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Effectiveness of a complex intervention on PRIoritising MULtimedication in Multimorbidity (PRIMUM) in primary care: results of a pragmatic cluster-randomised controlled trial.

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Key words:

Multimorbidity; Multiple Chronic Conditions[MeSH]; comorbidity [MeSH]; polypharmacy [MeSH]; complex intervention; medication reconciliation [MeSH]; drug therapy, computer-assisted [MeSH]; medication appropriateness index; primary care [MeSH]; general practice [MeSH]

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Abstract: (299 words)

Objectives: Investigate the effectiveness of a complex intervention aimed at improving the appropriateness of medication in older patients with multimorbidity in general practice.

Design: Pragmatic, cluster-randomised controlled trial with general practice as unit of randomisation. Outcomes were measured at patient level.

Setting: 72 general practices in Hesse, Germany.

Participants: 505 randomly sampled, cognitively intact patients (≥60 years, ≥3 chronic conditions under pharmacological treatment, ≥5 chronic drug prescriptions with systemic effects); 465 patients and 71 practices completed the study.

Interventions: Intervention group (IG): The health care assistant conducted a checklist-based interview with patients on medication-related problems and reconciled their medications. Assisted by a computerised decision-support system, the general practitioner optimized medication, discussed it with patients and adjusted it accordingly. The control group (CG) continued with usual care.

Outcome measures: The primary outcome was the medication appropriateness index (MAI), as rated in blinded medication reviews, and calculated as the difference between baseline and after 6 months; secondary outcomes: quality of life, functioning, medication adherence.

Results: At baseline, a high proportion of patients had appropriate to mildly inappropriate prescriptions (MAI 0-5 points: n=350 patients). Randomisation revealed balanced group sizes (IG: 36 practices/252 patients; CG: 36/253). Intervention had no significant effect on primary outcome: mean MAI sum scores decreased by 0.3 points in IG and 0.8 points in CG, resulting in a non-significant adjusted mean difference of 0.7 (95% CI -0.2 to 1.6) points in favour of CG. Secondary outcomes showed non-significant changes (quality of life slightly improved in IG but continued to decline in CG) or remained stable (functioning, medication adherence).

Conclusions: The intervention had no significant effects. The high proportion of participants receiving both appropriate prescriptions and enjoying good quality of life and functional status at baseline and outcomes measures that insufficiently reflected undertreatment, limited our ability to detect an effect.

Trial registration: Controlled Trials: ISRCTN99526053 - August 31, 2010 - http://www.controlled-trials.com/ISRCTN9952605 and ClinicalTrials.gov: NCT01171339 - July 27, 2010 - http://clinicaltrials.gov/ct2/show/NCT01171339?term=PRIMUM&rank=1

"Strengths and limitations of this study"

- The PRIMUM intervention was developed and piloted in accordance with the latest MRC guidance on complex interventions.
- The effectiveness of the PRIMUM intervention was evaluated in a rigorously conducted cluster-randomised trial that involved random sampling of patients, disclosure of treatment allocation after baseline completion, and adherence to the protocol.
- To evaluate the generic patient-centred strategy of applying PRIMUM, we used the commonly used medication appropriateness index (MAI), as this implicit measure allows individualized assessments.
- We blinded both the assessment of the primary outcome MAI and the statistical analyses.
- Key limitations were that the baseline values of MAI and the secondary outcomes did not provide enough scope for improvement, and that medication underuse in polypharmacy was not sufficiently reflected in our outcome measures.

Introduction:

The prevalence of multimorbidity, i.e. the co-occurrence of multiple chronic or acute diseases and medical conditions in one person,[1] increases with age, and most primary care consultations currently involve patients with multiple conditions.[2-4] Multiple disorders in patients are likely to result in multiple drug prescriptions. This increases the risk of drug-drug and drug-disease interactions, inappropriate dosages or drug selection, and non-adherence of patients. They may, however, also result in undertreatment, particularly in the elderly.[5-10] Inappropriate prescriptions may result in hospitalisations, falls and related injuries, decreased quality of life, cognitive and physical dysfunction, loss of autonomy, and increased mortality.[6-8,11-14] Negative health outcomes caused by inappropriate polypharmacy are responsible for high costs for hospital treatment, home care and nursing homes.[15-17] A high proportion of morbidity and costs may be preventable – for instance 20% to 50% of medication-related hospitalisations on internal wards have been estimated to be avoidable.[13,16,18-20] Recently, Dreischulte and co-researchers observed a reduction in hospital admission rates for gastrointestinal ulcers or bleeding in the DQIP trial evaluating a complex intervention addressing nine specific high-risk prescribing patterns such as nonsteroidal anti-inflammatory drugs (NSAIDs) in renal failure, or in combination with oral anticoagulants.[21] Similarly, the PINCER, the EFIPPS, and other trials evaluated interventions addressing safety indicators and achieved a reduction in high-risk prescribing through adherence to explicit criteria that are relevant to public health.[22,23] However, 'the range of reported effect sizes was modest, and it is unclear whether such interventions can result in clinically significant improvements in patient outcomes'.[24]

