


Reduction of potentially inappropriate medication in the elderly: design of a cluster-randomised controlled trial in German primary care practices (RIME)

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Abstract

Background: Potentially inappropriate medication (PIM) is considered to have potentially more harmful than beneficial health effects in elderly patients. A German example for a PIM list is the PRISCUS list that has been available since 2010. PIMs are associated with an increased risk of hospitalisation and adverse health outcomes. Furthermore, drug–drug interactions (DDI) may pose additional risks to patients. It is not yet clear how numbers of PIM and DDI can be reduced in community-dwelling seniors in primary care; nor is it clear whether patients would benefit from such deprescribing.

Methods: The cluster-randomised controlled study on the “Reduction of potentially Inappropriate Medication in the Elderly” (RIME study) is designed to examine whether an intervention based on the PRISCUS list can lower the proportion of community-dwelling people of ≥ 70 years taking at least one PIM and/or medication inducing at least one dangerous DDI. The intervention consists of professional education and training on the reduction of PIM and DDI, and will be offered to either general practitioners (GPs) alone or GPs and their office staff in the experimental study arm. The control group will be offered professional education and training on more general issues of prescribing in the elderly, not specifically addressing PIM or DDI. The primary endpoint is the difference in the proportion of patients with at least one PIM or DDI between the start of the study and study closure after 12 months as compared between intervention and control group. Secondary endpoints include overall mortality, number of hospitalisations during the course of the study, quality of life and costs. Secondary analyses will be explorative, with the cluster randomisation being factored in.

Discussion: The RIME study will contribute to answering the question of whether an intervention based on the PRISCUS list can reduce the proportion of community-dwelling seniors aged ≥ 70 years with at least one PIM and/or DDI, and whether this will result in positive health effects, for example, as regards hospitalisations.

Trial registration The Study has been registered in the German Clinical Trials Register (DRKS) under the number DRKS00003610.

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Lay summary

Reduction of potentially inappropriate medication in the elderly

Improper medication is a common problem in elderly with chronic diseases, and especially those with multiple diseases. Improper medication is assumed to cause side effects, reduced quality of life, more hospital admissions and other negative consequences. Improper medication may be avoided by lists like the German PRISCUS list published in 2010. The list contains drugs that are assumed to be improper in the opinion of experts. The list also gives

hints how drugs may interact, and how drugs should be dosed appropriately. A training of general practitioners based on such a list may reduce improper medication.

To evaluate this, a scientific project is planned and conducted. In a total of 140 general practitioner offices in the cities of Witten and Hannover, 12 patients in each office aged ≥ 70 years and taking at least 6 drugs on a regular basis will be examined. The treating physicians will either get usual recommendations towards pharmacotherapy in the elderly, or they will be advised and trained in new developed recommendations based on the PRISCUS list. After 12 months, the proportion of patients receiving at least one improper medication will be assessed, and the proportions will be compared between the differently trained physician groups. It is assumed that one in four patients will get at least one improper medication, and that the new developed recommendations will reduce the proportion of patients with improper medication by a third.

Keywords: cluster-randomised controlled trial, drug–drug interaction, elderly, medication therapy management, potentially inappropriate medication, primary care

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Background

Potentially inappropriate medication (PIM) is usually defined as either the prescription of medication with an unfavourable benefit/risk ratio than safer alternatives, or as the prescription of medication that should be avoided in the elderly at a certain dosage or in presence of specific comorbidities.¹ After publication of the first list of PIM for nursing home residents in the United States (US),² several other country-specific lists have been developed and published.^{3,4} These PIM lists use explicit criteria on the basis of the benefit/risk ratio of a drug, certain maximum doses and treatment durations without in-depth consideration of individual patients' characteristics. The PRISCUS list specifically covers the German drug market more appropriately than the US American Beers list or the French Laroche list.^{5–7} A German alternative, the FORTA criteria, names drugs to prescribe, as well as those to avoid.⁸

Potentially inappropriate pharmacotherapy in the elderly is a common phenomenon. Recent European and US–American studies suggest that about one-fifth of persons aged 65 years and above are prescribed at least one active drug that is considered potentially inappropriate.^{9,10} The risk of being prescribed a PIM increases with the number of comorbidities and the number of drugs prescribed. Among the risk groups of patients being frequently prescribed PIM are persons exposed to polypharmacy, particularly those in

institutional care, persons with dementia, and women.⁹ PIM appears to be associated with negative consequences for patient health, as reflected, for example, in adverse drug effects and increased hospitalisation.^{11,12} However, empirical evidence in this field is conflicting.^{13,14}

