNE classification V 6.2. Int J Clin Pharm. 2016;38:950–9.

80. Maes KA, Tremp RM, Hersberger KE, Lampert ML. Demonstrating the clinical pharmacist's activity: validation of an intervention oriented classification system. Int J Clin Pharm. 2015;37:1162–71.

81. Williams M, Peterson GM, Tenni PC, Bindoff IK, Stafford AC. DOCUMENT: a system for classifying drug-related problems in community pharmacy. Int J Clin Pharm. 2012;34:43–52.

82. Bondesson A, Eriksson T, Kragh A, Holmdahl L, Midlov P, Hoglund P. In-hospital medication reviews reduce unidentified drug-related problems. Eur J Clin Pharmacol. 2013;69:647–55.

83. Halvorsen KH, Ruths S, Granas AG, Viktil KK. Multidisciplinary intervention to identify and resolve drug-related problems in Norwegian nursing homes. Scand J Prim Health Care. 2010;28:82–8.

84. Molino Cde G, Carnevale RC, Rodrigues AT, Visacri MB, Moriel P, Mazzola PG. Impact of pharmacist interventions on drug-related problems and laboratory markers in outpatients with human immunodeficiency virus infection. Ther Clin Risk Manag. 2014;10:631–9.

85. Silva C, Ramalho C, Luz I, Monteiro J, Fresco P. Drug-related problems in institutionalized, polymedicated elderly patients: opportunities for pharmacist intervention. Int J Clin Pharm. 2015;37:327–34.

86. Gustafsson M, Sandman PO, Karlsson S, Isaksson U, Schneede J, Sjolander M, Lovheim H. Reduction in the use of potentially inappropriate drugs among old people living in geriatric care units between 2007 and 2013. Eur J Clin Pharmacol. 2015;71:507–15.

87. Forsetlund L, Eike MC, Gjerberg E, Vist GE. Effect of interventions to reduce potentially inappropriate use of drugs in nursing homes: a systematic review of randomised controlled trials. BMC Geriatr. 2011;11:16.

88. Hughes CM, Lapane KL. Administrative initiatives for reducing inappropriate prescribing of psychotropic drugs in nursing homes: how successful have they been? Drugs Aging. 2005;22:339–51.

89. Ramos GV, Guaraldo L, Japiassú AM, Bozza FA. Comparison of two databases to detect potential drug-drug interactions between prescriptions of HIV/AIDS patients in critical care. J Clin Pharm Ther. 2015;40:63–7.

90. Roblek T, Vaupotic T, Mrhar A, Lainscak M. Drug-drug interaction software in clinical practice: a systematic review. Eur J Clin Pharmacol. 2015;71:131–42.

91. Kuperman GJ, Bobb A, Payne TH, Avery AJ, Gandhi TK, Burns G, et al. Medication-related clinical decision support in computerized provider order entry systems: a review. J Am Med Inform Assoc. 2007;14:29–40.

92. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30:473–83.

93. Bech P, Gudex C, Johansen KS. The WHO (Ten) Well-Being Index: validation in diabetes. Psychother Psychosom. 1996;65:183–90.

94. Isetts BJ, Schondelmeyer SW, Heaton AH, Wadd WB, Hardie NA, Artz MB. Effects of collaborative drug therapy management on patients' perceptions of care and health-related quality of life. Res Social Adm Pharm. 2006;2:129–42.

95. Malone DC, Carter BL, Billups SJ, Valuck RJ, Barnette DJ, Sintek CD, et al. Can clinical pharmacists affect SF-36 scores in veterans at high risk for medication-related problems? Med Care. 2001;39:113–22.

96. World Health Organisation. Adherence to long-term therapies: evidence for action. 2003. Available at: http://www.who.int. Accessed 17 Jan 2017.

97. Haynes RB, Taylor DW, Sackett DL, editors. Compliance in health care. Baltimore: Md., Johns Hopkins University Press; 1979.

98. Meichenbaum D, Turk DC, editors. Facilitating Treatment Adherence: A Practitioner's Guide-book. New York: Plenum Press; 1987.

99. Delamater AM. Improving patient adherence. Clin Diabetes. 2006;24:71–7.

100. Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: its importance in cardiovascular outcomes. Circulation. 2009;119:3028–35.

101. Lindenmeyer A, Hearnshaw H, Vermeire E, van Royen P, Wens J, Biot Y. Interventions to improve adherence to medication in people with type 2 diabetes mellitus: a review of the literature on the role of pharmacists. J Clin Pharm Ther. 2006;31:409–19.

102. Heisler M, Hofer TP, Schmittdiel JA, Selby JV, Klamerus ML, Bosworth HB, et al. Improving blood pressure control through a clinical pharmacist outreach program in patients with diabetes mellitus in 2 high-performing health systems: the adherence and intensification of medications cluster randomized, controlled pragmatic trial. Circulation. 2012;125:2863–72.

103. Heisler M, Hogan MM, Hofer TP, Schmittdiel JA, Pladevall M, Kerr EA. When more is not better: treatment intensification among hypertensive patients with poor medication adherence. Circulation. 2008;117:2884–92.

104. Krolop L, Ko YD, Schwindt PF, Schumacher C, Fimmers R, Jaehde U. Adherence management for patients with cancer taking capecitabine: a prospective two-arm cohort study. BMJ Open 2013;3:pii:e003139

105. Carter BL, Bosworth HB, Green BB. The hypertension team: the role of the pharmacist, nurse, and teamwork in hypertension therapy. J Clin Hypertens (Greenwich). 2012;14:51–65.

106. Pauley TR, Magee MJ, Cury JD. Pharmacist-managed, physician-directed asthma management program reduces emergency department visits. Ann Pharmacother. 1995;29:5–9.

107. Stuart B, Loh FE, Roberto P, Miller LM. Increasing Medicare part D enrollment in medication therapy management could improve health and lower costs. Health Aff (Millwood). 2013;32:1212–20.

108. Burns ER, Stevens JA, Lee R. The direct costs of fatal and non-fatal falls among older adults - United States. J Safety Res. 2016;58:99–103.

109. Wittayanukorn S, Westrick SC, Hansen RA, Billor N, Braxton-Lloyd K, Fox BI, Garza KB. Evaluation of medication therapy management services for patients with cardiovascular disease in a self-insured employer health plan. J Manag Care Pharm. 2013;19:385–95.

110. Pharmaceutical Society of Australia. Guidelines for pharmacists providing Medicines Use Review (MedsCheck) and diabetes Medication Management (Diabetes MedsCheck) services. 2012. Available at: http://www.psa.org.au/download/guidelines/3612-medscheck-guidelines-c.pdf. Accessed 6 May 2016.

111. Hersberger KE, Messerli M. Development of Clinical Pharmacy in Switzerland: Involvement of Community Pharmacists in Care for Older Patients. Drugs Aging 2016;33:205-11

112. Chen TF. Pharmacist-Led Home Medicines Review and Residential Medication Management Review: The Australian Model. Drugs Aging. 2016;33:199–204.

113. Pharmaceutical Society of Australia. Guidelines for pharmacists providing Residential Medication Management Review (RMMR) and Quality Use of Medicines (QUM) services. 2012. Available at: https://www.psa.org.au/download/ practice-guidelines/rmmr-and-qum-services.pdf. Accessed 6 May 2016.

114. Australian Government, Department of Health. Medication management reviews. Available at: https://www.health.gov.au. Accessed 5 Apr 2016.

115. Pellegrino AN, Martin MT, Tilton JJ, Touchette DR. Medication therapy management services: definitions and outcomes. Drugs. 2009;69:393–406.

116. Latif A, Boardman HF, Pollock K. Understanding the patient perspective of the English community pharmacy Medicines Use Review (MUR). Res Social Adm Pharm. 2013;9:949–57.

117. Rosenthal M, Holmes E, Banahan B3. Making MTM implementable and sustainable in community pharmacy: Is it time for a different game plan? Res Social Adm Pharm. 2016;12:523–8.

118. George J, Phun YT, Bailey MJ, Kong DC, Stewart K. Development and validation of the medication regimen complexity index. Ann Pharmacother. 2004;38:1369–76.

119. Giberson S, Yoder S, Lee MP, Office of the Chief Pharmacist. U.S. Public Health Service. Improving Patient and Health System Outcomes through Advanced Pharmacy Practice. A Report to the U.S. Surgeon General. Available at: http://www.accp.com. Accessed 25 Sep 2015.

120. Centers for Medicare & Medicaid Services. 2010 Medicare Part D Medication Therapy Management (MTM) Programs. Available at: https://www.cms.gov. Accessed 11 Jan 2012.

121. Rose O. Neue Trends für die Pharmazie. Dtsch Apoth Ztg. 2012;152:534–6.

122. Sieber CC. Der ältere Patient--wer ist das? Internist (Berl). 2007;48:1190, 1192-4.

123. Bjerrum L, Rosholm JU, Hallas J, Kragstrup J. Methods for estimating the occurrence of polypharmacy by means of a prescription database. Eur J Clin Pharmacol. 1997;53:7–11.

124. Pharmaceutical Care Network Europe. PCNE-3rd Medication Review workshop-report 2012. Available at: http://www.pcne.org/upload/ms2012/WS%201%20Intro.pdf. Accessed 4 Mar 2015.

125. Isaksen SF, Jonassen J, Malone DC, Billups SJ, Carter BL, Sintek CD. Estimating risk factors for patients with potential drug-related problems using electronic pharmacy data. IMPROVE investigators. Ann Pharmacother. 1999;33:406–12.

126. Thompson RC, Allam AH, Lombardi GP, Wann LS, Sutherland ML, Sutherland JD, et al. Atherosclerosis across 4000 years of human history: the Horus study of four ancient populations. Lancet. 2013;381:1211–22.

127. Keller A, Graefen A, Ball M, Matzas M, Boisguerin V, Maixner F, et al. New insights into the Tyrolean Iceman's origin and phenotype as inferred by whole-genome sequencing. Nat Commun. 2012;3:698.

128. Eagle KA, Ginsburg GS, Musunuru K, Aird WC, Balaban RS, Bennett SK, et al. Identifying patients at high risk of a cardiovascular event in the near future: current status and future directions: report of a national heart, lung, and blood institute working group. Circulation. 2010;121:1447–54.

129. D'Agostino RB, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation. 2008;117:743–53.

130. Assmann G, Cullen P, Schulte H. Simple scoring scheme for calculating the risk of acute coronary events based on the 10-year follow-up of the prospective cardiovascular Münster (PROCAM) study. Circulation. 2002;105:310–5.

131. Conroy RM, Pyörälä K, Fitzgerald AP, Sans S, Menotti A, Backer G de, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J. 2003;24:987–1003.

132. Antman EM, Cohen M, Bernink PJ, McCabe CH, Horacek T, Papuchis G, et al. The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. JAMA. 2000;284:835–42.

133. Folsom AR, Kronmal RA, Detrano RC, O'Leary DH, Bild DE, Bluemke DA, et al. Coronary artery calcification compared with carotid intima-media thickness in the prediction of cardiovascular disease incidence: the Multi-Ethnic Study of Atherosclerosis (MESA). Arch Intern Med. 2008;168:1333–9.

134. Martí-Carvajal AJ, Solà I, Lathyris D. Homocysteine-lowering interventions for preventing cardiovascular events. Cochrane Database Syst Rev. 2015;1:CD006612.

135. Techniker Krankenkasse. Prävalenz und Demografie chronisch kranker Versicherter ohne indikationsspezifische pharmakotherapeutische Versorgung. Available at: http://www.tk.de. Accessed 5 May 2013.

136. Bohler S, Scharnagl H, Freisinger F, Stojakovic T, Glaesmer H, Klotsche J, et al. Unmet needs in the diagnosis and treatment of dyslipidemia in the primary care setting in Germany. Atherosclerosis. 2007;190:397–407.

137. Wittchen H-U, Glaesmer H, März W, Stalla G, Lehnert H, Zeiher AM, et al. Cardiovascular risk factors in primary care: methods and baseline prevalence rates--the DETECT program. Curr Med Res Opin. 2005;21:619–30.

138. Catapano AL, Graham I, de Backer G, Wiklund O, Chapman MJ, Drexel H, et al. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. Eur Heart J 2016;37:2999-3058.

139. Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet. 2010;376:1670–81.

140. Delahoy PJ, Magliano DJ, Webb K, Grobler M, Liew D. The relationship between reduction in low-density lipoprotein cholesterol by statins and reduction in risk of cardiovascular outcomes: an updated meta-analysis. Clin Ther. 2009;31:236–44.

141. Taylor F, Huffman MD, Macedo AF, Moore THM, Burke M, Davey Smith G, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2013;1:CD004816.

142. Mihaylova B, Emberson J, Blackwell L, Keech A, Simes J, Barnes EH, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet. 2012;380:581–90.

143. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129:S1-45.

144. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. N Engl J Med. 2015;372:2387–97.

145. Jarcho JA, Keaney JF. Proof That Lower Is Better--LDL Cholesterol and IMPROVE-IT. N Engl J Med. 2015;372:2448–50.

146. Sabatine MS, Giugliano RP, Wiviott SD, Raal FJ, Blom DJ, Robinson J, et al. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. N Engl J Med. 2015;372:1500–9.

147. Kohno T. Report of the American Heart Association (AHA) Scientific Sessions 2014, Chicago. Circ J. 2015;79:34–40.

148. Rahilly-Tierney CR, Lawler EV, Scranton RE, Gaziano JM. Cardiovascular benefit of magnitude of low-density lipoprotein cholesterol reduction: a comparison of subgroups by age. Circulation. 2009;120:1491–7.

149. Nola KM, Gourley DR, Portner TS, Gourley GK, Solomon DK, Elam M, Regel B. Clinical and humanistic outcomes of a lipid management program in the community pharmacy setting. J Am Pharm Assoc (Wash). 2000;40:166–73.

150. Yamada C, Johnson JA, Robertson P, Pearson G, Tsuyuki RT. Long-term impact of a community pharmacist intervention on cholesterol levels in patients at high risk for cardiovascular events: extended follow-up of the second study of cardiovascular risk intervention by pharmacists (SCRIP-plus). Pharmacotherapy. 2005;25:110–5.

151. Lindeman RD, Tobin J, Shock NW. Longitudinal studies on the rate of decline in renal function with age. J Am Geriatr Soc. 1985;33:278–85.

152. Cohen E, Nardi Y, Krause I, Goldberg E, Milo G, Garty M, Krause I. A longitudinal assessment of the natural rate of decline in renal function with age. J Nephrol. 2014;27:635–41.

153. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Circulation. 2003;108:2154–69.

154. Ruilope LM, Salvetti A, Jamerson K, Hansson L, Warnold I, Wedel H, Zanchetti A. Renal function and intensive lowering of blood pressure in hypertensive participants of the hypertension optimal treatment (HOT) study. J Am Soc Nephrol. 2001;12:218–25.

155. Mann JF, Gerstein HC, Pogue J, Bosch J, Yusuf S. Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: the HOPE randomized trial. Ann Intern Med. 2001;134:629–36.

156. Ravera M, Cannavò R, Noberasco G, Guasconi A, Cabib U, Pieracci L, et al. High performance of a risk calculator that includes renal function in predicting mortality of hypertensive patients in clinical application. J Hypertens. 2014;32:1245–54.

157. Vanholder R, Massy Z, Argiles A, Spasovski G, Verbeke F, Lameire N. Chronic kidney disease as cause of cardiovascular morbidity and mortality. Nephrol Dial Transplant. 2005;20:1048–56.