Furthermore, considering there are more than 10,000 known diseases, the number of possible interactions between diseases and treatments in patients with multimorbidity is vast, and patients may not be able to cope with the treatment burden.[25] Generic patient-centred strategies to assess potential interactions and to prioritise and individualise management in accordance with patients' preferences and shared treatment goals have been recommended for patients with multimorbidity and polypharmacy.[26-32] In these patients, evidence of interventions with proven effectiveness on clinical outcomes remains scarce. However, recent Cochrane reviews have identified strategies that appear to be beneficial in terms of reducing inappropriate prescribing.[33,34] Based on promising strategies to combat inappropriate polypharmacy and in accordance with guiding principles to manage patients with multimorbidity, we developed a complex intervention that also involves a health care assistant (HCA) from the practice.[35] In Germany, HCAs receive less training than nurses and are comparable to certified medical assistants in the USA. In usual care, HCAs work as receptionists, assist GPs (e.g. in diagnostic procedures or wound management) and conduct, for

instance, dietary counselling. On many occasions, HCAs have successfully participated in chronic care interventions where they have, for example, surveyed patients by following protocols with fixed interview questions for conditions such as osteoarthritis, major depression, and chronic heart failure, under the supervision of GPs.[36-40]

In accordance with Medical Research Council (MRC) guidance on developing and evaluating complex interventions, we tested the feasibility of the complex intervention in a pilot study.[35] Based on its findings we improved the intervention and trial design. This manuscript describes the results of a cluster-randomised trial investigating the effectiveness of the complex PRIMUM intervention on the appropriateness of prescriptions in older patients with multimorbidity and polypharmacy in general practice. To evaluate the generic patient-centred strategy of applying PRIMUM, we used the medication appropriateness index (MAI) as primary outcome, as this implicit (non-criteria-based) measure allows an individualized assessment of medication appropriateness.[41-43]

Methods:

Study design

The study was a pragmatic, cluster-randomised controlled trial with the general practice as the unit of randomisation. To further reduce contamination of the control group and unlike the pilot study, detailed information on the intervention treatment was only provided to the intervention group.[35] Primary and secondary outcomes were measured at patient level (web-appendix 1: study protocol).

Setting and participants

General practices in the German state of Hesse were eligible if they provided primary care under the German statutory health insurance system, and if at least one of the HCA staff members was able to access the internet in the practice. Practices specializing in unconventional treatments or in special indications (e.g. HIV) were excluded. To recruit practices, we sent letters to about 1,600 practice addresses provided by the Association of Statutory Health Insurance Physicians of Hesse – addressees were not exclusively active general practitioners. We checked inclusion and exclusion criteria for those who were interested by phone, and agreed upon a time for investigator training (**Figure 1**: icon "1").[44-66] GPs that did not respond to the original letter received a phone call reminder. We phoned a 10% random sample of those who did not respond to either the letter or the reminder up to three times and briefly interviewed them as far as possible on inclusion and exclusion criteria, practice characteristics, and reasons for non-participation.

[About here: Figure 1]

A random sample of seven patients per practice (**Figure 1**, patient recruitment, icons "c" to "e") that were ≥ 60 years old, had ≥ 3 chronic conditions under pharmacological treatment, ≥ 5 chronic drug prescriptions with systemic effects, ≥ 1 practice visit during the past quarter, and were able to fill in questionnaires and participate in telephone interviews, were included. To include a greater number of patients at risk of (manageable) interactions than in the pilot study,[35] patients had to have diseases from at least two different organ systems operationalized as two different chapters of ICD-10. The chapters "H" (diseases of the eyes and ears) and "E00" to "E04" (diseases of the thyroid gland without hyperthyroidism) were not counted because their potential for systemic interactions was considered to be low. We excluded patients with cognitive impairment (Mini-Mental Status Examination, MMSE < 26),[47] because we designed our intervention for cognitively intact patients and did not target caregivers. Further exclusion criteria were a life expectancy ≤ 12 months, alcohol and drug abuse (based on the GP's assessment), or participation in a clinical trial 30 days prior to inclusion.

Randomisation, allocation concealment, and blinding

The first patient from each practice served as the basis for randomisation (**Figure 1**, icon "i"). Patients registered thereafter were treated according to practice status (control or intervention), which was assigned in an allocation ratio of 1:1 using a block randomisation of variable block length. At the study centre, an external researcher generated the allocation sequence using the random number generator of Microsoft EXCEL. Allocation concealment was disclosed to the practice after baseline completion. Owing to the nature of the intervention, it was not possible to blind GPs, HCAs, patients, and the study team. Treatment allocation was blinded to the clinical pharmacologist conducting medication reviews for the primary outcome (medication appropriateness index, MAI) and to the statistician.