Apart from PIM, drug–drug interactions (DDI) represent a major problem for elderly, multimorbid patients, frequently exposed to polypharmacy.¹⁵ Elderly patients above the age of 65 years have a significantly higher risk of preventable adverse drug reactions (ADR) resulting in hospitalisation than younger patients.¹⁶ Moreover, almost half of the preventable ADR are based on unintended DDI, frequently occurring between antiplatelet drugs, oral anticoagulants and non-steroidal anti-inflammatory drugs (NSAID). These drugs, in addition to widely used diuretics, have been identified as drugs most frequently resulting in preventable hospitalisations in the elderly.¹⁷ Lapi *et al.* ascertained the common combination of an ACE-inhibitor or angiotensin receptor blocker in addition to a diuretic and in combination with a NSAID as an unhappy triad resulting in deterioration of renal function.¹⁸

Evidence on how to reduce the number of PIM prescriptions and/or DDI is collated in meta-analyses,^{19,20} indicating that a variety of interventions appears promising. Among these are: medication review by a pharmacist and/or

multidisciplinary team; training opportunities for prescribers; and computer-based decision tools. The meta-analysis of Ranking *et al.*²⁰ points out some limitations of the literature that need to be considered for the interpretation of effects. The overall quality of the study methodology, for instance, was assessed as being mediocre, which limits the validity of the study outcomes. Many studies were performed with inpatients, although the majority of drugs are prescribed to patients outside the hospital setting. None of the included studies was from Germany, and none of them used evaluation criteria applied in Germany, in particular the PRISCUS list or the FORTA criteria.^{5,8} Despite numerous tools and suggested approaches, more interventional studies on the basis of existing evidence are needed to establish an evidence-based intervention for the reduction and avoidance of PIM and the most dangerous DDI, and, consequently, adverse drug-related events in elderly outpatients with polypharmacy.

Methods

Study aim

The primary aim of this study is to verify whether an intervention based on the PRISCUS list can reduce the percentage of community-dwelling seniors aged ≥ 70 years taking at least one medication that is considered potentially inappropriate or being exposed to one out of a list of pre-defined DDI.⁵ PIM was defined in accordance with the PRISCUS list and a list of relevant DDI that had been observed frequently in earlier analyses by the PRISCUS Research Network and have been established as particularly harmful by others.^{16–18,21}

Design

A controlled, cluster-randomised trial will be conducted that is designed to compare among primary care practices the proportion of patients whose medication includes at least one PIM and/or one pre-selected DDI. The practices will be randomised 1:1 to either the intervention or the control group. The intervention physicians will have received training to reduce PIM and/or DDI to apply in the consultation, whereas the control physicians will not have received this specific training. The experimental intervention group will be randomised further into practices with the intervention recipients being only physicians, and

practices with recipients being both physicians and practice nurses.

Study population

All community-dwelling patients who are ≥ 70 years old will be eligible for study participation if they have seen their general practitioner (GP) for any health problem during the past 3 months and receive prescriptions for a minimum of six different active drugs for regular and continuous use. Further inclusion criteria are: a life expectancy of at least 6 months according to the opinion of their attending GP; patient's consent to participate in the data acquisition (assessment at study onset in the primary care practice, telephone interviews in the course of the study); accessibility by phone, accessible for interviewing (which, among others, relies on sufficient hearing ability and sufficient command of the interview language) and written informed consent to study participation. Criteria precluding patients' participation in the study are advanced cognitive impairment or dementia, legal incompetence or established legal guardianship.

Primary and secondary endpoints

Within each cluster, the difference *D* in the proportion of patients aged ≥ 70 years with at least one PIM or DDI between the start of the study and study closure after 12 months will be calculated. This difference *D* is the primary endpoint. The following secondary endpoints have been defined: overall mortality, number of hospitalisations, quality of life, patient satisfaction with treatment, functional impairments over the study period, and costs.