158. Manjunath G, Tighiouart H, Coresh J, Macleod B, Salem DN, Griffith JL, et al. Level of kidney function as a risk factor for cardiovascular outcomes in the elderly. Kidney Int. 2003;63:1121–9.

159. Kaplan B, Mason NA, La Shimp, Ascione FJ. Chronic hemodialysis patients. Part I: Characterization and drug-related problems. Ann Pharmacother. 1994;28:316–9.

160. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16:31–41.

161. Michels WM, Grootendorst DC, Verduijn M, Elliott EG, Dekker FW, Krediet RT. Performance of the Cockcroft-Gault, MDRD, and new CKD-EPI formulas in relation to GFR, age, and body size. Clin J Am Soc Nephrol. 2010;5:1003–9.

162. National Kidney Foundation. Chronic Kidney Disease: Evaluation, Classification and Stratification (2002) Guideline. Available at: https://www.kidney.org/professionals/guidelines/guidelines_commentaries. Accessed 15 Sep 2015.

163. Willems JM, Vlasveld T, den Elzen WP, Westendorp RG, Rabelink TJ, de Craen AJ, Blauw GJ. Performance of Cockcroft-Gault, MDRD, and CKD-EPI in estimating prevalence of renal function and predicting survival in the oldest old. BMC Geriatr. 2013;13:113.

164. Pai MP. Estimating the glomerular filtration rate in obese adult patients for drug dosing. Adv Chronic Kidney Dis. 2010;17:e53-62.

165. Green B, Duffull SB. What is the best size descriptor to use for pharmacokinetic studies in the obese? Br J Clin Pharmacol. 2004;58:119–33.

166. McLeay SC, Morrish GA, Kirkpatrick CMJ, Green B. The relationship between drug clearance and body size: systematic review and meta-analysis of the literature published from 2000 to 2007. Clin Pharmacokinet. 2012;51:319–30.

167. Hallynck TH, Soep HH, Thomis JA, Boelaert J, Daneels R, Dettli L. Should clearance be normalised to body surface or to lean body mass? Br J Clin Pharmacol. 1981;11:523–6.

168. Kidney Disease Improving Global Outcomes-KDIGO. KDIGO 2013 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Available at: http://www.kdigo.org. Accessed 15 Sep 2015.

169. Singh S, Bajorek B. Defining 'elderly' in clinical practice guidelines for pharmacotherapy. Pharm Pract (Granada). 2014;12:489.

170. World Health Organisation-WHO. Definition of an older or elderly person. Available at: http://www.who.int/healthinfo/survey/ageingdefnolder/en/index.html. Accessed 10 Dec 2012.

171. Deutsche Gesellschaft für Geriatrie. Definition Geriatrie. Available at: http://www.dggeriatrie.de/nachwuchs/was-ist-geriatrie.html. Accessed 10 Dec 2012.

172. van den Bussche H, Koller D, Kolonko T, Hansen H, Wegscheider K, Glaeske G, et al. Which chronic diseases and disease combinations are specific to multimorbidity in the elderly? Results of a claims data based cross-sectional study in Germany. BMC Public Health. 2011;11:101.

173. Wolf I-K, Busch M, Lange M, Kamtsiuris P, Doelle R, Richter A, et al. Mortalitäts-Follow-up der Studie zur Gesundheit Erwachsener in Deutschland (DEGS): Methodik und erste Ergebnisse. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2014;57:1331–7.

174. German Center of Gerontology. DZA – Report Altersdaten 1–2/ 2011, Krankheitsspektrum und Sterblichkeit im Alter. Available at: http://www.dza.de/informationsdienste/report-altersdaten.html. Accessed 23 Mar 2015.

175. Gorard DA. Escalating polypharmacy. QJM. 2006;99:797–800.

176. Hovstadius B, Hovstadius K, Astrand B, Petersson G. Increasing polypharmacy - an individual-based study of the Swedish population 2005-2008. BMC Clin Pharmacol. 2010;10:16.

177. Hajjar ER, Cafiero AC, Hanlon JT. Polypharmacy in elderly patients. Am J Geriatr Pharmacother. 2007;5:345–51.

178. Haider SI, Johnell K, Thorslund M, Fastbom J. Trends in polypharmacy and potential drug-drug interactions across educational groups in elderly patients in Sweden for the period 1992 - 2002. Int J Clin Pharmacol Ther. 2007;45:643–53.

179. Flaherty JH, Perry HM, Lynchard GS, Morley JE. Polypharmacy and hospitalization among older home care patients. J Gerontol A Biol Sci Med Sci. 2000;55:M554-9.

180. Payne RA, Abel GA, Avery AJ, Mercer SW, Roland MO. Is polypharmacy always hazardous? A retrospective cohort analysis using linked electronic health records from primary and secondary care. Br J Clin Pharmacol. 2014;77:1073–82.

181. Yach D, Hawkes C, Gould CL, Hofman KJ. The global burden of chronic diseases: overcoming impediments to prevention and control. JAMA. 2004;291:2616–22.

182. Delnoij D, Brenner G. Importing budget systems from other countries: what can we learn from the German drug budget and the British GP fundholding? Health Policy. 2000;52:157–69.

183. Ensing HT, Stuijt CC, van den Bemt BJ, van Dooren AA, Karapinar-Carkit F, Koster ES, Bouvy ML. Identifying the Optimal Role for Pharmacists in Care Transitions: A Systematic Review. J Manag Care Spec Pharm. 2015;21:614–36.

184. Johnson A, Guirguis E, Grace Y. Preventing medication errors in transitions of care: A patient case approach. J Am Pharm Assoc (2003). 2015;55:e264-74.

185. Ashjian E, Salamin LB, Eschenburg K, Kraft S, Mackler E. Evaluation of outpatient medication reconciliation involving student pharmacists at a comprehensive cancer center. J Am Pharm Assoc (2003). 2015;55:540–5.

186. Andrus, Anderson AD. A retrospective review of student pharmacist medication reconciliation activities in an outpatient family medicine center. Pharm Pract (Granada). 2015;13:518.

187. Boockvar KS, Carlson LH, Giambanco V, Fridman B, Siu A. Medication reconciliation for reducing drug-discrepancy adverse events. Am J Geriatr Pharmacother. 2006;4:236–43.

188. Leppee M, Culig J, Mandic K, Eric M. 3Ps--Pharmacist, Physician and Patient: Proposal for Joint Cooperation to Increase Adherence to Medication. West Indian Med J. 2014;63:744–51.

189. Smith M, Bates DW, Bodenheimer T, Cleary PD. Why pharmacists belong in the medical home. Health Aff (Millwood). 2010;29:906–13.

190. Scott MA, Hitch B, Ray L, Colvin G. Integration of pharmacists into a patient-centered medical home. J Am Pharm Assoc (2003). 2011;51:161–6.

191. Carter BL, Ardery G, Dawson JD, James PA, Bergus GR, Doucette WR, et al. Physician and pharmacist collaboration to improve blood pressure control. Arch Intern Med. 2009;169:1996–2002.

192. Muth C, Uhlmann L, Haefeli WE, Rochon J, van den Akker M, Beyer M, et al. PRIorisierung von MUltimedikation bei Multimorbidität (PRIMUM): Cluster-RCT in Hausarztpraxen zeigte keine Effekte auf die Angemessenheit der Verschreibung. 2014. Available at: http://www.egms.de/static/de/meetings/degam2014/14 degam043.shtml. Accessed 22 Aug 2016.

193. Pande S, Hiller JE, Nkansah N, Bero L. The effect of pharmacist-provided non-dispensing services on patient outcomes, health service utilisation and costs in low- and middle-income countries. Cochrane Database Syst Rev. 2013;2:CD010398.

194. Bero LA, Mays NB, Barjesteh K, Bond C. Expanding the roles of outpatient pharmacists: effects on health services utilisation, costs, and patient outcomes. Cochrane Database Syst Rev. 2000:CD000336.

195. Law MR, Ma T, Fisher J, Sketris IS. Independent pharmacist prescribing in Canada. Can Pharm J (Ott). 2012;145:17-23.

196. Tonna AP, Stewart D, West B, McCaig D. Pharmacist prescribing in the UK - a literature review of current practice and research. J Clin Pharm Ther. 2007;32:545–56.

197. Chau SH, Jansen AP, van de Ven PM, Hoogland P, Elders PJ, Hugtenburg JG. Clinical medication reviews in elderly patients with polypharmacy: a cross-sectional study on drug-related problems in the Netherlands. Int J Clin Pharm. 2016;38:46–53.

198. Zermansky AG, Alldred DP, Petty DR, Raynor DK, Freemantle N, Eastaugh J, Bowie P. Clinical medication review by a pharmacist of elderly people living in care homes--randomised controlled trial. Age Ageing. 2006;35:586–91.

199. Rose O, Schaffert C, Czarnecki K, Mennemann HS, Waltering I, Hamacher S, et al. Effect evaluation of an interprofessional medication therapy management approach for multimorbid patients in primary care: a cluster-randomized controlled trial in community care (WestGem study protocol). BMC Fam Pract. 2015;16:84.

200. World Medical Association. Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013;310:2191–4.

201. Medical Research Council. Developing and evaluating complex interventions: new guidance. Available at: www.mrc.ac.uk/documents/pdf/complex-interventions-guidance. Accessed 13 Apr 2012.

202. Hughes CM, McCann S. Perceived interprofessional barriers between community pharmacists and general practitioners: a qualitative assessment. Br J Gen Pract. 2003;53:600–6.

203. Dobson RT, Taylor JG, Henry CJ, Lachaine J, Zello GA, Keegan DL, Forbes DA. Taking the lead: community pharmacists' perception of their role potential within the primary care team. Res Social Adm Pharm. 2009;5:327–36.

204. Rubio-Valera M, Jové AM, Hughes CM, Guillen-Solà M, Rovira M, Fernández A. Factors affecting collaboration between general practitioners and community pharmacists: a qualitative study. BMC Health Serv Res. 2012;12:188.

205. Holt S, Schmiedl S, Thürmann PA. Potentially inappropriate medications in the elderly: the PRISCUS list. Dtsch Arztebl Int. 2010;107:543–51.

206. Unroe KT, Pfeiffenberger T, Riegelhaupt S, Jastrzembski J, Lokhnygina Y, Colon-Emeric C. Inpatient medication reconciliation at admission and discharge: A retrospective cohort study of age and other risk factors for medication discrepancies. Am J Geriatr Pharmacother. 2010;8:115–26.

207. van der Hooft CS, Sturkenboom MC, van Grootheest K, Kingma HJ, Stricker BH. Adverse drug reaction-related hospitalisations: a nationwide study in The Netherlands. Drug Saf. 2006;29:161–8.

208. Budnitz DS, Lovegrove MC, Shehab N, Richards CL. Emergency hospitalizations for adverse drug events in older Americans. N Engl J Med. 2011;365:2002–12.

209. Bundesanzeiger Verlag. Gesetz zur Neuordnung des Arzneimittelmarktes in der gesetzlichen Krankenversicherung (Arzneimittelmarktneuordnungsgesetz - AMNOG). Available at: https://www.bgbl.de. Accessed 18 Jan 2017.

210. Spinewine A, Schmader KE, Barber N, Hughes C, Lapane KL, Swine C, Hanlon JT. Appropriate prescribing in elderly people: how well can it be measured and optimised? Lancet. 2007;370:173–84.

211. Campbell MK, Elbourne DR, Altman DG. CONSORT statement: extension to cluster randomised trials. BMJ. 2004;328:702–8.

212. Brown CA, Lilford RJ. The stepped wedge trial design: a systematic review. BMC Med Res Methodol. 2006;6:54.

213. Woertman W, Hoop E de, Moerbeek M, Zuidema SU, Gerritsen DL, Teerenstra S. Stepped wedge designs could reduce the required sample size in cluster randomized trials. J Clin Epidemiol. 2013;66:752–8.

214. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12:189–98.

215. Tinetti ME. Performance-oriented assessment of mobility problems in elderly patients. J Am Geriatr Soc. 1986;34:119–26.

216. Deutsches Institut für Medizinische Dokumentation und Information, DIMDI. ICD-10-GM. Available at: http://www.dimdi.de. Accessed 14 Apr 2015.

217. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. Med Care. 1986;24:67–74.

218. Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). Arthritis Care Res (Hoboken). 2011;63 Suppl 11:S240-52.

219. Casella G, Berger RL. Statistical inference. 2nd ed. Pacific Grove, Calif.: Duxbury/Thomson Learning; 2002.

220. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972;18:499–502.

221. Martin SS, Blaha MJ, Elshazly MB, Brinton EA, Toth PP, McEvoy JW, et al. Friedewald-estimated versus directly measured low-density lipoprotein cholesterol and treatment implications. J Am Coll Cardiol. 2013;62:732–9.

222. Molnar FJ, Hutton B, Fergusson D. Does analysis using "last observation carried forward" introduce bias in dementia research? CMAJ. 2008;179:751–3.

223. Miller MD, Paradis CF, Houck PR, Mazumdar S, Stack JA, Rifai AH, et al. Rating chronic medical illness burden in geropsychiatric practice and research: application of the Cumulative Illness Rating Scale. Psychiatry Res. 1992;41:237–48.

224. Salvi F, Miller MD, Grilli A, Giorgi R, Towers AL, Morichi V, et al. A manual of guidelines to score the modified cumulative illness rating scale and its validation in acute hospitalized elderly patients. J Am Geriatr Soc. 2008;56:1926–31.

225. Koberlein-Neu J, Mennemann H, Hamacher S, Waltering I, Jaehde U, Schaffert C, Rose O. Interprofessional Medication Management in Patients With Multiple Morbidities. Dtsch Arztebl Int. 2016;113:741–8.

226. Catapano AL, Graham I, de Backer G, Wiklund O, Chapman MJ, Drexel H, et al. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias: The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)Developed with the special contribution of the European Assocciation for Cardiovascular Prevention & Rehabilitation (EACPR). Atherosclerosis. 2016;253:281-344.

227. Rose O, Mennemann H, John C, Lautenschlager M, Mertens-Keller D, Richling K, et al. Priority Setting and Influential Factors on Acceptance of Pharmaceutical Recommendations in Collaborative Medication Reviews in an Ambulatory Care Setting - Analysis of a Cluster Randomized Controlled Trial (WestGem-Study). PLoS ONE. 2016;11:e0156304.

228. Geurts MME, Talsma J, Brouwers, Jacobus R B J, de Gier JJ. Medication review and reconciliation with cooperation between pharmacist and general practitioner and the benefit for the patient: a systematic review. Br J Clin Pharmacol. 2012;74:16–33.

229. Westerlund T, Marklund B. Assessment of the clinical and economic outcomes of pharmacy interventions in drug-related problems. J Clin Pharm Ther. 2009;34:319–27.

230. Hanlon JT, Lindblad CI, Gray SL. Can clinical pharmacy services have a positive impact on drug-related problems and health outcomes in community-based older adults? Am J Geriatr Pharmacother. 2004;2:3–13.

231. Kaufmann CP, Stämpfli D, Hersberger KE, Lampert ML. Determination of risk factors for drug-related problems: a multidisciplinary triangulation process. BMJ Open. 2015;5:e006376.

232. Green JL, Hawley JN, Rask KJ. Is the number of prescribing physicians an independent risk factor for adverse drug events in an elderly outpatient population? Am J Geriatr Pharmacother. 2007;5:31–9.