Intervention and control groups

Intervention group

The PaTplot [67] (**Figure 1**, icons "j" and "3" to "5") shows the four elements of the complex intervention. It consists of (1) a brown bag review and (2) a checklist-based pre-consultation interview with the patient that is conducted by the HCA (**web-appendix 2**), (3) a computer-assisted medication review carried out by the GP and (4) a GP-patient consultation to optimise and prioritise medication. Trained HCAs and GPs (**Figure 1**, item "2") implemented the intervention on a single occasion, which took the GP and the HCA a per-patient average of 35 and 45 minutes respectively.[35] The practice team for the intervention group received the GP guidelines for ambulatory geriatric care prepared by the Hesse Guideline Group (**Figure 1**, item "k").[46]

Control group

The control group continued to receive usual care but the practice team also received the GP guidelines for ambulatory geriatric care (**Figure 1**, item "k")[46] to harmonize usual care in both groups.

Outcomes

The primary outcome was the difference in MAI sum score [41,68] at 6 months minus the corresponding baseline score (MAI T1–T0). The MAI is comprised of ten items: indication, correctness of dosage, correctness of direction, practicality of direction, drug–drug interactions, drug-disease interactions, unnecessary drug duplications, correctness of treatment duration, and costs. Each item is rated from '1' (appropriate) to '3' (inappropriate) where '2' represents a middle rating of uncertain appropriateness. MAI sum scores are calculated for the entire medication regimen. The clinical pharmacologist (SH) for the pilot study rated nine items per prescription in accordance with piloted procedures in a blinded chart review.[35] The MAI item on costs was omitted because variable discount contracts between pharmaceutical companies and statutory health insurers preclude cost comparisons in Germany. Based on the excellent intra-rater reliability of the MAI ratings in the pilot study (slightly better than inter-rater reliability),[35] we did not perform a duplicate MAI rating. MAI ratings were transformed by subtracting 1 from the original rating, resulting in values ranging from '0' (best rating) to '2' (worst rating), and summed to give an MAI score per prescription (theoretically ranging from 0 to 18) and across the entire medication regimen of the patient. Lower MAI sum scores denoted better prescribing appropriateness. A negative difference in MAI sum scores therefore reflected an improvement in prescribing quality.

Secondly, we measured the change in the MAI score after 9 months (MAI T2–T0). On the assumption improved medication appropriateness would result in improved health-related quality of life and functional status, we measured the differences in EQ-5D,[48,49] changes in perceived future life expectancy (a quality of life-related concept indicating wellbeing and positive life evaluation measured in years of expected and desired lifetime duration),[52,53] functional status (differences in vulnerable elderly survey, VES-13),[50] and all-cause hospitalisation after six and nine months (T1-T0 and T2-T0).

To explain intervention effects, we also measured changes in satisfaction with shared decision making (Man Son Hing scale, MSH)[54,55] and medication adherence after six and nine months (T1-T0 and T2-T0). We investigated a) self-reported adherence in accordance with Morisky (low scores indicating good adherence);[69] b) discrepancies between medicines actually taken (reported at patient's interviews) and medicines prescribed (reported by GP), as expressed in three scores.[70] The scores were based on ratios calculated as follows:

(1) The drug score (DS) representing the ratio of the number of drugs reported by the patients divided by the number of drugs reported by the GP,

(2) The dose score (DoS=d1(a1)+d2(a2)+d3(a3)+…/n), where d_i is the drug used by the patients (value 0 or 1), n is the number of drugs in the GP's report, and a_i is the dose-deviation ratio calculated by dividing the patient's reported daily dose with the daily dose prescribed by the GP, and

(3) The regimen score (RS=d1(b1)+d2(b2)+d3(b3)+…/n), where b_i is the regimen-deviation ratio calculated by dividing the patient's reported daily intake frequency (once daily, twice daily, etc.) with the corresponding frequency prescribed by the GP.[70]

Scores outside an interval of 0.8–1.2 were considered to be divergent. Further adherence-related measures assessed the complexity of medication (total number of prescriptions, number of single doses/day, and Medication Regimen Complexity Index, MRCI).[71]

Sample size

Based on the results obtained in previous studies,[35,72] a difference in the change values (MAI T1–T0) of at least 2 units between the treatment groups was considered clinically relevant. Based on the pilot study, a standard deviation of 6 units was expected, resulting in a Cohen's effect size d of 0.3 representing a small effect size.[73] Assuming an intracluster correlation coefficient (ICC) of 0.03 at practice level [74] and an average cluster size of 7 patients, a total of 62 practices and 434 patients (31 practices and 217 patients per treatment arm) were required to detect such an effect with 80%

power using a two-sample t-test at a two-sided significance level of α=0.05. The sample size calculation was performed using NCSS PASS 2008 (Inequality Tests for Two Means in a Cluster Randomised Trial). On the basis of an assumed drop-out rate of approximately 10%, the sample size was adjusted to a total of 70 practices and 490 patients (35 practices and 245 patients in each treatment group).

Statistical analysis

We performed descriptive analyses of the primary endpoint, the secondary endpoints, and all patient and practice characteristics (separately for patients in both groups) and calculated mean and standard deviation for continuous variables, and relative and absolute frequencies for categorical data.