All direct medical and non-medical resource use will be provided by patient's self-report using the FIMA questionnaire for the use of medical and non-medical services in old age.²² The practicality and validity of the FIMA questionnaire has been validated, and seniors fulfilling the entry criteria for the RIME study will be able to correctly answer the questions about health care utilisation and also offers the opportunity to catch over-the-counter medications. Health outcomes of the intervention are measured by, for example, clinical outcomes like mortality, number of re-hospitalisations or relevant adverse drug-related outcomes. Patient-reported outcomes such as health-related quality of life (EQ5D and SF-12) will be also considered.^{23,24} In addition to

PRISCUS-Karte

Achtung bei potenziell inadäquaten Medikamenten (PIM)

PRISCUS-PIM (Beispiele)	Begründung	Therapiealternativen ²
Tri- und Tetrazyklische Antidepressiva ■ Amitriptylin ¹ ■ Doxepin	erhöhtes Risiko für ■ anticholinerge UAE (peripher, zentral) ■ delirante Syndrome ■ Stürze ■ Arrhythmien	SSRI, z.B. ■ Citalopram ■ Sertralin Cave: gastrointestinale UAW, Elektrolytkontrolle nach Therapiebeginn, Blutungsrisiko
Benzodiazepine ■ Bromazepam, Diazepam ■ Lorazepam (> 1 mg/d) ■ Lormetazepam (> 0,5mg/d) Z-Substanzen ■ Zolpidem (> 5 mg/d) ■ Zopiclon (> 3,75 mg/d)	erhöhtes Risiko für ■ Stürze ■ Frakturen ■ paradoxe u. psych. Reaktionen ■ kognitive Funktionseinschränkungen	■ Schlafhygiene ■ niedrig dosierte Z-Substanzen (z.B. Zolpidem ≤ 5 mg/d) ■ niedrig dosierte kürzer wirksame Benzo. (z.B. Lorazepam 0,5 mg/d)
Möglichst keine Therapie mit Benzodiazepinen / Z-Substanzen beginnen bzw. Behandlungsdauer von max. 4 Wochen nicht überschreiten		
■ Doxazosin	■ orthostatische Hypotonie, Schwindel	■ andere Antihypertensiva (z.B. ACE-Hemmer, Diuretika) ■ BPH: selektive α_1 -Blocker (z.B. Tamsulosin, Alfuzosin)
Antiphlogistika und Antirheumatika ■ Coxibe (Etoricoxib, Celecoxib) ■ Oxicame (Piroxicam, Meloxicam) ■ Indometacin	■ Coxibe: kardiovaskuläre Kontraindikationen ■ sehr hohes Risiko für GI-Ulzerationen und Blutungen ■ Indometacin: ZNS-Störungen	Bei Entzündungszeichen: kurzwirksame, ggf. schwächere NSAR (z.B. Ibuprofen) plus PPI. Schmerz ohne Entzündungszeichen: Paracetamol, evtl. plus Tilidin; ggf. schwach wirksame Opioide
Urologika ■ Oxybutynin ■ Solifenacin ■ Tolterodin (nicht retardiert)	■ erhöhtes Risiko für anticholinerge UAE ■ kognitive Funktionseinschränkungen	■ nicht-medikamentöse Therapien (z.B. Beckenbodengymnastik, Physio- und Verhaltenstherapie) ■ Trosipium

¹ Einsatz der Therapiealternativen unter Berücksichtigung der Fachinformationen, Wechselwirkungen und individueller Nutzen-Risiko-Abschätzung
² Ausnahme: Amitriptylin niedrig dosiert, d.h. beginnend mit 25 mg/d und langsamer Dosissteigerung nach Wirkung und Verträglichkeit bis maximal 75 mg/d als Co-Analgetikum.

Figure 1. PRISCUS pocket card. A condensed version of the PRISCUS list of potentially inappropriate medication (PIM).

an exclusive consideration of health benefits of the intervention, corresponding cost effects play a crucial role in health economic analyses. Here, the data from Knappschaft, a cooperating health insurance provider, will be used to determine for the subgroup of those insured whether the information provided by patients is sufficiently valid for cost accounting. If this is the case for those insured with Knappschaft, sufficient validity of the data is also assumed for all included patients. If structural overestimations or underestimations are found, this result will be used for the overall sample as a basis for adjustments or sensitivity analyses.