233. Leendertse AJ, Egberts AC, Stoker LJ, van den Bemt PM. Frequency of and risk factors for preventable medication-related hospital admissions in the Netherlands. Arch Intern Med. 2008;168:1890–6.

234. Chinthammit C, Armstrong EP, Boesen K, Martin R, Taylor AM, Warholak T. Cost-effectiveness of comprehensive medication reviews versus noncomprehensive medication review interventions and subsequent successful medication changes in a Medicare Part D population. J Manag Care Spec Pharm. 2015;21:381–9.

235. Wagner EH. The role of patient care teams in chronic disease management. BMJ. 2000;320:569–72.

236. Pourrat X, Sipert A-S, Gatault P, Sautenet B, Hay N, Guinard F, et al. Community pharmacist intervention in patients with renal impairment. Int J Clin Pharm. 2015;37:1172–9.

237. Zhai XB, Gu ZC, Liu XY. Effectiveness of the clinical pharmacist in reducing mortality in hospitalized cardiac patients: a propensity score-matched analysis. Ther Clin Risk Manag. 2016;12:241–50.

238. Hohl CM, Dankoff J, Colacone A, Afilalo M. Polypharmacy, adverse drug-related events, and potential adverse drug interactions in elderly patients presenting to an emergency department. Ann Emerg Med. 2001;38:666–71.

239. Patel P, Zed PJ. Drug-related visits to the emergency department: how big is the problem? Pharmacotherapy. 2002;22:915–23.

240. van Roon EN, Flikweert S, Le Comte M, Langendijk PN, Kwee-Zuiderwijk WJ, Smits P, Brouwers JR. Clinical relevance of drug-drug interactions: A structured assessment procedure. Drug Saf. 2005;28:1131–9.

241. Bergk V, Gasse C, Rothenbacher D, Loew M, Brenner H, Haefeli WE. Drug interactions in primary care: impact of a new algorithm on risk determination. Clin Pharmacol Ther. 2004;76:85–96.

242. Salpeter SR, Ormiston TM, Salpeter EE. Cardioselective beta-blockers in patients with reactive airway disease: a meta-analysis. Ann Intern Med. 2002;137:715–25.

243. Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J. 2013;34:2949–3003.

244. Tran JN, Kao TC, Caglar T, Stockl KM, Spertus JA, Lew HC, et al. Impact of the 2013 Cholesterol Guideline on Patterns of Lipid-Lowering Treatment in Patients with Atherosclerotic Cardiovascular Disease or Diabetes After 1 Year. J Manag Care Spec Pharm. 2016;22:901–8.

245. Reddel HK, Bateman ED, Becker A, Boulet L-P, Cruz AA, Drazen JM, et al. A summary of the new GINA strategy: a roadmap to asthma control. Eur Respir J. 2015;46:622–39.

246. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J. 2013;34:2159–219.

247. Gerstein HC, Miller ME, Byington RP, Goff DC, JR, Bigger JT, Buse JB, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008;358:2545–59.

248. McGettigan P, Henry D. Cardiovascular risk with non-steroidal anti-inflammatory drugs: systematic review of population-based controlled observational studies. PLoS Med. 2011;8:e1001098.

249. Roberts E, Delgado Nunes V, Buckner S, Latchem S, Constanti M, Miller P, et al. Paracetamol: not as safe as we thought? A systematic literature review of observational studies. Ann Rheum Dis. 2016;75:552–9.

250. Chou R. 2009 Clinical Guidelines from the American Pain Society and the American Academy of Pain Medicine on the use of chronic opioid therapy in chronic noncancer pain: what are the key messages for clinical practice? Pol Arch Med Wewn. 2009;119:469–77.

251. Wilson SJ-A, Wells PS, Kovacs MJ, Lewis GM, Martin J, Burton E, Anderson DR. Comparing the quality of oral anticoagulant management by anticoagulation clinics and by family physicians: a randomized controlled trial. CMAJ. 2003;169:293–8.

APPENDICES

1. Patient information and written informed consent statement
2. Patient identification and participation card
3. Case report form
4. Brown bag review and patient assessment form
5. The Medication Review SOAP form (example)
6. Individual patient data on LDL-cholesterol concentrations (mg/dl)
7. Individual patient data on suggested and rated interventions
8. Response form for the general practitioner on acceptance of the suggested interventions
9. Individual patient data on the acceptance of the GPs

Appendix 1: Patient information and written informed consent statement

Patienteninformation

Prüfstelle/Studienzentrum: _____

_____

_____

Prüfarzt/Studienarzt _____

Prospektive, cluster-randomisierte, kontrollierte Studie zur Untersuchung des Wirksamkeit und der Kosten eines professions- und organisationsübergreifenden Medikationsmanagements bei multimorbiden Patienten mit Polypharmazie

Studien-Code: WestGem – GW 2076

Sehr geehrte Patientin, sehr geehrter Patient,

wir möchten Sie fragen, ob Sie bereit sind, an der nachfolgend beschriebenen Versorgungsstudie teilzunehmen.

Versorgungsstudien sind notwendig, um Erkenntnisse über die Behandlung von Patienten unter Routinebedingungen sowie weitere Erfahrungen und gesicherte Daten zum Versorgungsalltag, insbesondere Daten zu den Therapiekosten und der Lebensqualität sowie zur Sicherheit, Verträglichkeit und Wirksamkeit von zugelassenen Arzneimitteln und deren Kombinationen zu sammeln.
Die Versorgungsstudie, die wir Ihnen hier vorstellen, wird im Kreis Steinfurt und in der Stadt Ahlen durchgeführt; es sollen ca. 240 Personen daran teilnehmen.
Organisiert wird die Studie von der Bergischen Universität Wuppertal und finanziert von der Europäischen Union sowie vom Ministerium für Gesundheit, Emanzipation, Pflege und Alter des Landes Nordrhein-Westfalen.

Ihre Teilnahme an dieser Studie erfolgt freiwillig. Sie werden in diese Versorgungsstudie also nur dann einbezogen, wenn Sie dazu schriftlich Ihre Einwilligung erklären. Sie können jederzeit ohne Angabe von Gründen aus der Studie ausscheiden. Die Ablehnung der Teilnahme oder ein vorzeitiges Ausscheiden aus der Studie hat keine nachteiligen Folgen für Ihre medizinische Betreuung.

Sie wurden bereits auf die geplante Versorgungsstudie angesprochen. Der nachfolgende Text soll Ihnen die Ziele und den Ablauf erläutern. Bevor Sie sich dafür entscheiden, teilzunehmen, lesen Sie bitte dieses Informationsblatt sehr sorgfältig. Anschließend wird Ihr Arzt ein Aufklärungsgespräch mit Ihnen führen. Bitte zögern Sie nicht, alle Punkte anzusprechen, die Ihnen unklar sind. Sie werden danach ausreichend Bedenkzeit erhalten, um über Ihre Teilnahme zu entscheiden.

Zweck der Studie

Versorgungsstudien der letzten Jahre haben eine Zunahme an chronischen Erkrankungen in der Bevölkerung gezeigt. Hiervon betroffen ist vor allem die Gruppe der älteren Patienten, die zudem häufig an mehreren chronischen Erkrankungen gleichzeitig leidet. Diese Patienten müssen oftmals mit verschiedenen Medikamenten behandelt werden, wodurch es immer wieder zu Fällen von unerwünschten Arzneimittelereignissen, besser bekannt als „Nebenwirkungen", kommt.
Von der Durchführung der vorgesehenen Versorgungsstudie erhoffen wir uns neue Erkenntnisse für die Behandlung von Patienten, welche unter mehreren chronischen Erkrankungen leiden, sowie eine Verbesserung der Arzneimitteltherapie im häuslichen Umfeld der Betroffenen. Dies möchten wir über eine enge individuelle Betreuung der Studienteilnehmer durch den gewohnten Hausarzt, der örtlichen Pflege- und Wohnberatung sowie durch die Einbeziehung eines speziell ausgebildeten Apothekers erreichen.

Ablauf der Studie

Bei Aufnahme in die Versorgungsstudie wird ihre medizinische Vorgeschichte aus der Patientenakte erhoben. Die Möglichkeit Ihrer weiteren Teilnahme an dieser Studie wird von Ihrer Vorgeschichte abhängen.
Für eine Teilnahme müssen Sie 65 Jahre oder älter sein und an mindestens drei chronischen Erkrankungen leiden, wovon mindestens eine das Herz-Kreislaufsystem betreffen sollte. Zudem nehmen Sie fünf oder mehr Arzneimittel ein.

Ihre Teilnahme an der Studie wird 12 Monate dauern. Wann und wie oft Sie in dieser Zeit Ihren Arzt aufsuchen, liegt in Ihrem eigenen Ermessen und wird nicht durch die Teilnahme an der Studie bestimmt.
Im Laufe dieser 12 Monate wird sich die für Sie zuständige Pflege- und Wohnberatung bei Ihnen melden, um einen Termin bei Ihnen zu Hause zu vereinbaren. Dort wird der Pflege- und Wohnberater mit Ihnen über Ihre aktuellen Medikamente und Beschwerden sprechen. Zusammen mit Ihrem Hausarzt und speziell ausgebildeten Apothekern wird dann erörtert, ob und wie Ihre Arzneimittelzusammenstellung verbessert werden könnte.
Beratungs- oder Betreuungsangebote, die Sie derzeit bereits nutzen, z.B. einen Pflegedienst oder Ihre Stamm-Apotheke, können Sie auch weiterhin ohne Einschränkungen in Anspruch nehmen. Diese Leistungen werden durch die Teilnahme an der Studie nicht beeinflusst.

Durch Ihre Teilnahme an der Studie stimmen Sie zu, Ihren früheren, aktuellen und zukünftigen Gesundheitszustand zu schildern. Dazu gehören auch finanzielle Belastungen, die Ihnen durch die Krankheiten entstehen und andere Faktoren wie beispielsweise die Zeit, die Familienangehörige oder Bekannte aufbringen, um Sie im Alltag zu unterstützen.
Sie werden gebeten, bei Aufsuchen Ihres Hausarztes einen Erhebungsbogen in Ihrer Arztpraxis auszufüllen. Zudem werden Sie alle drei Monate von Mitarbeitern der Bergischen Universität Wuppertal angerufen werden, um telefonisch einen Fragebogen zu beantworten. Jedes dieser Telefonate wird etwa 20 Minuten beanspruchen.

Unbekannte Risiken

Jedes zugelassene Medikament kann zu Nebenwirkungen führen. Sollte im Rahmen der Studie Ihre Medikation verändert werden und es treten unerwartete Nebenwirkungen auf, besprechen Sie dies bitte umgehend mit Ihrem behandelnden Arzt. Dieser ist für Ihre gesamte Therapie, einschließlich der Überwachung, verantwortlich. Ihr individuelles Arzt-Patienten-Verhältnis wird durch die Studie nicht beeinflusst.

Behandlung persönlicher Daten

Die im Rahmen der geplanten Beobachtungsstudie erhobenen Daten werden in pseudonymisierter Form gesammelt und ausgewertet. Das heißt, dass ihre Daten dabei so verändert werden, dass sie Ihnen nicht mehr zugeordnet werden können. Hierfür werden alle von Ihnen erhobenen Daten mit einer Nummer verschlüsselt, damit Ihre Identität vertraulich bleibt. Nur zwei Personen werden in der Lage sein, diese Nummer Ihrer Person zuzuordnen: Ihr behandelnder Arzt und der zuständige Mitarbeiter der Pflege- und Wohnberatung.

Wir weisen jedoch darauf hin, dass zu Kontrollzwecken speziell autorisierten Personen unter Einhaltung der Datenschutzbestimmungen eine Einsichtnahme in Ihre Krankenakte gestattet werden kann. Mit Ihrem Einverständnis zur Teilnahme an der Studie stimmen Sie auch dieser beschränkten Offenlegung zu. Wir sichern Ihnen zu, dass Ihre personenbezogenen Daten absolut vertraulich behandelt, nicht aus der Arztpraxis herausgetragen oder an unbefugte Dritte weitergegeben werden, insbesondere nicht an die Öffentlichkeit gelangen.
Sie haben das Recht, jederzeit die über Sie erhobenen Daten einzusehen und Informationen, die Sie für falsch halten, zu korrigieren.
Sie können Ihr Einverständnis zur Verwendung Ihrer medizinischen Daten jederzeit zurückziehen. Sollten Sie Ihr Einverständnis zur Verwendung Ihrer Daten zurückziehen, können Sie nicht mehr an der Studie teilnehmen.

Kostenregelung

Durch den Einschluss Ihrer Daten in die Studie entstehen weder für Sie noch für Ihre Krankenkasse zusätzliche Kosten.
Die Studie wird durch die Europäische Union und das Land NRW finanziell gefördert.

Fragen zur Studie

Ihr Arzt wird Ihnen vor und während der Studie gerne jede Frage beantworten.

Wenn Sie nun keine weiteren Fragen mehr haben und sich für eine Teilnahme an der Studie entschieden haben, dann unterschreiben Sie bitte die beiliegende Einwilligungserklärung sowie die Einverständniserklärung zur Datenerfassung.
Sie erhalten dann von der Patienteninformation und Ihren Einverständniserklärungen jeweils eine Kopie für Ihre persönlichen Unterlagen.

Bei weiteren Fragen im Zusammenhang mit dieser Studie oder zu Ihrer Therapie wenden Sie sich bitte an Ihren behandelnden Arzt:

(Praxisstempel & Telefon)

Praxis-ID ☐☐-☐☐☐ Studien-ID ☐☐-☐☐

WestGem-Studie

Praxis-ID ☐☐-☐☐☐ Studien-ID ☐☐-☐☐

Einwilligungserklärung des Patienten

Prospektive, cluster-randomisierte, kontrollierte Studie zur Untersuchung des Wirksamkeit und der Kosten eines professions- und organisationsübergreifenden Medikationsmanagements bei multimorbiden Patienten mit Polypharmazie

Studien-Code: WestGem – GW 2076

- Ich bin in einem persönlichen Gespräch durch meinen behandelnden Arzt über die Studie sowie über das Wesen, Bedeutung, Risiken und Tragweite dieser Versorgungsstudie aufgeklärt worden.
- Ich hatte Gelegenheit, mit meinem behandelnden Arzt über den Gegenstand und den Ablauf der Studie zu sprechen und Fragen zu stellen, die alle zu meiner Zufriedenheit beantwortet wurden.
- Ich hatte ausreichend Zeit, über eine Teilnahme an der Studie zu entscheiden und ich stimme freiwillig zu, an dieser teilzunehmen.
- Ich habe den Inhalt der Patienteninformation sowie der Datenschutzerklärung gelesen und verstanden.

Hiermit gebe ich mein Einverständnis für die Teilnahme an der Studie unter dem Vorbehalt, jederzeit von der Studie - auch ohne Angabe von Gründen - zurückzutreten, ohne dass mir daraus Nachteile für meine medizinische Behandlung entstehen.

Ich habe jede Seite der Patienteninformation, der Einwilligungserklärung sowie der Datenschutzerklärung gelesen und mir wurde je ein Exemplar davon ausgehändigt.