In the primary analysis and using a two-sided significance level of α=0.05, we tested the null hypothesis H0: μ1 = μ2 (the mean difference MAI T1–T0 is equal in the two groups) against the alternative hypothesis H1: μ1 ≠ μ2 (the mean MAI T1–T0 are different in the two groups). Because of cluster randomisation, we used a multilevel regression approach with patients at level one and practices at level two. The primary model included treatment group and MAI baseline as fixed factors and practice as a random factor. A compound symmetry correlation structure was assumed. The results are presented as the adjusted mean between-group difference in MAI T1–T0 with the corresponding 95% confidence interval. In addition, the practice-related ICC was estimated. The primary analysis was performed in adherence to the intention-to-treat principle,[75] and additional sensitivity analyses were conducted on a per-protocol analysis set. In the multilevel approach, we made use of the missing at random assumption, assuming that the baseline or the treatment variable can explain missing data in the response. Thus, no additional imputation of missing data was conducted. In a sensitivity analysis, we replaced missing values for the primary endpoint using the baseline observation carried forward (BOCF) approach. The statistical analyses of the secondary endpoints used the same multilevel approach as the primary analysis. A linear, binary or Poisson mixed model was fitted in accordance with the scaling of the considered endpoint. The obtained p-values in the secondary analyses are only interpreted exploratively.

Results:

Participant flow and non-responders

Of the 1,662 practice addresses we sent letters to (1,332 of them also received a phone call reminder), 1,325 did not reply at all, 102 answered but were not interested in further information, and 235 general practices asked for further details and were assessed for eligibility. Of those, 153 practices finally declined to participate, three did not meet inclusion criteria, and seven were not able to create screening lists using their practice computer. Of the 72 included practices, 3,478 IDs for potentially eligible patients were provided of which a random sample of 1,346 IDs was drawn at the study centre and sent to the practices. In total, 505 patients were consecutively included from the random sample and 465 completed the study (intervention group 238/252, control group 227/253) (flow chart: **web-appendix 3**).

Of the 1,325 practices that did not reply, we called 132 randomly selected practices. Six practices did not answer the phone, 51 were willing to answer all questions, and 75 provided partial information. Sixty-one interviewed practices (48%) were not eligible (seven were not active GPs; 51 had no internet access, and three declined to say). Practice characteristics and reasons for not responding are provided in **web-appendix 3**.

Baseline characteristics of participants

Most practices were single-handed (57%), medium-sized (64%), and located in small to mid-sized towns (57%). Slightly more male GPs (57%) participated; most of them were specialized in primary care (83%). On average, they were 51 years of age, had more than 23 years of clinical experience, and had worked in private practice for about 15 years. With one exception, HCAs were female. They averaged about 40 years of age, had about 17 years of clinical experience, and had worked in the practice at various employment levels (49% less than full time) for an average of 10 years. About three-quarters were qualified HCAs. Patients were slightly more often female (52%), had a median age of 72 years, and averaged eight prescriptions in nine single doses per day. Almost all patients were covered by statutory health insurance (96%), and looked after themselves (94%). 58% participated in one of the national disease management programs (DMP) (baseline characteristics: **Table 1**[76]).

[About here: Table 1: Baseline characteristics of practices and patients]

Outcomes

Our study found the intervention to have no significant effect. The mean MAI sum scores had decreased minimally in both groups six months after baseline – by 0.3 points in the intervention group and 0.8 points in the control group – revealing a non-significant adjusted mean difference of 0.7 (95% CI -0.2 to 1.6) points in favour of the control group (ITT, per protocol analysis and BOCF approach did not differ). To control for the effects of oversampled patients registered in a DMP, we compared DMP participants with non-participants, which revealed no effects on MAI. Furthermore, socio-demographic factors did not have an influence (**web-appendix 4**). To explore our results, we conducted additional, non-prespecified analyses. As the sample size was not sufficiently large to perform subgroup analyses, we calculated multilevel models, which revealed strong effects of the baseline values of MAI sum scores on the primary outcome MAI T1-T0 ($p < 0.001$) (**Figure 2a**)**.** The figure also shows the low proportion of patients with high inappropriateness at baseline, and the size and direction of the MAI changes in both groups after six months. To explain the relationship between the number of prescriptions and MAI values, we conducted exploratory regression analysis, which approximately revealed a square function (**Figure 2b**).

[About here: Figure 2]

Secondary outcomes showed small, non-significant changes. In the intervention group, patients' self-reported quality of life improved minimally (about 2.3% in EQ-5D, 0.5 years in both expected and desired lifetime) after six and nine months, whereas it continued to decline in the control group (**Figure 3**). Additionally, in the intervention group the mean number of hospital stays decreased and the mean number of days spent in hospital had dropped by half after six months, but in both groups the event rate was too small to show significant differences (intention-to-treat analyses of the primary and secondary outcomes: **Web-appendix 4**).