Intervention

For practical use and comfortable handling by the practice staff involved, a condensed version of the PRISCUS list of PIMs (active drugs and most frequently used product names), the so-called 'PRISCUS pocket card' (Figure 1), will be compiled for the experimental intervention. Selection of PIM is guided by prevalence of use, that is, active drugs are included in the pocket card for which, according to the literature reviewed, prescription rates are highest.^{25,26} The pocket card also includes three frequent, clinically relevant, drug interactions that, according to the pertinent

literature, often contribute to hospitalisation and should be avoided.^{15,16,18} This card also entails a few suggestions for the general approach to medication and to polypharmacy, especially in the elderly.²⁷ A simplified version for practice nurses is also prepared (Figure 2). The pocket card and its simplified version are designed as hard copies to lie ready to hand on desk tops. In addition to the pocket card, a comprehensive manual will be provided. In the manual, a detailed discussion of the set of problems encountered with PIM is offered, as well as extensive information on the listed active drugs, their risks, and alternative options, as also given in the PRISCUS list.⁵ Based on all resources available, a slide set will be prepared and approved for lectures and presentations for doctors and their office staff as part of the experimental intervention. A telephone hotline will also be established to enable specific questions to be discussed with a clinical pharmacist when considered necessary by GPs. An overview is given in Table 1.

GPs and their practice nurses, where applicable, randomised to the experimental intervention will first be invited to a professional training event. During, or shortly after, the event they will be given the PRISCUS pocket card and the comprehensive manual. Practitioners and practice staff

PRISCUS-Karte für die Medizinische Fachangestellte

PIM: potentiell inadäquate Medikamente.

Hierbei handelt es sich um Medikamente, die bei älteren Patienten (ab 65 Jahren) vermieden werden sollten, da diese Arzneimittel oder Arzneimittelgruppen keine ausreichende Wirksamkeit und/ oder ein hohes Risiko für unerwünschte Arzneimittelwirkungen aufweisen. Sichere Therapiealternativen sind in den meisten Fällen vorhanden!

Bitte beachten: Je höher die Dosis, desto wahrscheinlicher wird eine unerwünschte Arzneimittelwirkung!

Nicht vergessen:

Nach Verordnungen anderer Ärzte fragen!

Nach Symptomen fragen, welche durch Medikation hervorgerufen sein könnte: Stürze, Kognitionsstörung (Delir, Somnolenz, Demenz)

Liegt eine Polypharmazie mit mehr als 5 Wirkstoffe pro Tag vor?

Medikationscheck: mindestens 1 x pro Jahr oder nach stationärem Aufenthalt.

Tri- und Tetrazyklische Antidepressiva

werden angewendet z.B. bei Depressionen, Angst- und Zwangsstörungen, innerer Unruhe; unterstützend in der Schmerztherapie und bei Schlafstörungen.

Wirkstoffe	Medikamenten- bzw. Handelsnamen	
	Handelsnamen bei Generika-Präparaten häufig Wirkstoff plus Herstellername	
Amitriptylin (-oxid)	Amineurin® Syneudon® Equilibrin®	Saroten® Amioxid-neuraxpharm®
Doxepin	Aponal® Mareen®	Doneurin®
Trimipramin	Herphonal® Trimineurin®	Stangyl®
Clomipramin	Anafranil®	
Maprotilin	Ludiomil®	Maprolu®
Imipramin	Tofranil®	

Benzodiazepine

Werden in die Gruppen lang-, kurz- und mittelwirksam eingeteilt und wirken angstlösend, krampflösend, muskelentspannend, beruhigend, schlaffördernd, aber auch stimmungsaufhellend bis zur Euphorie.

Wirkstoffe	Medikamenten- bzw. Handelsnamen	
	Handelsnamen bei Generika-Präparaten häufig Wirkstoff plus Herstellername	
Diazepam	Faustan® Valocordin-Diazepam®	Valium®
Bromazepam	Bromazanyl® Lexostad® neo OPT®	Gityl® Lexotanil® Normoc®
Flunitrazepam	Fluninoc®	Rohypnol®
Nitrazepam	Imeson® Novanox®	Mogadan® Radedorm®
Dikaliumclorazepat	Tranxilium®	
Medazepam	Rudotel®	Rusedal®
Flurazepam	Dalmadorm®	Staurodorm Neu®
Clobazam	Frisium®	
Prazepam	Demetrin®/Mono Demetrin®	
Chlordiazepoxid	Radepur®	Librium®
Tetrazepam (Ind: Muskelrelaxanz)	Musaril®	

Figure 2. Simplified version of the PRISCUS pocket card for practice staff.