_____
Name des Patienten in Druckbuchstaben

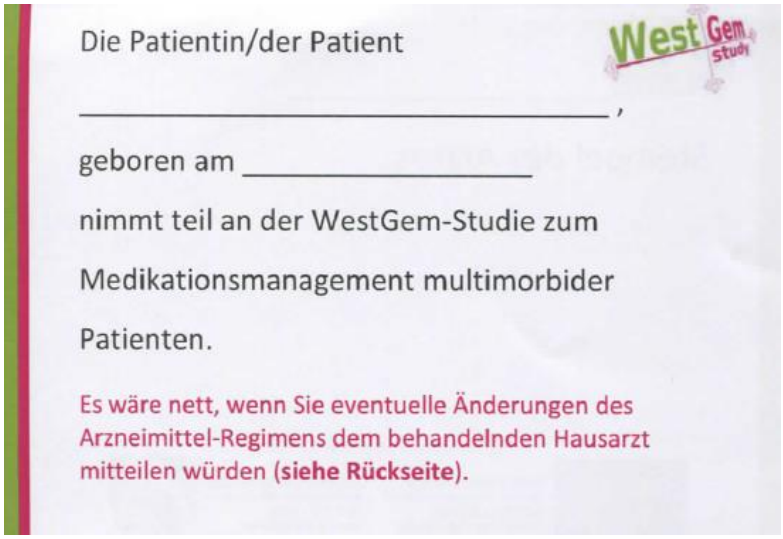
_____
Ort, Datum Unterschrift des Patienten

Ich habe das Aufklärungsgespräch geführt und die Einwilligung des Patienten eingeholt.

_____
Name des behandelnden Arztes in Druckbuchstaben

_____
Ort, Datum Unterschrift des behandelnden Arztes

Appendix 2: Patient identification and participation card



Die Patientin/der Patient

WestGem study

_____,

geboren am _____

nimmt teil an der WestGem-Studie zum Medikationsmanagement multimorbider Patienten.

Es wäre nett, wenn Sie eventuelle Änderungen des Arzneimittel-Regimens dem behandelnden Hausarzt mitteilen würden (**siehe Rückseite**).

Name_____

Stempel des Arztes:

WestGem-Studie, ein gefördertes Projekt:

EUROPÄISCHE UNION
Investition in unsere Zukunft
Europäischer Fonds
für regionale Entwicklung

Ministerium für Gesundheit, Emanzipation, Pflege und Alter des Landes Nordrhein-Westfalen

Appendix 3: Case report form

WestGem-Studiengruppe vertreten durch:

Bergisches Kompetenzzentrum für Gesundheitsmanagement und Public Health

Bergische Universität Wuppertal

Rainer-Gruenter-Str. 21

42119 Wuppertal

Case Report Form (CRF) für den Hausarzt

Prospektive, cluster-randomisierte, kontrollierte Studie zur Untersuchung der Wirksamkeit und der Kosten eines professions- und organisationsübergreifenden Medikationsmanagements bei multimorbiden Patienten mit Polypharmazie

Kurztitel: Medikationsmanagement bei multimorbiden Patienten

Studien-Code: WestGem – GW 2076

Studiennummer |__|__|

Studienzentrum |__|__|

Studien-ID |__|__| - |__|__|
Zentrum - Studiennummer

Stempel des Studienzentrums:

Studienkoordination:
Jr.-Prof. Dr. Juliane Köberlein-Neu
Bergisches Kompetenzzentrum für Gesundheitsmanagement und Public Health
Tel.: 0202/439-1381
Fax: 0202/439-138

WestGem-Studie: Medikationsmanagement bei multimorbiden Patienten

Studien-ID |__|__| - |__|__| Datum: |__|__|.|__|__|.|__|__|__|__| Doku **1**
Zentrum - Studiennummer

Eingangsuntersuchung

EINSCHLUSSKRITIERIEN

Kriterien		**Ja**	**Nein**
Alter	65 oder älter	☐	☐
Diagnose	mindestens drei chronische Erkrankungen aus zwei verschiedenen Organsystemen	☐	☐
	mindestens eine kardiovaskuläre Erkrankung	☐	☐
	mindestens eine Erkrankung muss bereits seit drei oder mehr Quartalen der letzten 12 Monate bestehen	☐	☐
Medikation	fünf oder mehr Dauermedikationen (> 3 Monate) mit systemischen Effekten	☐	☐
Kontakt	mindestens ein Besuch beim Hausarzt in jedem der letzten 3 Quartale	☐	☐
Bereitschaft	Patient ist mit der Studienteilnahme einverstanden und hat die Einverständniserklärung unterzeichnet	☐	☐

Falls eine der obigen Fragen mit "Nein" beantwortet wurde,
darf der Patient nicht in die Studie eingeschlossen werden.

AUSSCHLUSSKRITERIEN

Kriterien		**Ja**	**Nein**
Diagnose	Erkrankung, die eine Lebenserwartung von weniger als 12 Monaten bedingt	☐	☐
sonstiges	Patient hat innerhalb der letzten 30 Tage an einer anderen Studie teilgenommen	☐	☐

Falls eine der obigen Fragen mit " Ja " beantwortet wurde,
darf der Patient nicht in die Studie eingeschlossen werden.

Der Patienten-Fragebogen für die Dokumentation 1 wurde dem Patienten ausgehändigt ☐ **ja**

WestGem-Studie: Medikationsmanagement bei multimorbiden Patienten

Studien-ID |__|__| - |__|__| (Zentrum / Studiennummer) Datum: |__|__| |__|__|.|__|__|__|__| Doku **1**

Eingangsuntersuchung

PATIENTENIDENTIFIKATION

Geburtsdatum: |__|__|.|__|__|.|__|__|__|__|

Größe: |__|__|__| cm Gewicht: |__|__|__| kg

RR: |___/___| mmHg HF: |____|

Geschlecht: ☐ männlich ☐ weiblich

Wie ist der Patient krankenversichert?

☐ ausschließlich privat versichert

☐ in einer gesetzlichen Krankenversicherung

☐ AOK ☐ DAK ☐ IKK

☐ Knappschaft ☐ BarmerGEK ☐ TK

☐ KKH/Allianz ☐ sonstige: _____

Liegt beim Patienten eine Pflegestufe vor?

☐ nicht bekannt ☐ Nein ☐ Ja, welche: _____

ANAMNESE

Leidet der Patient an Allergien oder bestimmten Unverträglichkeiten?

☐ Nein ☐ Ja

Wenn ja, welche?

Allergien/Unverträglichkeiten	

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Eingangsuntersuchung

AKUTE UND CHRONISCHE ERKRANKUNGEN

An welchen akuten und chronischen Erkrankungen litt der Patient in den letzten sechs Monaten einschließlich heute?

Bitte geben Sie bei jeder Diagnose an, ob die Erkrankung chronisch verläuft.

Zeitraum seit bzw. Tag.Monat-Tag.Monat	**Diagnose (ICD-10 Codierung)**	**chronisch**
		☐
		☐
		☐
		☐
		☐
		☐
		☐
		☐
		☐
		☐
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		☐
		☐
		☐
		☐
		☐

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Eingangsuntersuchung

BEEINTRÄCHTIGUNG DER ORGANSYSTEME

Bitte beurteilen Sie den Schweregrad der Beschwerden, die in den aufgeführten Organsystemen vorliegen. Bei jedem Organsystem ist eine Eintragung vorzunehmen. Je Organsystem kann jeweils nur eine Stufe vergeben werden.
Sollten beim Patienten mehrere Beschwerden innerhalb eines Organsystems vorliegen, gehen Sie bei Ihrer Einschätzung bitte von den Beschwerden mit der größtmöglichen Beeinträchtigung aus.

Organsystem	Stufe 0	Stufe 1	Stufe 2	Stufe 3	Stufe 4
Herz	☐	☐	☐	☐	☐
Bluthochdruck und Gefäße	☐	☐	☐	☐	☐
Blutbildendes und lymphatisches System	☐	☐	☐	☐	☐
Lunge und Atemwege	☐	☐	☐	☐	☐
HNO und Augen	☐	☐	☐	☐	☐
Oberer Gastrointestinaltrakt	☐	☐	☐	☐	☐
Unterer Gastrointestinaltrakt	☐	☐	☐	☐	☐
Leber, Galle und Pankreas	☐	☐	☐	☐	☐
Nieren	☐	☐	☐	☐	☐
Urogenitaltrakt	☐	☐	☐	☐	☐
Bewegungsapparat und Haut	☐	☐	☐	☐	☐
Nervensystem	☐	☐	☐	☐	☐
Endokrinium, Brustdrüse und Stoffwechselstörungen	☐	☐	☐	☐	☐
Psychische Störung	☐	☐	☐	☐	☐

Stufe 0: Keine Erkrankung;
Stufe 1 milde oder überstandene schwere Erkrankung;
Stufe 2: mäßige Funktionsstörung oder Erkrankung, Basistherapie erforderlich;
Stufe 3: schwere, chronische Funktionsstörungen, nicht beherrschbare chronische Erkrankung;
Stufe 4: sehr schwere Funktionsstörungen, sofortige Therapie erforderlich, Organversagen

Studien-ID |__|__| - |__|__| Datum: |__|__|.|__|__|.|__|__|__|__| Doku **1**
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Eingangsuntersuchung

MOBILITÄT UND STURZGEFAHR

Der Test ist in eine Untersuchung des Gleichgewichts (Stand und Balance) sowie des Gehens unterteilt.

Teil 1: Gleichgewicht

Kriterien			**Punkte**
Gleichgewicht (im Sitzen)	unsicher	☐	0
	sicher, stabil (ohne Lehne zu gebrauchen)	☐	1
Aufstehen vom Stuhl	nicht möglich	☐	0
	nur mit Hilfe möglich	☐	1
	diverse Versuche, rutscht nach vorne	☐	2
	braucht Armlehne oder Halt	☐	3
	in einer fließenden Bewegung	☐	4
Balance (in den ersten 5 Sekunden nach dem Aufstehen)	unsicher (starkes Schwanken, sucht Halt)	☐	0
	sicher, aber nur mit Halt	☐	1
	sicher, ohne Halt	☐	2
Stehsicherheit	unsicher (starkes Schwanken, sucht Halt)	☐	0
	sicher, aber ohne geschlossene Füße	☐	1
	sicher mit geschlossenen Füßen	☐	2
Balance (mit geschlossenen Augen und Füßen	unsicher (starkes Schwanken, sucht Halt)	☐	0
	sicher, ohne Halt, geschlossene Füße	☐	1
Drehung 360° (mit offenen Augen)	unsicher (starkes Schwanken, sucht Halt)	☐	0
	diskontinuierlich (Patient setzt den einen Fuß ganz auf den Boden ab, bevor er den anderen hebt)	☐	1
	kontinuierlich und sicher, ohne Halt	☐	2
Stoß gegen die Brust (leicht)	würde ohne Hilfe oder Halt fallen	☐	0
	muss Korrekturschritte ausführen	☐	1
	gibt sicheren Widerstand	☐	2
Hinsetzen	lässt sich plumpsen, braucht Lehne	☐	0
	flüssige Bewegung, fähig sich fließend zu setzten	☐	1
	Gesamtpunktzahl Teil 1		.....

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Eingangsuntersuchung

FORTSETZUNG MOBILITÄT UND STURZGEFAHR

Teil 2: Gehen

Kriterien			Punkte
Schrittauslösung	Gehen ohne fremde Hilfe nicht möglich	☐	0
	zögert, mehrere Versuche, stockender Beginn	☐	1
	beginnt zu gehen ohne zu zögern	☐	2
Schritthöhe (von der Seite beobachtet)	Gehen ohne fremde Hilfe nicht möglich	☐	0
	Schlurfen oder übertriebenes Hochziehen	☐	1
	Fuß berührt Boden nicht, normale Schritthöhe	☐	2
Schrittlänge	Gehen ohne fremde Hilfe nicht möglich	☐	0
	weniger als Fußlänge	☐	1
	mindestens Fußlänge	☐	2
Schrittsymetrie (von der Seite beobachtet)	Schrittlänge variiert oder Patient hinkt	☐	0
	Schrittlänge ist beidseits gleich	☐	1
Gangkontinuität	Schrittlänge variiert oder Patient hinkt	☐	0
	Phasen mit beiden Beinen am Boden	☐	1
	beim Absetzen des einen Fußes wird der andere gehoben	☐	2
Wegabweichung (von hinten beobachtet)	der Fuß weicht mal auf die eine, mal auf die andere Seite ab oder ständig in eine Richtung	☐	0
	leichte Abweichung	☐	1
	Füße werden entlang einer geraden imaginären Linie abgesetzt	☐	2
Rumpfstabilität (von hinten beobachtet)	Rücken und Knie nicht gestreckt, unsicher, Arme werden zur Stabilisierung benötigt	☐	0
	Rücken und Knie gestreckt, kein Schwanken	☐	1
Schrittbreite (von hinten beobachtet)	Gang breitbeinig oder überkreuzt	☐	0
	Füße berühren sich beinahe beim gehen	☐	1
		Gesamtpunktzahl Teil 2	.....

WestGem-Studie: Medikationsmanagement bei multimorbiden Patienten

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Eingangsuntersuchung

KOGNITION

Teil 1: Zeitliche Orientierung

Kenntnis des heutigen Datums		**Ja**	**Nein**
Bitte erfragen Sie vom Patienten den Tag.	Korrekt wiedergegeben?	☐	☐
Bitte erfragen Sie vom Patienten den Monat.	Korrekt wiedergegeben?	☐	☐
Bitte erfragen Sie vom Patienten das Jahr.	Korrekt wiedergegeben?	☐	☐

Teil 2: Merkfähigkeit

Bitte lesen Sie dem Patienten die folgende Wortliste langsam vor Lassen Sie sich anschließend vom Patienten alle Wörter nennen, an die er sich erinnern kann. Auf die Reihenfolge kommt es dabei nicht an. Versichern Sie dem Patienten, dass die meisten Menschen sich nur an einige Wörter erinnern.

Bitte kreuzen Sie die Wörter in der Liste an, die der Patient genannt hat.

- Butter ☐
- Arm ☐
- Brief ☐
- Königin ☐
- Karte ☐
- Gras ☐
- Ecke ☐
- Stein ☐
- Buch ☐
- Stock ☐
- Keines davon ☐

Teil 3: Benennen

Bitten Sie den Patienten, so viele verschiedene Tiere zu nennen, wie ihm einfallen. Geben Sie ihm dafür eine Minute Zeit.

Anzahl der genannten Tiere: _____

Studien-ID |__|__| - |__|__| Datum: |__|__|.|__|__|.|__|__|__|__| Doku 1
Zentrum Studiennummer

Eingangsuntersuchung

Teil 4: Aufmerksamkeit und Rechnen

Bitten Sie den Patienten, bei 100 beginnend in 7er Schritten rückwärts zu zählen. Halten Sie nach 5 Subtraktionen (93, 86, 79, 72, 65) an und zählen Sie die in der richtigen Reihenfolge gegebenen Antworten.
Bitten Sie daraufhin das Wort **"Preis"** rückwärts zu buchstabieren. Die Wertung entspricht der Anzahl von Buchstaben in der richtigen Reihenfolge (z.B. SIERP=5, SIREP=3). Die höhere der beiden Wertungen, d.h. Rechenaufgabe oder Buchstabieren wird gezählt.

Welche Punktezahl hat der Patient erreicht? _____

Teil 5: Erinnerung

Fragen Sie den Patienten, an wie viele Wörter der in Teil 2 vorgelesenen Liste er sich erinnert. Lassen Sie sich die Wörter aufzählen.