[About here: Figure 3: Secondary outcomes related to patients' self-reported quality of life measures]

Discussion:

Key findings of the study

This study found the complex PRIMUM intervention to have no significant effects in older patients with multimorbidity and polypharmacy in general practice. According to baseline values, many patients already received appropriate prescriptions and enjoyed good quality of life and functional status. We can therefore conclude that in our study, there was not enough scope for improvement.

Strengths and limitations of study

The systematic development and stepwise evaluation of the PRIMUM intervention in accordance with MRC guidance on complex interventions[77] was a strength as demonstrated by refinements in the design of the main trial, based on the results of pilot testing.[35] Recruitment to target, random sampling of patients, minimal attrition (we lost one cluster to follow-up because the GP moved to another town), and adherence to the protocol are additional strengths when compared with previous studies.[78,79] However, our study also had several limitations.

Firstly, there is no agreed definition of polypharmacy and patient inclusion at the numerical threshold of ≥5 prescriptions was somewhat arbitrary,[80,81] but using a higher threshold would have meant losing patients whose medication was highly inappropriate (Figure 2b). Moreover, the association between the number of prescriptions and health outcomes is not linear: Payne and co-authors found only the most extreme levels of polypharmacy to be associated with increased admission rates in patients with multimorbidity,[82] while Gnjidic and her co-researchers identified the best discriminating threshold to be between 4.5 and 6.5 medicines for associations with frailty, disability, mortality, and falls.[83]

Secondly, our study population may limit the generalisability of the results. Our study was population-based and involved no pre-selection, and the response rate was low. We cannot rule out that relatively ambitious GPs volunteered more frequently. As far as the choice of patients is concerned, we took a random sample within each practice and our selection criteria aimed at including a broad range of diseases involving as many organ systems as possible. We applied the cognition test during recruitment and after consent. However, we excluded patients with dementia, and who were unable to fill in questionnaires, or to answer telephone calls (e.g., nursing home residents), because our ultimate aim was to support regular practice consultations. To enable random sampling, we applied a systematic case finding based on prescription costs as a proxy but oversampled DMP participants. However, German DMPs do not address multimorbidity or polypharmacy and we did not find any DMP impact on outcomes in our study.

Thirdly, our efforts to reduce contamination of controls through a cluster-randomised design and by withholding intervention details may have been substantially contradicted by a potentially important

Hawthorne effect, as has been the case in other studies.[78,84] We also observed improvements in MAI mean values in the control group at first follow-up (Figure 2a), and a slight decrease in the average numbers of prescriptions.

Fourthly, our outcome measures were slightly insensitive. In the intervention group, the marginal increase in the average number of prescriptions indicates that GPs had more often begun to prescribe patients a new medicine. If undertreatment had been a key problem in our study, having the MAI as the main outcome variable would have led us to underestimate its impact, because it does not reliably detect underuse.[42]

Comparison with other studies

Most primary care studies have investigated pharmacist-led interventions, and have shown inconclusive results in various outcomes.[33,85-89] However, pharmacist-led interventions may be difficult to implement in health care contexts in which pharmacists have no access to clinical information (e.g. patients' diagnoses, laboratory tests), patients often visit many different pharmacies, and inter-professional relationships between GPs and pharmacists are not well established, as in Germany.[78,79] In this context in particular, information technology systems have been identified by European GPs as supporting safer prescribing.[90-92] Further factors that have been addressed include support from other health care professionals such as nurses, systematic medication reviews, and greater involvement of the patient.[90-92] However, the efficacy of these measures is inconclusive: Olsson and co-investigators found that a physician-led medication review had no effect on indicators of high-risk prescribing in older patients with polypharmacy .[93] In contrast, a large-scale cluster-randomised controlled trial achieved reductions in unintentional drug duplications, drug-drug interactions, and new prescriptions of potentially inappropriate medications, but failed to show an impact on the discontinuation of inappropriate medicines.[94]

No evidence yet exists that polypharmacy interventions lead to decrease in mortality and hospitalisations,[87] functional decline and falls,[95,96] and health-related quality of life[78,79,93,97-100]. A recent meta-analysis revealed a modest reduction in the number of drugs (on average -0.2 in the intervention group vs.+0.2 in controls) but the results of the included studies differed widely [87] and, considering the frequency and potential impact of medication underuse,[6-8] a reduction in net prescription numbers is an ambiguous study endpoint.

Possible explanations and implications of the study

Our study showed the intervention to have no significant effect. We cannot rule out that there was not enough scope for improvement in our study (Figure 2a: the MAI of the patients included in the left two box plots in both groups could not improve). Additionally, there was a relevant Hawthorne effect (Figure 2a: the patients included in the four box plots of the control group on the right hand side also improved). The patients depicted in the four box plots of the intervention group on the right hand side (Figure 2a) improved less than corresponding patients in the control group, which probably reflects the small numbers of patients and the lack of an intervention effect. In addition, given the MAI's inability to detect changes in inappropriate underuse, it may have not been sensitive enough for the purpose of our study. As any newly prescribed drug worsens the MAI score, unless it is completely appropriate, this may at least partially explain the difference. Ongoing process evaluation may provide further explanations of the outcomes and information on the implications of the study.