Table 1. Elements of the intervention.

No.	Intervention group	Control group
1.	CME event dealing primarily with potentially inappropriate medication (PIM), strategies to avoid PIM, and drug-drug interaction (DDI)	CME event dealing with general aspects of pharmacotherapy for elderly patients
2.	PRISCUS card: modified and abbreviated PRISCUS list containing 17 drugs, 3 interactions, and several clues on drug monitoring	Not provided
3.	PRISCUS manual: comprehensive overview of PIM, strategies to avoid PIM, and the PRISCUS list	Not provided
4.	peer educational outreach visit offered as an addition to the CME event, focusing on questions of potentially inappropriate medication in patients/cases of the office/practice	Not provided
5.	telephone hotline opportunity for pharmacological counselling, addressing potentially inappropriate medication and other issues of pharmacotherapy, as requested by participating physicians	telephone hotline offered for general counselling on issues of pharmacotherapy in elderly patients

CME, continuous medical education; DDI, drug–drug interaction; PIM, potentially inappropriate medication.

not able to attend the training event at any of the alternative dates suggested, will be offered training in their practice by qualified and experienced GPs of the study team, that is ‘training by peers’.^{28,29}

Physicians from the subgroup of the experimental intervention, in which both physicians and their practice staff are involved, also attend the above mentioned professional training event. Yet the training of the practice teams will always be in their respective practices. Physicians/practices randomised to the control group will be invited to attend a professional training event that includes a lecture about general aspects of geriatric pharmacotherapy without any further take-home materials.

Recruitment of participants and study procedure

GPs of the practice networks of the universities of Witten/Herdecke ($n=900$) and Hannover Medical School ($n=1045$), both Germany, including both rural and urban settings, will be informed about the study and the opportunity for participation. Participating doctors should intend to continue practicing for at least one more year and have to provide written informed consent. In the practice, patients aged ≥ 70 years who presented in the

practice during the preceding 3 months for any health problem, and who have been prescribed six or more drugs for regular use, will be identified. Eligible patients will be contacted by the practices, informed briefly about the planned study and invited to participate. If patients are interested, an appointment at the physician’s office will be arranged to receive written and verbal information about the aims of the study and study arrangements as well as a check on the inclusion and exclusion criteria. After written informed consent has been obtained, a subsequent appointment will be arranged for the assessment of baseline data (t0). Apart from gender and age, baseline data include educational level, insurance status, and all information required to calculate the Charlson Comorbidity Index.³⁰ The cooperation partners from General Practice will design an easily manageable, comprehensive, and informative geriatric assessment (MAGIC Assessment) based on the formerly explored STEP Assessment. The MAGIC Assessment shall be deployed within both arms of the RIME study to provide a solid overview about relevant health problems that have to be included into the pharmaceutical treatment plan of elderly general practice patients. Therewith we intend to attract GPs attention to the complexity of multimorbidity, and that the latter should be accounted for when aiming to improve the quality