Anzahl der Wörter _____

Erreichte Gesamtpunktzahl: _____ Punkte

LABORUNTERSUCHUNGEN

Bitte tragen Sie hier die zuletzt verfügbaren Laborparameter ein. Diese können alternativ auch ausgedruckt und beigelegt werden.

Parameter	Wert	Einheit	Datum des Befunds
Natrium			
Kalium			
Glucose			
Harnsäure			
Serum-Kreatinin		mg/dL	
Leberwerte			
ALAT/ALT/SGPT		U/L	
AST/ASAT/SGOT		U/L	
Lipidwerte			
LDL		mg/dL	

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Eingangsuntersuchung

Trigylceride		mg/dL	
HDL		mg/dL	
Blutbild			
Leukozyten		Tsd./µl	
Erythrozyten		Mio./µl	
Hämoglobin		g/dl	
Hämatokrit		%	
Thrombozyten		Tsd./µ	
Diagnoseabhängige Werte			
CRP		mg/L	
INR			
HbA_{1c}		%	
FEV1		%	
TSH		mU/L	

MEDIKATION UND THERAPIE

Bitte tragen Sie hier **alle Medikamente** ein, die der Patient nach Ihrem Wissen in den letzten 6 Monaten eingenommen hat oder aktuell einnimmt.

Name/Wirkstoff/Darreichungsform	**(tägl.) Dosis** mg/ml/Tropfen	**Häufigkeit der Verabreichung** z.B. 1-0-1	**Einnahmezeitraum** seit bzw. Tag.Monat-Tag.Monat

WestGem-Studie: Medikationsmanagement bei multimorbiden Patienten

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Eingangsuntersuchung

Fortsetzung: Medikamente der letzten 6 Monate

Name/Wirkstoff/Darreichungsform	**(tägl.) Dosis** mg/ml/Tropfen	**Häufigkeit der Verabreichung** z.B. 1-0-1	**Einnahmezeitraum** seit bzw. Tag.Monat-Tag.Monat

Bitte tragen Sie alle Heilmittel (z.B. Physiotherapie, Ergotherapie) ein, die der Patient nach Ihrem Wissen in den letzten 6 Monaten erhalten hat oder aktuell erhält.

Therapeut/Fachrichtung	**Leistung**	**Anzahl der Leistungen/ Einheiten**	**Zeitraum** seit bzw. Tag.Monat-Tag.Monat

Studien-ID |__|__| - |__|__| (Zentrum / Studiennummer) Datum: |__|__|.|__|__|.|__|__|__|__| Doku **1**

Eingangsuntersuchung

Bitte tragen Sie alle Hilfsmittel (z.B. Hörgerät, Rollstuhl) ein, die der Patient nach Ihrem Wissen in den letzten 6 Monaten erhalten hat.

Name des Hilfsmittels	Datum Tag.Monat.Jahr

UNERWÜNSCHTE ARZEIMITTELEREIGNISSE

Hat der Patient in den letzten sechs Monaten von Beschwerden berichtet, die in Zusammenhang mit seiner Medikation stehen könnten?

☐ Nein ☐ Ja

Wenn ja, welche?

Art	Beschreibung
Allergische Reaktionen (z.B. Hautausschlag, Juckreiz)	
Blutungen (z.B. Einblutung, Nasenbluten)	
Gastrointestinale Probleme (z.B. Durchfall, Übelkeit, Erbrechen)	
Kardiovaskuläre Probleme (z.B. Hypotonie, neue Ödeme)	
Neurobiologische Probleme (z.B. Schwindel, Gleichgewichtsstörungen)	
Psychiatrische Probleme (z.B. Verwirrtheit, Somnolenz, Delir)	
Rettungsdienstliche Maßnahmen (z.B. Hausärztlicher Notdienst, Notarzt)	

Studien-ID |__|__| - |__|__| (Zentrum / Studiennummer) Datum: |__|__|.|__|__|.|__|__|__|__| Doku **1**

Eingangsuntersuchung

AMBULANTE VERSORGUNG

Wie viele Arztbesuche des Patienten fanden in den letzten sechs Monaten bei Ihnen statt?

Gesamtzahl: _____

Beratungs-/Behandlungsgrund	Gebührenordnung	Ziffer
	☐ EBM ☐ GOÄ	
	☐ EBM ☐ GOÄ	
	☐ EBM ☐ GOÄ	
	☐ EBM ☐ GOÄ	
	☐ EBM ☐ GOÄ	
	☐ EBM ☐ GOÄ	
	☐ EBM ☐ GOÄ	
	☐ EBM ☐ GOÄ	
	☐ EBM ☐ GOÄ	
	☐ EBM ☐ GOÄ	

Welche Arztbesuche des Patienten fanden nach Ihrem Wissen in den letzten sechs Monaten bei anderen niedergelassene Ärzten/Fachärzten statt?

Fachrichtung	Behandlungsgrund

WestGem-Studie: Medikationsmanagement bei multimorbiden Patienten

Studien-ID |__|__| - |__|__| (Zentrum / Studiennummer) Datum: |__|__|.|__|__|.|__|__|__|__| Doku **1**

Eingangsuntersuchung

KRANKENHAUSAUFENTHALTE

Wurde der Patienten in den letzten sechs Monaten stationär behandelt?

☐ Nein ☐ Ja, _____ mal

Grund der Aufnahme Diagnose	**DRG** wenn vorhanden	**Maßnahme** z.B. Beobachtung, OP	**Zeitraum** Tag.Monat.Jahr	**Einweisung**
				☐ elektiv ☐ eigenständig ☐ Rettungsdienst
				☐ elektiv ☐ eigenständig ☐ Rettungsdienst
				☐ elektiv ☐ eigenständig ☐ Rettungsdienst
				☐ elektiv ☐ eigenständig ☐ Rettungsdienst
				☐ elektiv ☐ eigenständig ☐ Rettungsdienst

REHABILITATION

Fand im Anschluss an einen Krankenhausaufenthalt in den letzten sechs Monaten ein Reha-Aufenthalt statt?

☐ Nein ☐ Ja

Wenn ja, welche?

Rehabilitationsgrund Diagnose	**Fachabteilung** falls bekannt	**Zeitraum** Tag.Monat.Jahr

Datum:_____ Unterschrift Ärztin/Arzt:_____

Appendix 4: Brown bag review and patient assessment form

Studien-ID 0 - 0 Datum: 18.02.2015 **Assessment zur Arzneimitteltherapie**

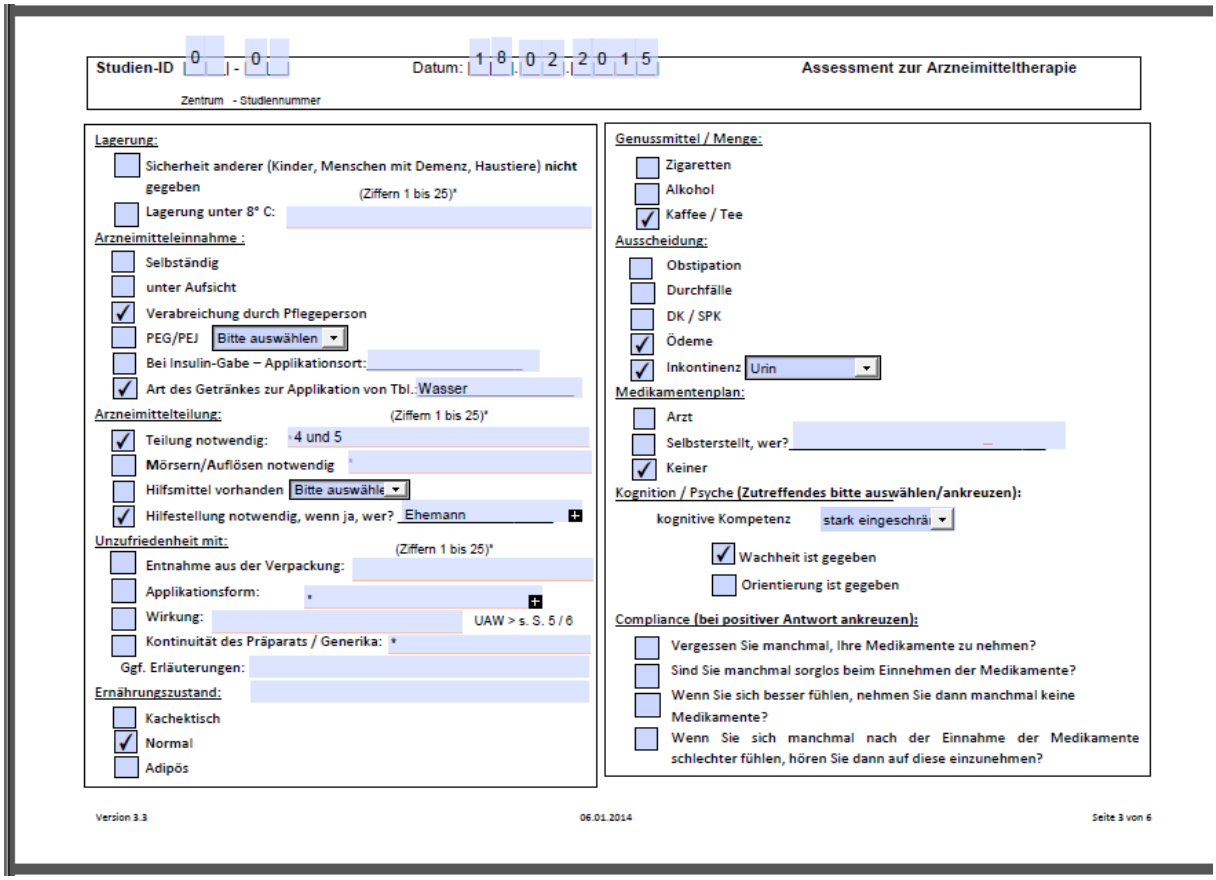
Zentrum - Studiennummer

Arzneimittelname Wirkstoff in mg Namenzusatz (forte, etc.) PZN	Herkunft: (Fach)Arzt, Selbstmed.	Dosis z.B. (bei Bed.-Med. Einzeldosis eintragen) ½ - 0- ½	Darreich-ungsform (bei Insulingabe: Pen? Nadelwechsel?)	Tägl. (T) Bedarfsmed. (B) (Tagesdosis eintragen)	Dispensierinter valle (wöchtl., tgl., situativ, gar nicht)	Einnahme-zeitpunkt Nüchtern, Mit dem Essen	Indikation lt. Patient
1. Decortin H 5 mg 0263047	Arzt	1-0-0	Tbl.	T	tgl.	M	nicht bekannt
2. Concor 5 mg 02091573	Arzt	1-0-0	w.o.	T	tgl.	M	w.o.
3. Esomeprazol TAD 20 mg	Arzt	1-0-0	Kps.	T	tgl.	M	w.o.
4. HCT 25 mg 6453257	Arzt	1/2 Tbl. (ca. 1-2 x wöch.) Dosis	w.o.	B, 1/2 Tbl. (ca. 1-2 x wöch.)	situativ	M	w.o.
5. Phenprogamma 3 mg 2704917	Arzt	1/4 Tbl. tgl., 1 Tag keine Tbl.	w.o.	T	tgl.	M	
6. Risperidon 0,25 mg 6322727	abgesetzt						
7. Novodigal mite 0,1 mg 1414488	Arzt	1-0-0	w.o.	T	tgl.	M	nicht bekannt
8. Voltaren resinat 145,6 mg	Arzt	1 x tgl. (ca. alle 2 Tage)	Kps.	B, (ca. alle 2 Tage)	situativ	M	Schmerzen
9. Dekristol 20000IE 4007393	abgesetzt						
10. Dulcolax	abgesetzt						
11. Novaminsulfon 500 mg 1384563	abgesetzt						
12. Dolormin Extra 400 mg 0091089	abgesetzt						
13. Voltaren forte Gel	selbst	tgl.	Gel	B	w.o.		Schmerzen

Studien-ID 0 - 0 Datum: 18.02.2015 **Assessment zur Arzneimitteltherapie**

Zentrum - Studiennummer

Arzneimittelname Wirkstoff in mg Namenzusatz (forte, etc.) PZN	Herkunft: (Fach)Arzt, Selbstmed.	Dosis z.B. (bei Bed.-Med. Einzeldosis eintragen) ½ - 0- ½	Darreich-ungsform (bei Insulingabe: Pen? Nadelwechsel?)	Tägl. (T) Bedarfsmed. (B) (Tagesdosis eintragen)	Dispensierinter valle (wöchtl., tgl., situativ, gar nicht)	Einnahme-zeitpunkt Nüchtern, Mit dem Essen	Indikation lt. Patient
14. Quetiapin 25 mg 9090051	Arzt (neu)	2-0-3	Tbl.	T	tgl.	M	Demenz
15.							
16.							



Studien-ID 0 0 - 0 0 (Zentrum - Studiennummer) Datum: 18.02.2015 **Assessment zur Arzneimitteltherapie**

Lagerung:
- ☐ Sicherheit anderer (Kinder, Menschen mit Demenz, Haustiere) **nicht** gegeben (Ziffern 1 bis 25)*
- ☐ Lagerung unter 8° C:

Arzneimitteleinnahme :
- ☐ Selbständig
- ☐ unter Aufsicht
- ☑ Verabreichung durch Pflegeperson
- ☐ PEG/PEJ Bitte auswählen
- ☐ Bei Insulin-Gabe – Applikationsort:
- ☑ Art des Getränkes zur Applikation von Tbl.: Wasser

Arzneimittelteilung: (Ziffern 1 bis 25)*
- ☑ Teilung notwendig: 4 und 5
- ☐ Mörsern/Auflösen notwendig
- ☐ Hilfsmittel vorhanden Bitte auswähle
- ☑ Hilfestellung notwendig, wenn ja, wer? Ehemann

Unzufriedenheit mit: (Ziffern 1 bis 25)*
- ☐ Entnahme aus der Verpackung:
- ☐ Applikationsform:
- ☐ Wirkung: UAW > s. S. 5 / 6
- ☐ Kontinuität des Präparats / Generika:

Ggf. Erläuterungen:

Ernährungszustand:
- ☐ Kachektisch
- ☑ Normal
- ☐ Adipös

Genussmittel / Menge:
- ☐ Zigaretten
- ☐ Alkohol
- ☑ Kaffee / Tee

Ausscheidung:
- ☐ Obstipation
- ☐ Durchfälle
- ☐ DK / SPK
- ☑ Ödeme
- ☑ Inkontinenz Urin

Medikamentenplan:
- ☐ Arzt
- ☐ Selbsterstellt, wer?
- ☑ Keiner

Kognition / Psyche (Zutreffendes bitte auswählen/ankreuzen):

kognitive Kompetenz: stark eingeschrä

- ☑ Wachheit ist gegeben
- ☐ Orientierung ist gegeben

Compliance (bei positiver Antwort ankreuzen):
- ☐ Vergessen Sie manchmal, Ihre Medikamente zu nehmen?
- ☐ Sind Sie manchmal sorglos beim Einnehmen der Medikamente?
- ☐ Wenn Sie sich besser fühlen, nehmen Sie dann manchmal keine Medikamente?
- ☐ Wenn Sie sich manchmal nach der Einnahme der Medikamente schlechter fühlen, hören Sie dann auf diese einzunehmen?