Further research is needed into the identification of patients that stand to benefit significantly from an intervention that aims to support the care of complex patients with multimorbidity and high treatment burden.[101,102] Future studies may also benefit from considering a refined choice of outcome measures that adequately takes underuse into account.

Conclusion

We did not find the intervention to have significant effects. The high proportion of participants receiving both appropriate prescriptions and enjoying good quality of life and functional status may have limited our ability to detect a potential effect. Further research should seek to identify groups of patients that are most likely to benefit from such resource-intensive interventions. Outcome measures should be patient-relevant and detect changes in underuse.

(Statements)

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Author's contribution: CM drafted the manuscript, coordinated the study and contributed to the conception, design, data collection and data analyses. SH contributed to the conception and design and conducted the MAI ratings. FMG was the guarantor of the study. JR and LU contributed to the conception, design and conducted data analyses. WEH contributed to the conception and design and provided the study version of CDSS. CG, MB, FO, RP, MvdA, AK, JVM and FMG provided specific advice on the conception, methods, and coordination of the study. All authors critically revised and agreed on the final version of the manuscript.

Ethics approval: The ethics commission of the medical faculty of the Johann Wolfgang Goethe University, Frankfurt / Main approved the study (resolution number E 46/10, file number 123/10, date: 20/05/2010) and all of the participants gave their written informed consent before taking part.

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Table 1: Baseline characteristics of practices and patients

	Control group	Intervention group
Practices	**n=36**	**n=36**
Location (number, percentage):		
City (>100,000 inhabitants)	16 (44)	6 (17)
Mid-sized town (20,000 to 100,000)	6 (17)	10 (28)
Small town (5,000 to 20,000)	10 (28)	15 (41)
Rural area (<5,000 inhabitants)	4 (11)	5 (14)
Single-handed practices (number, percentage)	21 (58)	20 (56)
Panel size‡ (number, percentage):		
fewer than 1,000	11 (31)	12 (33)
1,000-1,499	14 (39)	11 (31)
1,500 or more	11 (31)	13 (36)
General practitioners		
Age (mean, SD)	50.2 ± 7.6	51.9 ± 7.0
Male sex (number, percentage)	21 (58)	20 (56)
Board certificate GP (number, percentage)	30 (83)	30 (83)
Years of clinical experience (mean, SD)	22.6 ± 8.6	23.3 ± 7.9
Years at practice site (mean, SD)	14.3 ± 9.1	15.7 ± 8.4
Health care assistants		
Age (mean, SD)	40.1 ± 8.8	37.8 ± 12.6
Female sex (number, percentage)	36 (100)	35 (97)
Fully qualified HCA (number, percentage)	25 (69)	27 (75)
Years of professional experience (mean, SD)	18.4 ± 9.3	15.9 ± 10.6
Years at practice site (mean, SD)	10.4 ± 8.2	9.6 ± 8.5
Full-time employment (number, percentage)	17 (47)	20 (56)
Patients	**n=253**	**n=252**
Age (mean, SD)	71.7 ± 7.4	72.5 ± 6.5
Female sex (number, percentage)	131 (52)	133 (53)
Covered by statutory health insurance (number, percentage)	243 (96)	243 (96)
Participation in a DMP (number, percentage)	139 (55)	153 (61)
Consultation with specialists in previous six months (number, percentage)	222 (88)	227 (90)
Living with spouse: yes (number, percentage)	166 (67)	152 (61)
Fending for themselves (number, percentage)	236 (94)	237 (94)
Home care situation rated as 'good' or 'very good' in GP assessment (number, percentage)	233 (92)	239 (95)
CASMIN educational classification (number, percentage):		
High	25 (10)	14 (6)
Middle	80 (32)	66 (27)
Low	144 (58)	169 (68)
BMI (mean, SD)	30.3 ± 7.5	30.1 ± 5.6
Charlson comorbidity score (mean, SD)	3.2 ± 2.4	3.0 ± 2.0
CIRS sum score (mean, SD)	7.3 ± 4.3	8.1 ± 4.8
CIRS number of affected organ systems (mean, SD)	4.4 ± 2.3	4.6 ± 2.4

	Control group	Intervention group
Geriatric Depression Scale (mean, SD)	2.4 ± 2.3	2.3 ± 2.2
Previous hospitalisations (number, percentage)	40 (16)	42 (17)
Potential ADR symptoms[†] (number, percentage):		
- Bleeding diathesis[#]	44 (17)	33 (13)
- Ankle edema	78 (31)	84 (33)
- Dizziness[#]	54 (21)	54 (21)
- Dyspnea[#]	86 (34)	70 (28)
- Difficulties urinating	51 (20)	64 (25)
- Abdominal pain[#]	36 (14)	37 (15)
- Tachycardia or palpitation[#]	36 (14)	36 (14)
- Nausea or vomiting[#]	16 (6)	11 (4)