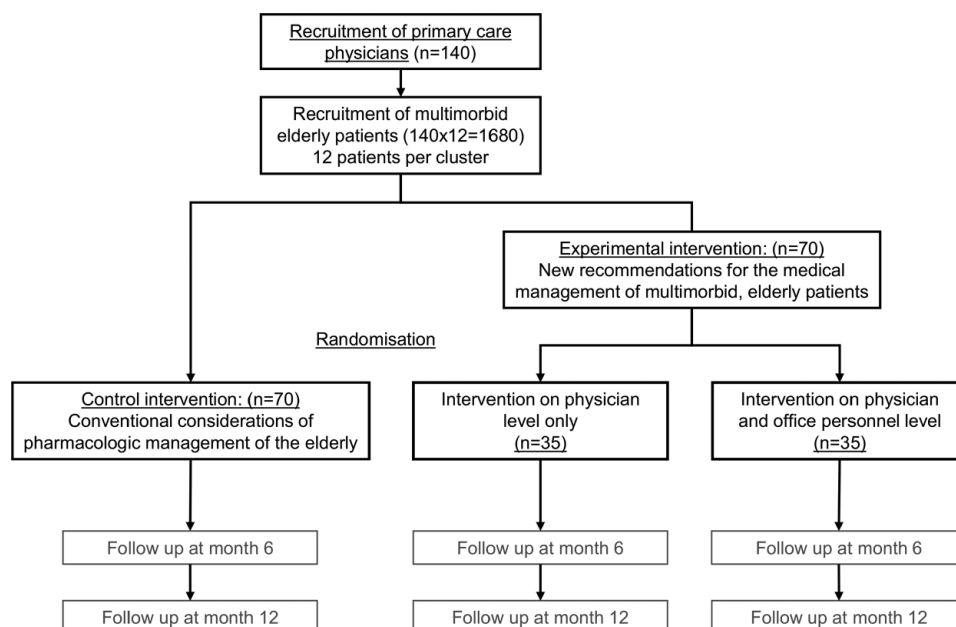


Figure 3. Overview of the proposed study procedure.

of prescribing. Moreover, the MAGIC Assessment will provide baseline data to characterise the health status of the RIME study population.³¹ Apart from specific health problems, the MAGIC assessment also covers tests of functional abilities, for example, mobility, cognition and depressive mood. Laboratory values for sodium, potassium and serum creatinine will be taken from the practice database where the most recent value available will be documented for the RIME study.

After collection of baseline data, a date for the first telephone interview will be arranged with patients. This should be as close as possible to the baseline appointment, that is, within the next 3 weeks. Trained staff will ask patients about all medications prescribed as well as over-the-counter products with PZN codes ('Pharmazentralnummer', German standard identification number for marketed medicinal products), which can be found on medication packages. This code characterises a unique medication, that is, active substance, dose per unit, number of units per package and manufacturer. In addition, patients will be asked for the number of doctors' appointments, use of medical aids and appliances, surgeries and times spent in rehabilitation centres. The telephone interview also includes enquiries regarding lifestyle, pain, depression (using the Geriatric Depression Scale GDS-5), quality of life

(EQ-5D, SF-12), and physical activity (PRISCUS-PAQ).^{23,24,32,33} Frailty is assessed by means of the 'Vulnerable Elders Survey 13', VES-13.³⁴ The interview is expected to last approximately 45 min.

Participating patients will again be interviewed by phone after 6 and 12 months. These interviews are designed to capture patients' present medications and thereby identify PIM and/or DDI as the primary endpoint. In addition, secondary endpoints will be gathered and potential adverse events recorded. The telephone interview after 12 months will be the end of patient participation in the study. Figure 3 gives an overview of the proposed study procedure. The scope and times of data acquisition are listed in Table 2. Data management including issues of data safety, quality checks, etc. will be performed centrally, and in accordance with established internal standards.

Randomisation and masking

Once 12 participants have been recruited in a given practice, the practice will be randomised to either the group with experimental intervention or to the control group. Randomisation will include blocks of variable length that will be stratified for the two practice-recruiting regions, Witten/Herdecke and Hannover. Randomisation

Table 2. Data assessment.

No.	Items/questions/questionnaires	Baseline	6 months	12 months
1.	Demographic data	x		
2.	Current medication	x	x	x
3.	Compliance with medication (self-reported)	x	x	x
4.	Selected symptoms/possible side effects	x	x	x
5.	Life style variables (for example, smoking habits, alcohol intake)	x		
6.	Sleep quality	x	x	x
7.	Falls and fractures	x	x	x
8.	Charlson comorbidity index (adapted version)	x		
9.	PRISCUS physical activity questionnaire (PRISCUS-PAQ)			x
10.	MAGIC assessment	x		
11.	GDS-5	x	x	x
12.	vulnerable elders survey questionnaire (VES-13)	x		
13.	Ten word list (for immediate and delayed recall)	x	x	x
14.	EQ-5D quality of life questionnaire	x	x	x
15.	SF-12 quality of life questionnaire	x	x	x
16.	FIMA questionnaire	x	x	x

EQ, EuroQuol; FIMA, Health-related resource use in the elderly; GSD, geriatric depression scale; MAGIC, Manageable Geriatric; PRISCUS-PAQ, PRISCUS physical activity questionnaire; VES-13, vulnerable elders survey.

will be performed centrally under the responsibility of the leading statistician. Fax will be used for communication.

Primary care practitioners and practice participants will be blinded as to the group to which they are assigned. Practitioners in both groups are merely informed about the requirement of participating in a training course. However, it cannot be ruled out that some GPs will ask for further information in the course of the trial. In addition, the tasks of the GPs are to make a first appointment with the patients and briefly explain the study and later pass on laboratory values of the patients.