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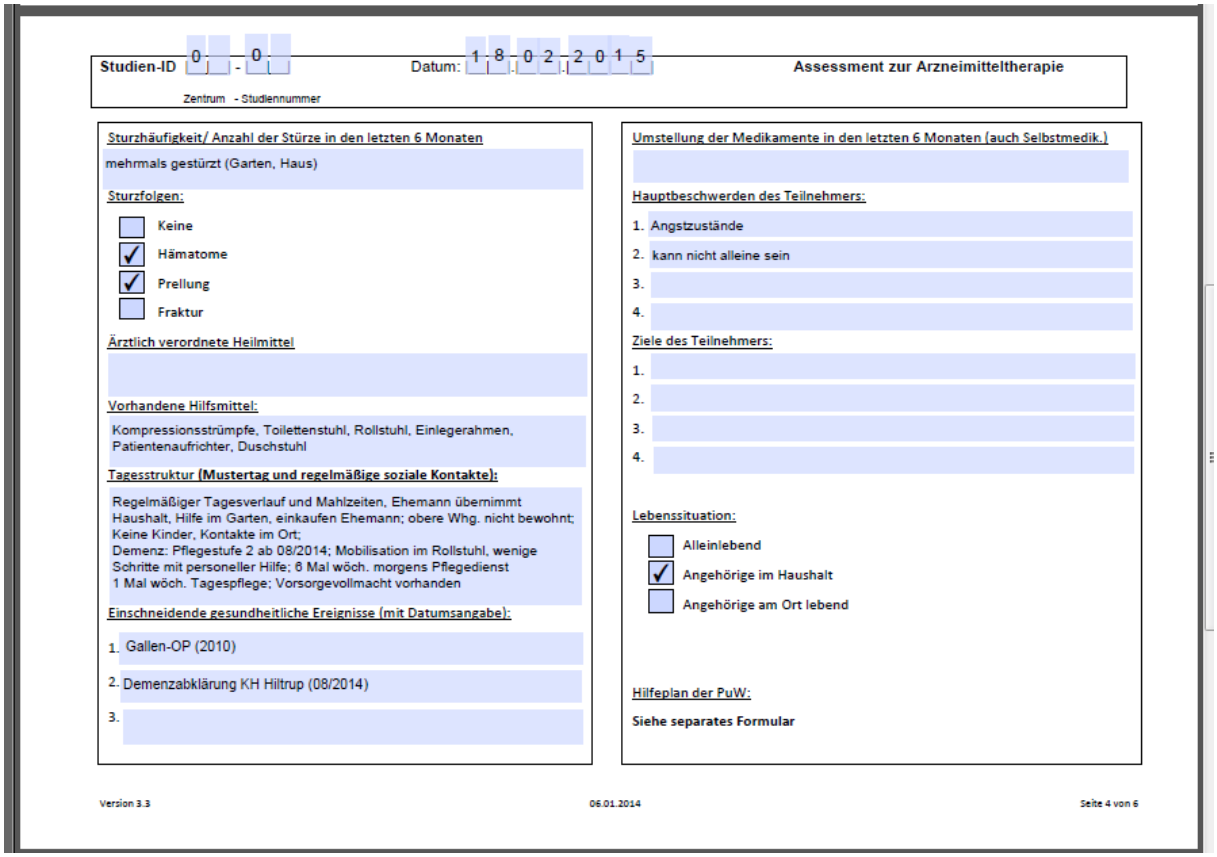

Studien-ID 0 - 0 Datum: 18.02.2015 **Assessment zur Arzneimitteltherapie**

Zentrum - Studiennummer

Sturzhäufigkeit/ Anzahl der Stürze in den letzten 6 Monaten

mehrmals gestürzt (Garten, Haus)

Sturzfolgen:

- ☐ Keine
- ☑ Hämatome
- ☑ Prellung
- ☐ Fraktur

Ärztlich verordnete Heilmittel

Vorhandene Hilfsmittel:

Kompressionsstrümpfe, Toilettenstuhl, Rollstuhl, Einlegerahmen, Patientenaufrichter, Duschstuhl

Tagesstruktur (Mustertag und regelmäßige soziale Kontakte):

Regelmäßiger Tagesverlauf und Mahlzeiten, Ehemann übernimmt Haushalt, Hilfe im Garten, einkaufen Ehemann; obere Whg. nicht bewohnt; Keine Kinder, Kontakte im Ort;
Demenz: Pflegestufe 2 ab 08/2014; Mobilisation im Rollstuhl, wenige Schritte mit personeller Hilfe; 6 Mal wöch. morgens Pflegedienst
1 Mal wöch. Tagespflege; Vorsorgevollmacht vorhanden

Einschneidende gesundheitliche Ereignisse (mit Datumsangabe):

1. Gallen-OP (2010)
2. Demenzabklärung KH Hiltrup (08/2014)
3.

Umstellung der Medikamente in den letzten 6 Monaten (auch Selbstmedik.)

Hauptbeschwerden des Teilnehmers:

1. Angstzustände
2. kann nicht alleine sein
3.
4.

Ziele des Teilnehmers:

1.
2.
3.
4.

Lebenssituation:

- ☐ Alleinlebend
- ☑ Angehörige im Haushalt
- ☐ Angehörige am Ort lebend

Hilfeplan der PuW:

Siehe separates Formular

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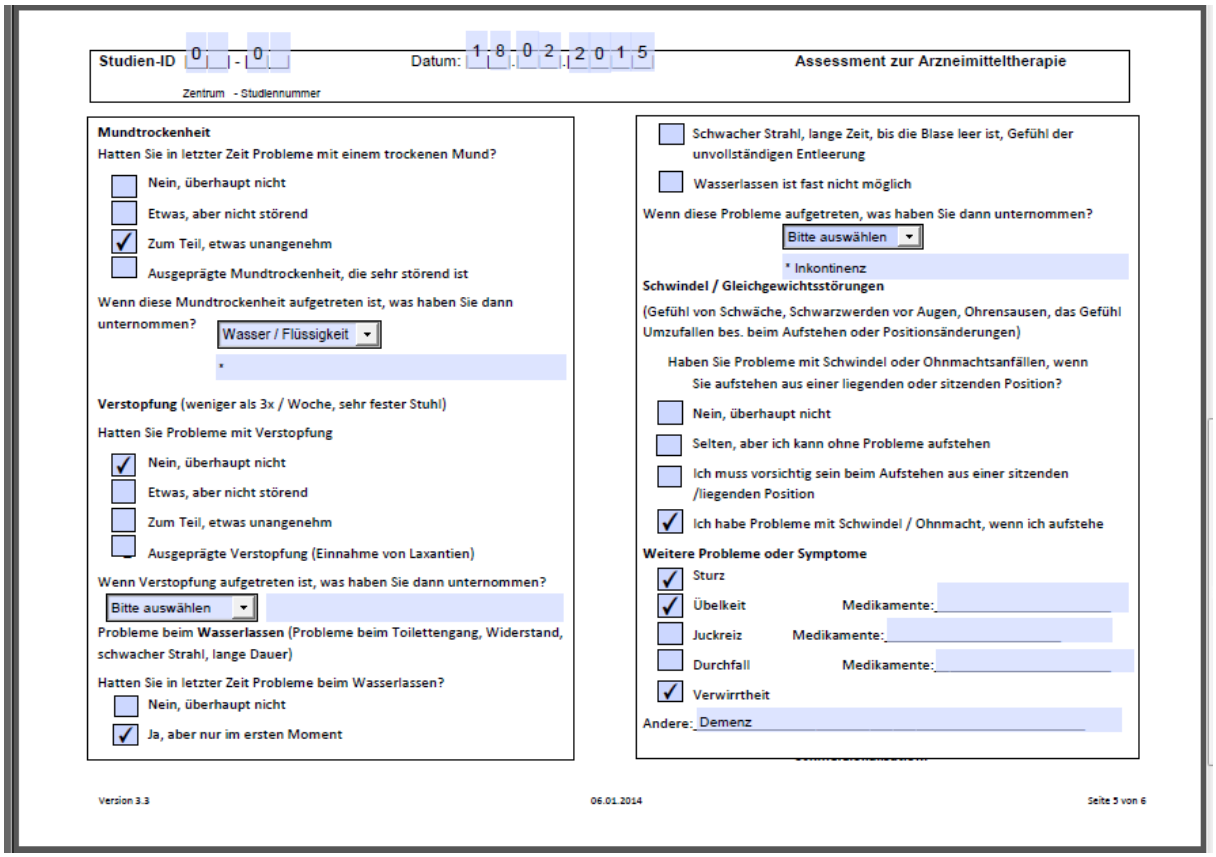

Studien-ID 0 - 0 Datum: 18.02.2015 **Assessment zur Arzneimitteltherapie**

Zentrum - Studiennummer

Mundtrockenheit

Hatten Sie in letzter Zeit Probleme mit einem trockenen Mund?

- ☐ Nein, überhaupt nicht
- ☐ Etwas, aber nicht störend
- ☑ Zum Teil, etwas unangenehm
- ☐ Ausgeprägte Mundtrockenheit, die sehr störend ist

Wenn diese Mundtrockenheit aufgetreten ist, was haben Sie dann unternommen? Wasser / Flüssigkeit

*

Verstopfung (weniger als 3x / Woche, sehr fester Stuhl)

Hatten Sie Probleme mit Verstopfung

- ☑ Nein, überhaupt nicht
- ☐ Etwas, aber nicht störend
- ☐ Zum Teil, etwas unangenehm
- ☐ Ausgeprägte Verstopfung (Einnahme von Laxantien)

Wenn Verstopfung aufgetreten ist, was haben Sie dann unternommen? Bitte auswählen

Probleme beim **Wasserlassen** (Probleme beim Toilettengang, Widerstand, schwacher Strahl, lange Dauer)

Hatten Sie in letzter Zeit Probleme beim Wasserlassen?

- ☐ Nein, überhaupt nicht
- ☑ Ja, aber nur im ersten Moment
- ☐ Schwacher Strahl, lange Zeit, bis die Blase leer ist, Gefühl der unvollständigen Entleerung
- ☐ Wasserlassen ist fast nicht möglich

Wenn diese Probleme aufgetreten, was haben Sie dann unternommen? Bitte auswählen

* Inkontinenz

Schwindel / Gleichgewichtsstörungen

(Gefühl von Schwäche, Schwarzwerden vor Augen, Ohrensausen, das Gefühl Umzufallen bes. beim Aufstehen oder Positionsänderungen)

Haben Sie Probleme mit Schwindel oder Ohnmachtsanfällen, wenn Sie aufstehen aus einer liegenden oder sitzenden Position?

- ☐ Nein, überhaupt nicht
- ☐ Selten, aber ich kann ohne Probleme aufstehen
- ☐ Ich muss vorsichtig sein beim Aufstehen aus einer sitzenden /liegenden Position
- ☑ Ich habe Probleme mit Schwindel / Ohnmacht, wenn ich aufstehe

Weitere Probleme oder Symptome

- ☑ Sturz
- ☑ Übelkeit Medikamente:
- ☐ Juckreiz Medikamente:
- ☐ Durchfall Medikamente:
- ☑ Verwirrtheit

Andere: Demenz

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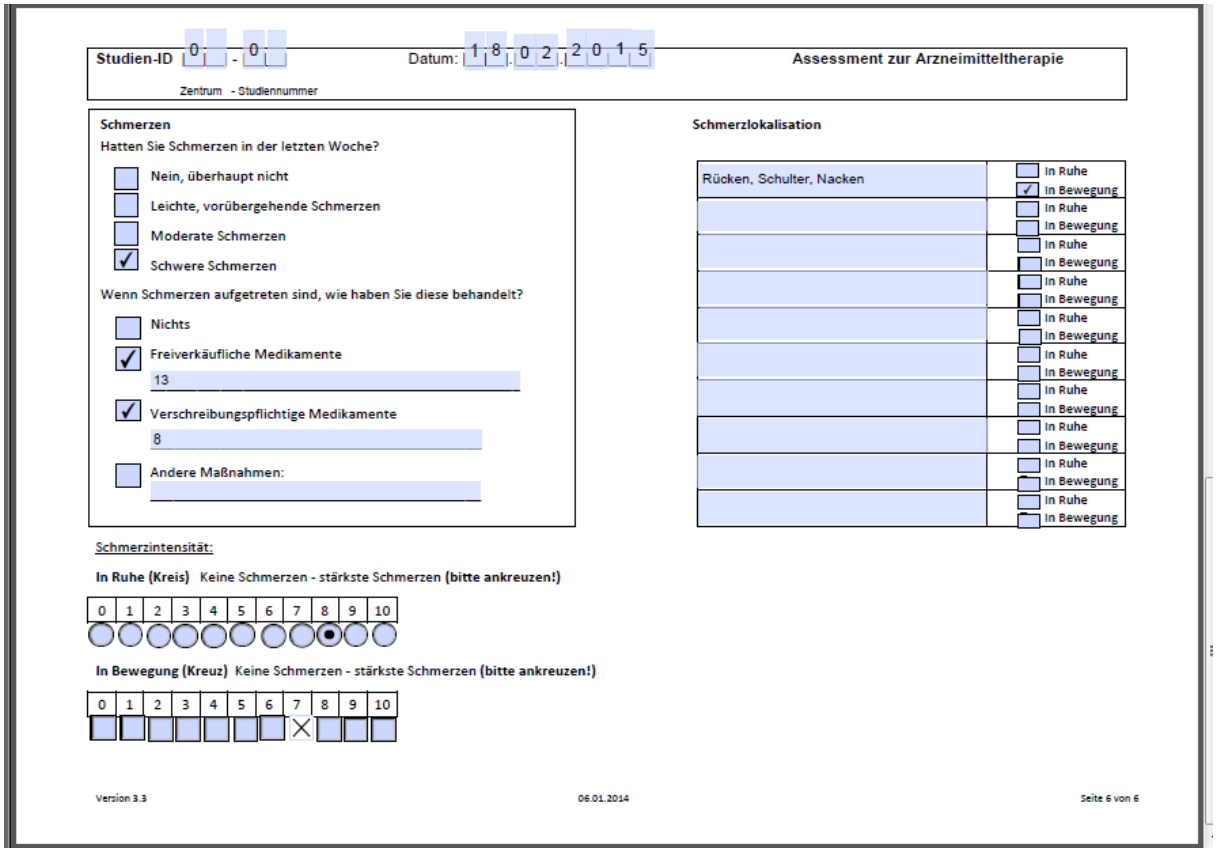

Studien-ID 0 - 0 (Zentrum - Studiennummer) Datum: 18.02.2015

Assessment zur Arzneimitteltherapie

Schmerzen

Hatten Sie Schmerzen in der letzten Woche?

- ☐ Nein, überhaupt nicht
- ☐ Leichte, vorübergehende Schmerzen
- ☐ Moderate Schmerzen
- ☑ Schwere Schmerzen

Wenn Schmerzen aufgetreten sind, wie haben Sie diese behandelt?