[‡]The number of patient registrations in a practice over a 3-month period, [†]for details see Figure 1, item "h", [#]symptoms appeared on at least several or almost every day;
Abbreviations: ADR – adverse drug reaction, BMI – body mass index, CASMIN - Comparative Analysis of Social Mobility in Industrial Nations,[76] CIRS - Cumulative Illness Rating Scale, GP – general practitioner, HCA – health care assistant, SD – Standard Deviation

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Supplemental files:

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- Web-appendix 3: CONSORT flowchart and practice characteristics of non-responders
- Web-appendix 4: Table 1: results of the intention to treat analyses of primary and secondary outcomes; Table 2: Symptoms for potential adverse drug reactions (ADR) - descriptive analysis
- CONSORT and TIDieR checklists

List of abbreviations

ADR	Adverse Drug Reaction
BMI	Body Mass Index
BMQ	Beliefs about Medicines Questionnaire
CASMIN	Comparative Analysis of Social Mobility in Industrial Nations
CDSS	Computerized Decision Support System
CIRS	Cumulative Illness Rating Scale
CRF	Case Report Form
DS	Drug Score
DoS	Dose Score
GDS	Geriatric Depression Scale
GP	General Practitioner
ICC	Intra-Cluster Correlation-coefficient
ID	Identifier
ITT	Intention To Treat
HCA	Health care assistant
MAI	Medication Appropriateness Index
MediMoL	Medication Monitoring List
MMSE	Mini Mental Status Exam

MRCI	Medication Regimen Complexity Index
RS	Regimen Score
SD	Standard Deviation

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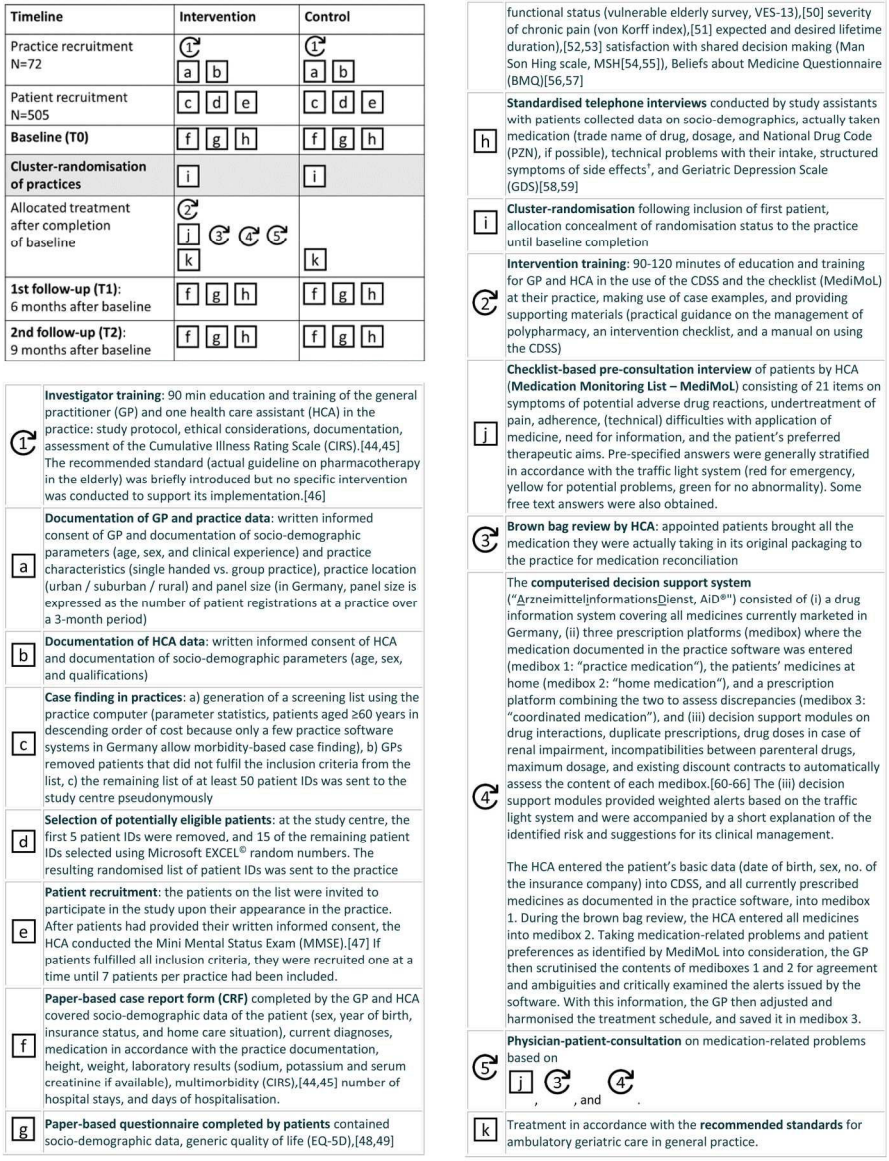

Figure 1: PaT plot of the PRIMUM trial.
Legend: †structured symptoms of side effects: dizziness, dyspnea, tachycardia / palpitations, nausea / vomiting, abdominal pain, bleeding diathesis, difficulties urinating, ankle oedema - frequency expressed as occurrence on one day / several days / almost every day during the past two weeks. Abbreviations: GP - general practitioner; HCA - health care assistant.