We think that this involvement is rather small and will not cause sustained heightened awareness or change behaviour.

Data collection for the primary endpoint – the capture of current medication according to the participants' own information – and for secondary endpoints, will be performed by trained call-centre staff who are blinded to group allocation.

Sample size estimation

Based on international literature and on analyses of the prevalence of PRISCUS PIM,^{9,25,26} we assume a prevalence of potentially inappropriate medication of at least 25% in the study population. We consider this as a rather conservative estimate, as DDIs are not included in this sample size estimation. A 9% reduction in the proportion of patients with PIM down to 16%, which corresponds to a relative risk (RR) of 0.64, is considered a clinically meaningful effect size. In similar studies, the expected maximum

intra-cluster correlation coefficient (ICC) indicated for the primary care sector was about 0.085.^{35–37} With 12 patients per cluster, this means inflating the sample size ('inflation factor' due to cluster randomisation) by 1.935. On this basis, a sample size of 1680 patients (12 per cluster in 140 clusters) was determined necessary to reach a test power of 90% at a 5% level of significance using *t*-test. For the screening needed to establish patient eligibility and readiness to participate, we factored in 20% more practices (168 instead of 140 clusters) and 25% more patients per cluster (15 instead of 12 patients), totalling an overall number of 2520 patients (168 × 15).

Statistical analysis

Analysis will be performed following the intention-to-treat principle. The efficacy of the intervention in reducing PIMs will be established by comparing the difference *D* of the proportions of patients with PIM and/or DDI between baseline and 12 months follow up between the intervention and the control group. For comparison of the difference *D* between the intervention and the control group, an analysis of variance (ANOVA) with study centre (Hannover or Witten) as covariable will be used. The evaluation of secondary endpoints will be explorative using mixed models. Potential unintended effects of the intervention, like falls, hospitalisation or death, will be reported descriptively.

Subgroup analysis

Two pre-defined subgroup analyses are planned. The first will compare the effects of the intervention between the two subgroups of the intervention group: one with physician only training, and one with physician and practice staff training. The assumption is that training of the whole practice team, physicians and their practice staff, will be more effective than training physicians alone. The second subgroup analysis will restrict the analysis to participants considered to be vulnerable as identified by the VES-13 tool.³⁴ The assumption is that elderly people of advanced age and with functional limitations, that is, frail elderly, are at higher risk of experiencing medication side effects due to PIM and/or DDI. We assume that the subgroup of frail elderly may benefit more from the intervention.

Ethics and study registration

Like any research involving human subjects, this study is to comply with the ethical principles stipulated in the Declaration of Helsinki. All applicable national legislation, including data protection regulations, will be followed and monitored during the planning and conduct of the study. The trial protocol and other study documentation were submitted to the competent Ethics Committee for evaluation. The Ethics Committee of Witten/Herdecke University approved the project by vote on 28 February 2012 (application no. 147/2011). The vote of approval by the Ethics Committee of the Hannover Medical School was obtained on 23 February 2012 (application no. 1361–2012). All relevant protocol modifications, for example inclusion or exclusion criteria, outcomes, etc., and relevant changes in study arrangements will be reported to the ethics committee as amendments. The study was registered in the 'German Clinical Trials Registry' (DRKS) under number DRKS00003610. Study results will be reported to participating physicians and their practice staff after finishing the main analysis. Scientific meetings, media and journal publications will be used to disseminate results, once available.

Discussion

RIME investigates the effect of professional training on the subject of reducing PIM by focussing on criteria of the PRISCUS list and important DDI in community-dwelling elderly patients. The design of this study offers several advantages over previous studies. First, the intervention is performed in GP primary care practices, that is, in the setting where most drugs are prescribed. If the intervention turns out to be effective, a high number of patients will benefit. The majority of previous studies on the reduction of potentially inappropriate medication have been conducted in in-patient settings, so that their concepts are not readily transferable.^{38–41} The results of European multinational trials are expected shortly.^{42,43} Our target group are those elderly, community-dwelling patients who are able to visit their GP, and having an estimated life expectancy of 6 months or longer. This population represents a large group of patients visiting GP offices and can be further analysed with regard to vulnerability testing.