- ☐ Nichts
- ☑ Freiverkäufliche Medikamente: 13
- ☑ Verschreibungspflichtige Medikamente: 8
- ☐ Andere Maßnahmen:

Schmerzlokalisation

Rücken, Schulter, Nacken	☐ In Ruhe ☑ In Bewegung
	☐ In Ruhe ☐ In Bewegung
	☐ In Ruhe ☐ In Bewegung
	☐ In Ruhe ☐ In Bewegung
	☐ In Ruhe ☐ In Bewegung
	☐ In Ruhe ☐ In Bewegung
	☐ In Ruhe ☐ In Bewegung
	☐ In Ruhe ☐ In Bewegung
	☐ In Ruhe ☐ In Bewegung
	☐ In Ruhe ☐ In Bewegung

Schmerzintensität:

In Ruhe (Kreis) Keine Schmerzen - stärkste Schmerzen **(bitte ankreuzen!)**

0	1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	●	○	○

In Bewegung (Kreuz) Keine Schmerzen - stärkste Schmerzen **(bitte ankreuzen!)**

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	X	☐	☐	☐

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Appendix 5: The Medication Review SOAP form (example)

WestGem-Studie: Patient

WestGem-Pharma: Patient Datum: .2014
Dokumentenbenennung: _SOAP1

Liebe Studienärztin, lieber Studienarzt,
dieses Medikationsmanagement enthält die sorgfältig erstellten Ergebnisse unseres Medikationsbefundes. Es soll Ihnen erste Hinweise geben wo spezielle arzneimittelbezogene Probleme bei diesem Patienten bestehen können. Da es anonymisiert und ohne Interaktion mit Ihnen angefertigt wurde, kann es keine endgültige Therapieempfehlung sein sondern Sie nur in Ihrer Therapieentscheidung unterstützen. Sofern Sie noch weitergehende Fragen zu diesem Medikationsmanagement haben, können Sie uns gerne eine Mail an pharma@westgem.de senden. Bitte schreiben Sie die Patienten-ID in die Betreffzeile, damit wir sie direkt dem richtigen Bearbeiter zuordnen können.

S./Patient und Hauptbeschwerden

XX ist eine 84-jährige Dame mit Hypertonie, Vorhofflimmern, depressiver Episode, nicht näher bezeichneter neurotischer Störung, Nervosität, Oberbauchbeschwerden und nicht näher bezeichneter Weichteilerkrankung (‚Rheumatische Erkrankung'). Ihre Hauptbeschwerden sind Abgeschlagenheit, Unruhe, Einschlafprobleme

O./auffällige Parameter:

RR 110/60
Kalium 3,4 mmol/l (Hypokaliämie)
Leukozyten 12,4
GFR: 46,3 (errechnet)

A./Befund:

Abgleich Arzt/PuW:
Abweichungen:

Arzneistoff	Arzt	Patient	Anmerkungen
Prednison	Prednison (Decortin 5)	PrednisoLON (Decortin H5)	prüfen und vereinheitlichen
Esomeprazol TAD 20	nicht verordnet	1-0-0	
Bromazepam 3 mg	0-0-0-0,5	nicht vorhanden	
Candesartan 4 mg	1-0-0	nicht vorhanden	
Naproxen 500	bei Bedarf	nicht vorhanden	
Risperidon 0,25	nicht verordnet	½-0-½	neu seit 21.7., v
Dekristol	nicht verordnet	1/Monat	
Novaminsulfon 500	nicht verordnet	bei Bedarf	
Dolormin extra	Selbstmedikation	bei Bedarf	
Voltaren Gel forte	Selbstmedikation	täglich	
Dulcolax	Selbstmedikation	bei Bedarf	

WestGem-Studie: Patient

Unterschiede zwischen ärztlichem Medikationsplan und tatsächlich eingenommenen Medikamenten sind für eine Vielzahl von arzneimittelbezogenen Problemen verantwortlich und können hier aufgedeckt werden. Allerdings ist auch eine fehlerhafte Übermittlung der Daten an uns eine mögliche Ursache für Abweichungen.

Interaktionen (nach klinischer Relevanz sortiert):

1. Digoxin, verschiedene NSAR, HCT, Candesartan, Dulcolax: Auswirkungen auf den Kaliumspiegel, Maßnahme: Kaliumspiegel überwachen (aktuell 3,4, Hypokaliämie)
2. Phenprocoumon, NSAR, Kortikosteroid: erhöhtes Risiko für (GI-) Blutungen, Maßnahme: PPI beibehalten, NSAR absetzen
3. HCT, Esomeprazol: erhöhtes Risiko für Hypomagnesiämie, Maßnahme: Magnesiumspiegel messen
4. Candesartan, HCT, NSAR: erhöhtes Risiko für Nierenfunktionsstörungen, Maßnahme: NSAR absetzen, GFR überwachen
5. Bromazepam, Esomeprazol: verlängerte Wirkdauer des Bromazepams, Maßnahme: Wechsel/Absetzen von Bromazepam

Kontraindikationen, auch Laborwerte, GFR
GFR: 46,3 ml/min, Digoxin sollte bei dieser Nierenfunktion nur in halber Dosierung gegeben werden (hier durch Verordnung von ‚mite' vermutlich berücksichtigt. Digi**toxin** wird unabhängig von der Nierenfunktion eliminiert und wäre auf Dauer günstiger, bei einer etwaigen Umstellung müsste ggf. eine Therapiepause von 3-4 Tagen eingehalten werden.

Leitlinien
Osteoporose
Bonviva wurde bis 2013 gegeben, Diagnose Osteoporose ggf. nachtragen, Vitamin D (Patientin nimmt Dekristol, in Patientenakte nachtragen) und Calcium-Gabe je nach Nahrungsaufnahme überdenken. Falls mit Bonviva nach mehr als 5 Jahren Therapie eine Therapiepause gemacht wurde ist der Zeitpunkt der erneuten Therapie zu prüfen (je nach Risiko nach ca. einem Jahr Pause).

Nicht näher bezeichnete rheumatoide Erkrankung
Abhängig von genauer Diagnose prüfen, ob Therapie mit einem Basistherapeutikum sinnvoll ist und Dauermedikation mit Prednison/Prednisolon hinterfragen.

Hypertonie
Der Blutdruck ist derzeit übermäßig behandelt (RR 110/60). Bisoprolol wird möglicherweise auch wegen des Vorhofflimmerns (in Kombination mit Digoxin) zur Frequenzkontrolle eingesetzt, Candesartan und HCT wären im Therapieregime am ehesten verzichtbar. Für den Einsatz von HCT spricht allerdings die Ödembildung, dagegen die Hypokaliämie. Die Empfehlung lautet daher, dass Candesartan unter Blutdruck- und Kaliumkontrolle ganz abgesetzt werden kann, ggf. kann es ausgeschlichen werden (über ca. 7 Tage eine halbe Tablette (2mg/Tag)). Von HCT kann auf eine Kalium-sparende Diuretikakombination gewechselt werden, (Amilorid/HCT).

Handhabungsprobleme:

Das Stellen und die Gabe der Medikamente ist XX nicht mehr möglich, es erfolgt durch den Ehemann. Der Therapieplan mit hauptsächlich morgendlicher Einnahme ist bereits sehr gut und schlank.

Therapieziel:
Die Patientin wünscht sich eine Verbesserung des Allgemeinzustandes, weniger Abgeschlagenheit, Unruhe, Schlafstörungen und Harninkontinenz. Möglicherweise bessert sich das subjektive Gefühl etwas durch den höheren Blutdruck. Die Unruhe wird durch das kürzlich angesetzte Antipsychotikum vielleicht verbessert. Um die Schlafprobleme zu verbessern könnte ein Austausch von Risperidon hin zu dem stärker sedierende Quetiapin zur Nacht hilfreich sein (s.u).

Schlaf:
Einschlafprobleme werden als Hauptbeschwerden angegeben. Bromazepam ist geriatrisch ungeeignet, derzeit abgesetzt. Das vermutlich vom Psychiater neu angesetzte Risperidon wirkt nur schwach sedierend. Ggf. Wechsel auf stärker sedierendes Quetiapin erwägen oder Kombination mit sedierendem Antidepressivum. Aufgrund der allgemeinen Abgeschlagenheit ist zu befürchten, dass die Patientin auch tagsüber schläft, was zu den Einschlafstörungen beitragen kann. Das sedierende Quetiapin wäre eine Alternative zum Risperidon.

Geriatrisch ungeeignet:
Patientin hat ein sehr hohes Sturzrisiko und Osteoporose, Bromazepam ist wegen der langen Halbwertszeit, die hier durch Interaktionen noch verlängert wird, ungeeignet, wurde möglicherweise vom FA für Psychiatrie aber auch schon abgesetzt.

Einnahmezeitpunkt problematisch:
Esomeprazol statt während des Frühstückes 30 Min. vor der Mahlzeit einnehmen.

Doppelverordnungen:

- Prednison und Prednisolon sind möglicherwiese (in der Apotheke oder beim Rezeptieren) vertauscht worden. Dies ist zwar unproblematisch, sollte aber konsistent sein um spätere durch den Patienten veranlasste Doppelverordnungen auszuschließen.

- NSAR: Die Patientin verwendet eine ganze Reihe von NSAR zwar nur bei Bedarf, aber in der Annahme, dass sie für verschiedene Schmerzarten sind, möglicherweise auch gleichzeitig. NSAR sind hier wegen der Marcumarisierung und der kardiovaskulären Risiken eher ungünstig. Da auch Novaminsulfon genommen wird (allerdings nicht rezeptiert wurde und somit unbekannter Herkunft ist), sollte man sich hierauf beschränken und alle NSAR absetzen.

Indikation ohne Medikament:
Osteoporose
Bonviva wurde bis 2013 gegeben, Diagnose Osteoporose ggf. nachtragen, Vitamin D und Calcium-Gabe überdenken, falls mit Bonviva nach mehr als 5 Jahren Therapie eine Therapiepause gemacht wurde ist der Zeitpunkt der erneuten Therapie zu erwägen (je nach Risiko nach ca. einem Jahr Pause).

WestGem-Studie: Patient

Depressive Episode
derzeit nicht behandelt, ließe sich ggf. mit Schlafmedikation kombinieren, Gabe eines sedierenden Antidepressivums ohne anticholinerge Eigenschaften (Verwirrtheit wird von der Patientin angegeben) zur Nacht, beste Option: Mirtazapin

Nebenwirkungen:
Abgeschlagenheit und Benommenheit können durchaus von der Medikation stammen, hier ist neben der Schlafmedikation und der starken Blutdrucksenkung auch Digoxin (eingeschränkte GFR) ein möglicher Kandidat.

Kostenaspekt:
Sofern die verschiedenen NSAR aus der Bedarfs- und Selbstmedikation abgesetzt werden können, ist auch Esomeprazol möglicherweise verzichtbar. Durch die Behandlung der Depression können sich Mehrkosten ergeben.

Plan:

Absetzen von:

I-#	Arzneistoff	Grund
I1	Dolormin extra	CV-Risiko, GI-Risiko und Interaktionen
I2	Voltaren resinat	CV-Risiko, GI-Risiko und Interaktionen
I3	Naproxen 500	CV-Risiko, GI-Risiko und Interaktionen
I4	Esomeprazol 20	ohne NSAR keine Indikation
I5	HCT 25 mg	Hypokaliämie, Umstellung auf Amilorid/HCT-Kombi

Gabe von:

I-#	Arzneistoff und Stärke	Gabe	Kommentar (z.B. neu)
	Concor 5 mg (Bisoprolol)	1-0-0	unverändert
I6	Amilorid5mg/HCT 50 mg (z.B. Amilorid comp. ratiopharm)	1/2-0-0	neu statt HCT, muss leider geteilt werden, da passende Stärke nicht verfügbar
	Novodigal mite	1-0-0	unverändert, ggf. Umstellung auf Digitoxin nach 4 Tagen Therapiepause
	Phenprogamma 3 mg (Marcumar)	nach Plan	unverändert
	Risperidon 0,25	1/2-0-1/2	unverändert, neu vom Facharzt
I7	Mirtazapin 15 mg	0-0-01	falls keine Besserung der Schlafstörung und Behandlung der Depression gewünscht
I8	Prednison 5 mg (Decortin)	1-0-0	Prüfen, ob Dauertherapie sinnvoll oder therapeutische Alternative (Rheuma-Basistherapeutikum) besser geeignet
	Colecalciferol 20000 (Dekristol)	1/Monat	wird aktuell von Patientin genommen, scheint auch weiterhin sinnvoll, ggf. nachtragen

WestGem-Studie: Patient

Bei Bedarf			
	Novaminsulfon 500 mg	nach Bedarf bis zu 1-1-1	unverändert
	Voltaren forte Gel	nach Bedarf	unverändert

weitere Interventionen

I-#	Art der sonstigen Intervention
I9	Impfstatus für saisonale Grippe und Pneumokokken überprüfen

Monitoring:

Monitoringvorschlag speziell bei diesem Patienten wichtig:
Kaliumspiegel (wegen Hypokaliämie und ggf. Umstellung) ,
Magnesiumspiegel (nur falls Esomeprazol weiter gegeben wird)
RR nach Absetzen von Candesartan

Allgemeine Monitoringvorschläge für diesen Patienten:
RR, INR

Hinweise zur Patientenschulung durch den Arzt:

Besondere Schulungsvorschläge bei diesem Patienten:
PPI Einnahme 30 Min. vor der Mahlzeit

Hinweise an PuW:

Sturzprophylaxe notwendig?

Ja: unbedingt
Begründung: Medikation, Marcumarisierung, Allgemeinzustand, Sturzhistorie, Osteoporose

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Für interne Kontrolle:

Freigabe Bearbeiter (Kürzel): OR
Freigabe Kontrolle Rater 1 (Kürzel): DMK, OR
Übermittelt als PDF (Kürzel):OR

Appendix 6: Individual patient data on LDL-cholesterol concentrations (mg/dl)

ID	LDL1	LDL2	LDL3	LDL4	LDL5	LDL6	LDL7	Zentr.	Interv.	ITT
103	148	148	70	97	70	43	48	1	1.7.2014	1
105	117	117	121	121	102	102	113	1	1.7.2014	1
111	86	86	86	77	66	75	75	1	1.7.2014	1
112	170	170	170	115	140	77	88	1	1.7.2014	1
113	91	91	91	86	86	86	86	1	1.7.2014	1
118	117	117	117	138	148	134	134	1	1.7.2014	1
124	77	77	77	85	69	85	85	1	1.7.2014	1
133	72	72	71	68	63	69	55	1	1.7.2014	1
137	125	125	110	114	114	116	112	1	1.7.2014	1
140	107	107	106	117	110	137	134	1	1.7.2014	1
207	159	159	112	117	83	118	109	2	1.1.2014	1
211	100	100	100	115	119	130	101	2	1.1.2014	1
213	85	85	91	81	62	60	57	2	1.1.2014	1
216	101	98	104	64	62	62	60	2	1.1.2014	1
217	102	102	102	98	98	102	102	2	1.1.2014	1
219	119	119	111	128	116	122	121	2	1.1.2014	1
220	91	91	91	77	83	87	66	2	1.1.2014	1
221	107	107	107	107	107	103	118	2	1.1.2014	1
222	80	80	72	83	87	92	76	2	1.1.2014	1
225	175	175	175	191	191	187	179	2	1.1.2014	1

ID	LDL1	LDL2	LDL3	LDL4	LDL5	LDL6	LDL7	Zentr.	Interv.	ITT
231	144	144	144	144	144	137	139	2	1.1.2014	1
233	77	55	35	35	45	49	54	2	1.1.2014	1
234	110	110	113	113	77	77	77	2	1.1.2014	1
236	90	90	90	90	78	78	97	2	1.1.2014	1
304	188	188	188	188	188	183	183	3	1.4.2014	1
333	115	115	115	115	115	115	115	3	1.4.2014	1
334	82	82	82	82	82	82	82	3	1.4.2014	1
401	66	66	74	74	66	66	66	4	1.4.2014	1
412	117	117	117	117	117	117	117	4	1.4.2014	1
414	100	100	115	115	115	115	115	4	1.4.2014	1
416	129	129	129	129	129	129	129	4	1.4.2014	1
501	104	104	108	92	99	99	105	5	1.1.2014	1
503	74	74	74	99	99	99	99	5	1.1.2014	1
504	144	144	130	108	111	152	147	5	1.1.2014	1
505	99	99	115	84	94	94	107	5	1.1.2014	1
506	90	90	90	106	106	106	106	5	1.1.2014	1
511	82	82	82	101	86	86	86	5	1.1.2014	1
512	219	219	219	240	240	239	252	5	1.1.2014	1
517	86	86	86	106	106	106	106	5	1.1.2014	1
523	104	104	104	104	100	92	92	5	1.1.2014	1
529	66	66	80	77	87	94	89	5	1.1.2014	1
530	77	77	50	50	57	57	62	5	1.1.2014	1

ID	LDL1	LDL2	LDL3	LDL4	LDL5	LDL6	LDL7	Zentr.	Interv.	ITT
533	104	104	118	118	118	118	118	5	1.1.2014	1
535	181	181	171	171	171	171	178	5	1.1.2014	1
539	126	126	96	86	86	86	86	5	1.1.2014	1
540	82	82	82	82	121	121	138	5	1.1.2014	1
602	158	158	133	117	96	103	116	6	1.7.2014	1
619	187	187	187	176	176	176	176	6	1.7.2014	1
622	103	103	93	126	109	101	94	6	1.7.2014	1
625	141	141	141	141	141	141	141	6	1.7.2014	1
626	65	65	66	62	59	65	51	6	1.7.2014	1
629	80	80	91	71	53	73	73	6	1.7.2014	1
630	165	165	165	165	165	165	165	6	1.7.2014	1
636	65	65	65	79	79	64	81	6	1.7.2014	1
637	88	88	88	62	66	66	66	6	1.7.2014	1
639	134	116	116	101	100	115	112	6	1.7.2014	1
705	94	94	94	86	86	103	92	7	1.7.2014	1
707	134	134	127	127	100	101	114	7	1.7.2014	1
712	194	194	194	194	78	78	87	7	1.7.2014	1
716	107	107	120	172	157	136	161	7	1.7.2014	1
718	78	78	78	68	68	78	81	7	1.7.2014	1
719	150	150	150	150	150	150	150	7	1.7.2014	1
720	107	107	98	98	98	98	98	7	1.7.2014	1
811	171	171	171	171	171	171	171	8	1.4.2014	1

ID	LDL1	LDL2	LDL3	LDL4	LDL5	LDL6	LDL7	Zentr.	Interv.	ITT
902	97	97	97	97	113	113	113	9	1.1.2014	1
906	95	87	96	72	149	121	104	9	1.1.2014	1
908	125	125	127	127	141	141	141	9	1.1.2014	1
909	121	121	121	93	93	66	66	9	1.1.2014	1
910	103	103	86	86	105	98	74	9	1.1.2014	1
911	137	137	137	97	97	92	103	9	1.1.2014	1
912	137	137	163	150	142	147	147	9	1.1.2014	1
917	141	141	146	118	142	125	125	9	1.1.2014	1
919	77	77	119	113	89	74	96	9	1.1.2014	1
920	142	142	136	1,8	1,8	137	137	9	1.1.2014	1
921	249	249	249	222	166	166	166	9	1.1.2014	1
1102	140	140	140	118	122	122	136	11	1.1.2014	1
1105	140	140	140	117	97	109	109	11	1.1.2014	1
1112	81	81	78	78	78	70	94	11	1.1.2014	1
1115	92	92	92	92	125	100	100	11	1.1.2014	1
1116	78	78	78	53	53	69	57	11	1.1.2014	1
1117	96	96	96	107	107	107	107	11	1.1.2014	1
1123	112	112	112	112	90	90	73	11	1.1.2014	1
1131	99	99	99	120	125	130	130	11	1.1.2014	1
1133	117	117	117	100	100	79	79	11	1.1.2014	1
1134	106	106	106	106	106	106	106	11	1.1.2014	1
1135	120	120	113	113	106	106	113	11	1.1.2014	1

ID	LDL1	LDL2	LDL3	LDL4	LDL5	LDL6	LDL7	Zentr.	Interv.	ITT
1203	84	84	103	103	103	149	109	12	1.7.2014	1
1206	125	125	125	125	125	101	109	12	1.7.2014	1
1208	60	60	60	60	60	60	55	12	1.7.2014	1
1211	86	86	81	92	92	92	98	12	1.7.2014	1
1409	138	138	138	138	62	62	62	14	1.4.2014	1
1419	92	92	100	100	100	100	100	14	1.4.2014	1

Appendix 7: Individual patient data on suggested and rated interventions

Patient-ID	suggested interventions by pharmacist	rated interventions by GP
0103	12	0
0105	17	0
0111	9	0
0112	14	0
0113	9	0
0118	13	0
0124	6	0
0133	18	0
0137	14	0
0140	9	0
0207	19	13
0208	12	4
0210	13	9
0211	10	10
0213	10	10
0216	13	11
0217	9	7
0219	18	14
0220	9	8
0221	9	8
0222	9	9
0225	14	9

Patient-ID	suggested interventions by pharmacist	rated interventions by GP
0227	16	13
0231	10	10
0233	12	12
0234	14	14
0236	11	9
0238	18	10
0304	23	12
0305	9	9
0309	16	15
0333	12	12
0334	8	8
0401	11	0
0404	14	14
0410	12	0
0412	11	0
0414	13	0
0416	16	4
0417	7	0
0501	27	27
0503	10	5
0504	12	12
0505	16	16

Patient-ID	suggested interventions by pharmacist	rated interventions by GP
0506	14	10
0511	17	15
0512	13	12
0517	14	14
0523	15	12
0529	10	10
0530	17	7
0535	13	12
0539	15	15
0540	11	3
0601	8	8
0602	10	0
0604	10	0
0611	10	0
0612	13	0
0614	12	0
0617	12	0
0619	12	0
0620	16	0
0622	12	0
0625	10	5
0626	16	3

Patient-ID	suggested interventions by pharmacist	rated interventions by GP
0628	13	0
0629	3	0
0630	15	4
0632	8	2
0636	14	14
0637	16	0
0639	11	2
0705	11	10
0707	8	8
0708	16	16
0712	13	13
0713	6	6
0716	10	10
0718	11	11
0719	15	15
0720	12	12
0801	10	10
0811	18	17
0815	5	5
0818	13	13
0820	15	15
0823	10	10

Patient-ID	suggested interventions by pharmacist	rated interventions by GP
0824	10	10
0828	17	16
0830	5	5
0832	12	12
0840	10	1
0845	20	15
0902	7	7
0904	9	9
0906	14	14
0908	14	14
0909	9	9
0910	18	18
0911	7	7
0912	16	16
0917	15	13
0919	14	14
0920	14	11
0921	19	19
0940	18	18
1102	15	15
01102	12	0
1105	10	10

Patient-ID	suggested interventions by pharmacist	rated interventions by GP
1106	16	16
1112	8	8
1114	17	17
1115	16	16
1116	10	10
1117	7	7
1122	18	18
1123	13	12
1127	13	13
1131	14	14
1132	16	16
1133	14	14
1134	13	13
1135	15	15
1203	13	0
1206	16	0
1208	7	0
1211	10	0
1401	9	6
1402	13	6
1409	13	8
1418	5	2

Patient-ID	suggested interventions by pharmacist	rated interventions by GP
1419	19	3
1423	16	6
1424	10	3
1427	12	3
1431	12	3
1438	20	12
1440	6	3
total	1753	1130
	mean	mean
	12,6	8,1

Appendix 8: Response form for the general practitioner on acceptance of the suggested interventions

WestGem-Studie: Medikationsmanagement bei multimorbiden Patienten

Studien-ID |0|2| - |1|6| Datum: |0|7|.|0|3|.|2|0|1|4| Doku **3**
Zentrum - Studiennummer

3 Monate nach Rekrutierungsende

BEWERTUNG DER EMPFEHLUNGEN

Sind Sie zum Dokumentationszeitpunkt 3 in die Konzeptgruppe gewechselt und haben von der Pflege- und Wohnberatung Informationen/Empfehlungen zur weiteren Behandlung des Patienten erhalten, dann dokumentieren Sie bitte im Folgenden, inwieweit Sie diese in der Therapie verwenden bzw. umsetzten konnten.
Gleiches gilt, falls Sie bereits die Ergebnisse des Folge-Assessments von der Pflege- und Wohnberatung erhalten haben.

Interventions-Nr.	Code	Interventions-Nr.	Code	Interventions-Nr.	Code
I-1	1	I-6	1	I-11	3
I-2	4	I-7	1	I-12	
I-3	1	I-8	1	I-13	
I-4	3	I-9	3	I-14	
I-5	3	I-10	3	I-15	

Einzutragender Code: 1 = weitere Informationen notwendig; 2 = Intervention teilweise übernommen; 3 = Intervention angenommen; 4 = Intervention abgelehnt, weil medizinische falsch; 5 = Intervention abgelegt aus Kostengründen; 6 = Intervention aus anderen Gründen abgelehnt

Appendix 9: Individual patient data on the acceptance of the GPs

Patient-ID	‘stop a drug’ processed?		‘start a drug’ processed		‘change in dose’ processed?	
	yes	no	yes	no	yes	no
0103	0	0	0	0	0	0
0105	0	0	0	0	0	0
0111	0	0	0	0	0	0
0112	0	0	0	0	0	0
0113	0	0	0	0	0	0
0118	0	0	0	0	0	0
0124	0	0	0	0	0	0
0133	0	0	0	0	0	0
0137	0	0	0	0	0	0
0140	0	0	0	0	0	0
0207	1	1	2	1		
0208	0	0	0	0	0	0
0210	1	2			1	1
0211	3		5			1
0213	2	1	1	3	2	1
0216	1	1	1		2	
0217		1			3	
0219	3	3		1	2	1
0220		2	1	1		1
0221						1

Patient-ID	‘stop a drug’ processed?		‘start a drug’ processed		‘change in dose’ processed?	
0222		2		1		2
0225	3	1	3	1		
0227	1	3	3			1
0231	1	2		3	1	
0233	1	1	1	1	1	
0234	1				3	1
0236	1		2		3	
0238	1	2	4	3		
0304		4	4	1	1	1
0305			3		1	
0309	2	1	4			
0333		1	4	2		1
0334	1		3		2	
0401	0	0	0	0	0	0
0404	5	1	3	1	1	
0410	0	0	0	0	0	0
0412	0	0	0	0	0	0
0414	0	0	0	0	0	0
0416	2				2	
0417	0	0	0	0	0	0
0501	1	3			1	
0503	2	1			1	

Patient-ID	‘stop a drug’ processed?		‘start a drug’ processed		‘change in dose’ processed?	
0504	1	1	2	2	2	1
0505	1	1		1	1	
0506	3	1	3		2	
0511	3	2	1		2	
0512	1	1	1	1		
0517		1	2		1	
0523	1	2	1	3	1	
0529					1	
0530	1					
0535			1			
0539	1	1				
0540	1	1	2		2	
0601	1	1	1	1		
0602			1			
0604	0	0	0	0	0	0
0611	0	0	0	0	0	0
0612	0	0	0	0	0	0
0614	0	0	0	0	0	0
0617	0	0	0	0	0	0
0619	0	0	0	0	0	0
0620	0	0	0	0	0	0
0622						

Patient-ID	‘stop a drug’ processed?		‘start a drug’ processed		‘change in dose’ processed?	
0625	2		1			1
0626	1		1			
0628	0	0	0	0	0	0
0629	0	0	0	0	0	0
0630	1		1			
0632	0	0	0	0	0	0
0636		2		1	1	2
0637	0	0	0	0	0	0
0639	1					
0705		1		5	1	
0707	1	1	1		3	1
0708		4	3	4	1	
0712	1			4		2
0713		1		3		1
0716	1	5	1			1
0718		1		4	3	
0719	2		1	2	4	2
0720	1	1	1	3		
0801	2		6			
0811	6		8		2	
0815					1	1
0818	3		1		1	

Patient-ID	‘stop a drug’ processed?		‘start a drug’ processed		‘change in dose’ processed?	
0820		4	2		3	3
0823	1		1	1		1
0824		4	1	2	1	
0828	4	4	3	1	2	2
0830	2					
0832	2	1		2		3
0840	1	0	1	0	0	0
0845	3	3	5	1		2
0902	1	1		1	2	1
0904	1	1	1	3		1
0906	1				3	
0908	1	3	1	4		
0909		2		2		3
0910		3		1	2	
0911		2		1	1	
0912	3	1		2	3	1
0917	1	2	1	4		1
0919	3		1	2	2	2
0920	2		3	1	2	1
0921	2	4		5		2
0940	2	5		5	2	2
1102	1	2		2	3	

Patient-ID	‘stop a drug’ processed?		‘start a drug’ processed		‘change in dose’ processed?	
01102	0	0	0	0	0	0
1105	1		1	1	2	1
1106	2	3	2	3		
1112					1	1
1114	1	1	1	1	6	1
1115	2	3	4	1	1	2
1116	1		2	1	1	
1117			4			
1122	3	1	2	2	3	
1123	2	2	2	4		1
1127	1	4	1	2	2	
1131	6	1	1		2	
1132	1	2		4	1	
1133	4	1	2	3	1	
1134	2	1	2	2	1	1
1135	1	1		4		1
1203	0	0	0	0	0	0
1206	0	0	0	0	0	0
1208	0	0	0	0	0	0
1211	0	0	0	0	0	0
1401	1		1		2	
1402	1				2	2

Patient-ID	‘stop a drug’ processed?		‘start a drug’ processed		‘change in dose’ processed?	
1409	3	2		1	1	
1418	1					1
1419					1	1
1423		3			1	
1424	1				1	
1427		1				1
1431				2	1	
1438	3	2	2	4	1	
1440					1	1
	‘stop a drug’ processed?		‘start a drug’ processed		‘change in dose’ processed?	
total	137	131	131	128	114	63
	yes	no	yes	no	yes	no
	total number	704				

VERFASSERERKLÄRUNG

Ich erkläre hiermit, dass ich die vorliegende Arbeit selbständig verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel verwendet habe.

Münster, den 17.1.2017 Olaf Rose

CURICULUM VITAE AND PUBLICATION LIST

Publications related to this dissertation

Rose O, Schaffert C, Czarnecki K, Mennemann HS, Waltering I, Hamacher S, et al. Effect evaluation of an interprofessional medication therapy management approach for multimorbid patients in primary care: a cluster-randomized controlled trial in community care (WestGem study protocol). BMC Fam Pract. 2015;16:84.

Rose O, Mennemann H, John C, Lautenschlager M, Mertens-Keller D, Richling K, et al. Priority Setting and Influential Factors on Acceptance of Pharmaceutical Recommendations in Collaborative Medication Reviews in an Ambulatory Care Setting - Analysis of a Cluster Randomized Controlled Trial (WestGem-Study). PLoS ONE. 2016;11:e0156304.

Koberlein-Neu J, Mennemann H, Hamacher S, Waltering I, Jaehde U, Schaffert C, Rose O. Interprofessional Medication Management in Patients With Multiple Morbidities. Dtsch Arztebl Int. 2016;113:741–8.

Submitted December 22, 2016 and currently under review at the journal Research in Social and Administrative Pharmacy: Discrepancies and their relevance in Medication Reconciliation between the medication assessed at patient's home versus medication documented by primary care physicians.