An important aspect of our intervention lies in the fact that the target group are the GPs and their practice staff in primary care. This means that the intervention of our study does not consist of a predefined medication review in which to assess and modify patients' medications, for example, by trained pharmacists,³⁶ but rather in the training and mentoring of GPs, which is expected to result in a change of their medication management. A positive effect would prove that the intervention works, even in the absence of implementation of an additional health care professional, and concurs with the current routine in Germany. In other studies, attending inpatient doctors adopted the recommendations of an external consultant or of a team of experts,^{39,41} so that the effect of the recommendations cannot clearly be distinguished from the influence exerted by the specialists or teams of experts.

Our study uses the design of cluster-randomised clinical studies. This is necessary because randomisation units refer to practices/the participating GP rather than individual study participants. This design is considered the gold standard in precluding contamination effects. In previous studies, the intervention was often carried out in one single institution or single hospital. A mutual influence between the two different intervention groups *via* the medical staff involved in treating the study groups, therefore, could not be fully ruled out.

Finally, software-assisted decision tools or other measures requiring preparations in the practice will not be necessary.⁴³ Instead, the intervention relies on easily implemented ways of informing and training doctors and practice staff in the existing context of the primary care system in Germany. In this respect, the approach chosen for the present study is a pragmatic one. German general practices work with different practice software and may already use electronic prescribing warning. The PRISCUS list has been implemented in some GP software systems lately, after the start of the trial. However, GPs often switch off the warning system, as the alert threshold is rather low. In addition, we expect equal distribution of use or non-use of the warning systems following randomisation.

In this trial, patient telephone interviews are used to gather information about drug use, outcomes and health care utilisation. This approach has

been tested in previous studies and allows for data collection without disturbing the workflow in primary care practices.⁴⁴ As over-the-counter medication contributes significantly to polypharmacy and DDIs, direct information will be obtained from patients.

It is important to note that training of not only GPs can be implemented, but also practice staff. Medical assistants play an important part in patient contact and arranging appointments. Due to their organising functions, they communicate more frequently with patients, and are able to pre-sort and focus on patients' current concerns and problems. Involving the practice staff in the intervention increases the chance of identifying problems in a patient's medication and of adequately addressing them. If an intervention is successful, its impact may be increased when involving medical assistants. This version of training the practice staff and not merely the doctors of a practice, therefore, will be evaluated in the subgroup of the intervention group.

Many comparable studies have chosen the number of potentially inappropriate drugs as their primary endpoint.²⁰ While this approach is widely accepted, the clinical significance of this endpoint is not clear. For this reason, the primary endpoint for the present study is defined as the difference in the proportion of patients with at least one potentially inappropriate medication or one inappropriate interaction. It follows, therefore, that it is not merely reducing prescriptions of PIMs that is the essential difference between the experimental and the control intervention, but the proportion of patients who will not be on any PIM at all. The secondary endpoints, for example, hospitalisations, potential adverse events, and quality of life, will be monitored much like in previous studies.¹⁹

The question to what extent PIM can be reduced in elderly patients has not yet been fully answered. Several studies conducted in diverse settings suggest that various modifications to drug prescription and supply may lead to a reduction of PIM for the elderly. The study presented here will produce new information as to whether, and to what extent, PIM and DDI in the primary care setting can be reduced or precluded by a pragmatic approach that can be implemented easily in everyday practice.

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Author contributions

UT, SW, WG, HJT and PT are coordinating investigators responsible for the study, PT being the principal investigator. All were involved in the application for funding and planning of the study. UT, HJT, HR and PT drafted the manuscript. SW, CM and GT planned recruitment of physicians and participants, and SW, CM, GT, UT and PT planned the interventions. CM and GT were responsible for development of the MAGIC assessment. WG is responsible for the health economic part of the study. UT, HR and HJT planned telephone interviews, follow-up, data management and data analysis. All authors revised and approved the submitted manuscript.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

Availability of data and material

Not applicable.

Consent for publication

Not applicable.

Ethics approval and consent to participate

The Ethics Committee of Witten/Herdecke University approved the project by vote on 28 February 2012 (application no. 147/2011). The vote of approval by the Ethics Committee of the

Hannover Medical School was obtained on 23 February 2012 (application no. 1361–2012). Both the participating primary care physicians and all study participants provided written informed consent. The study was registered in the “German Clinical Trials Registry” (DRKS) under number DRKS00003610.

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