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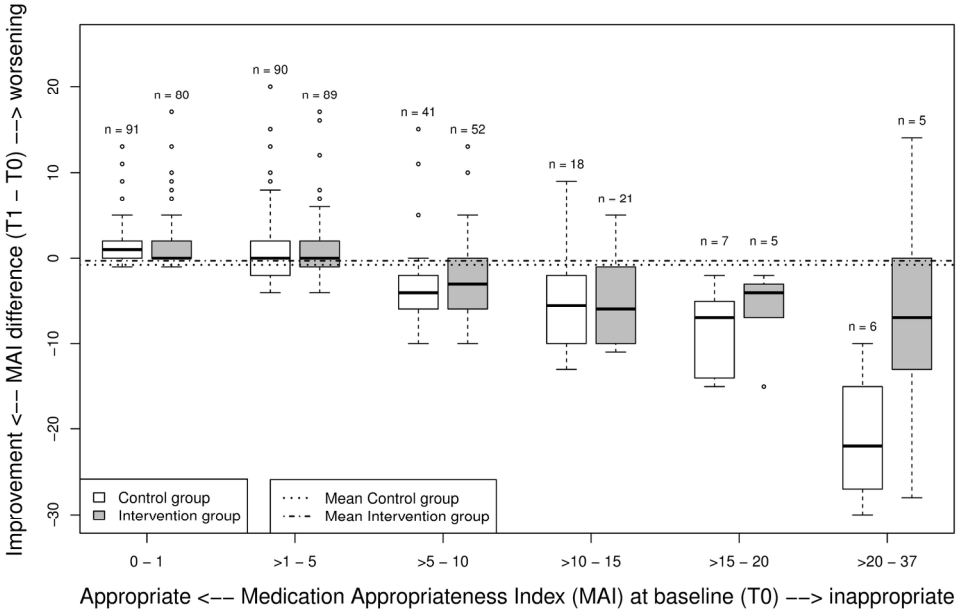

Figure 2: Distribution and changes in the medication appropriateness index (MAI) using baseline values and number of prescriptions

Figure 2a: Changes in MAI scores in intervention and control groups six months after baseline compared to baseline values (absolute numbers of study participants and boxes and whiskers per subgroup are provided)

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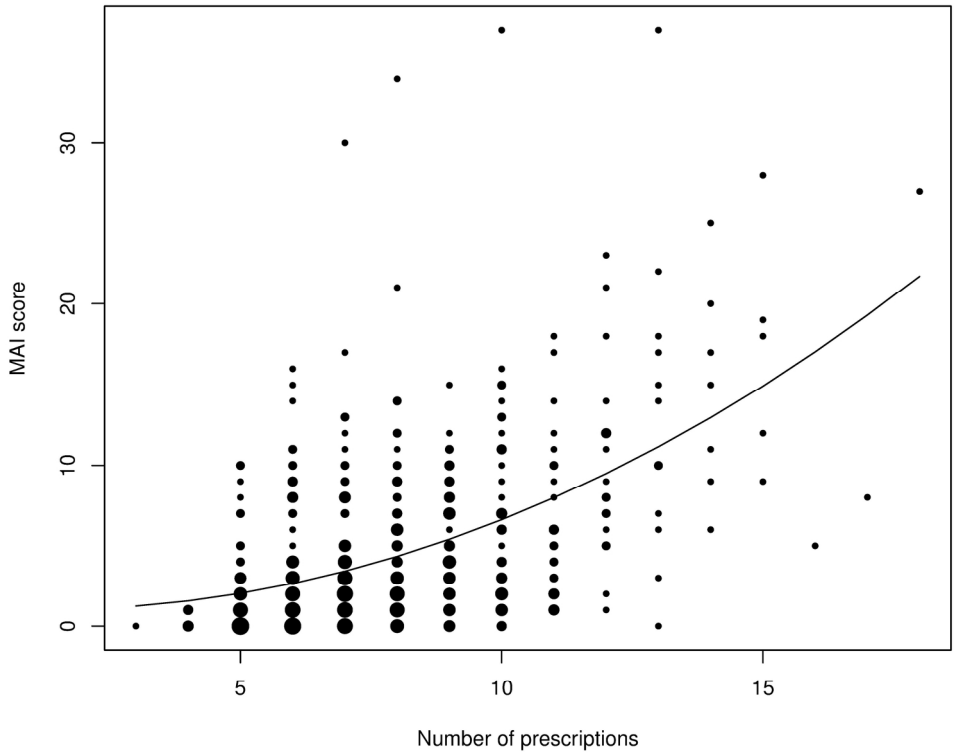

Figure 2b: MAI scores at baseline in terms of the number of prescriptions (higher diameters of drops represent higher numbers of study participants)

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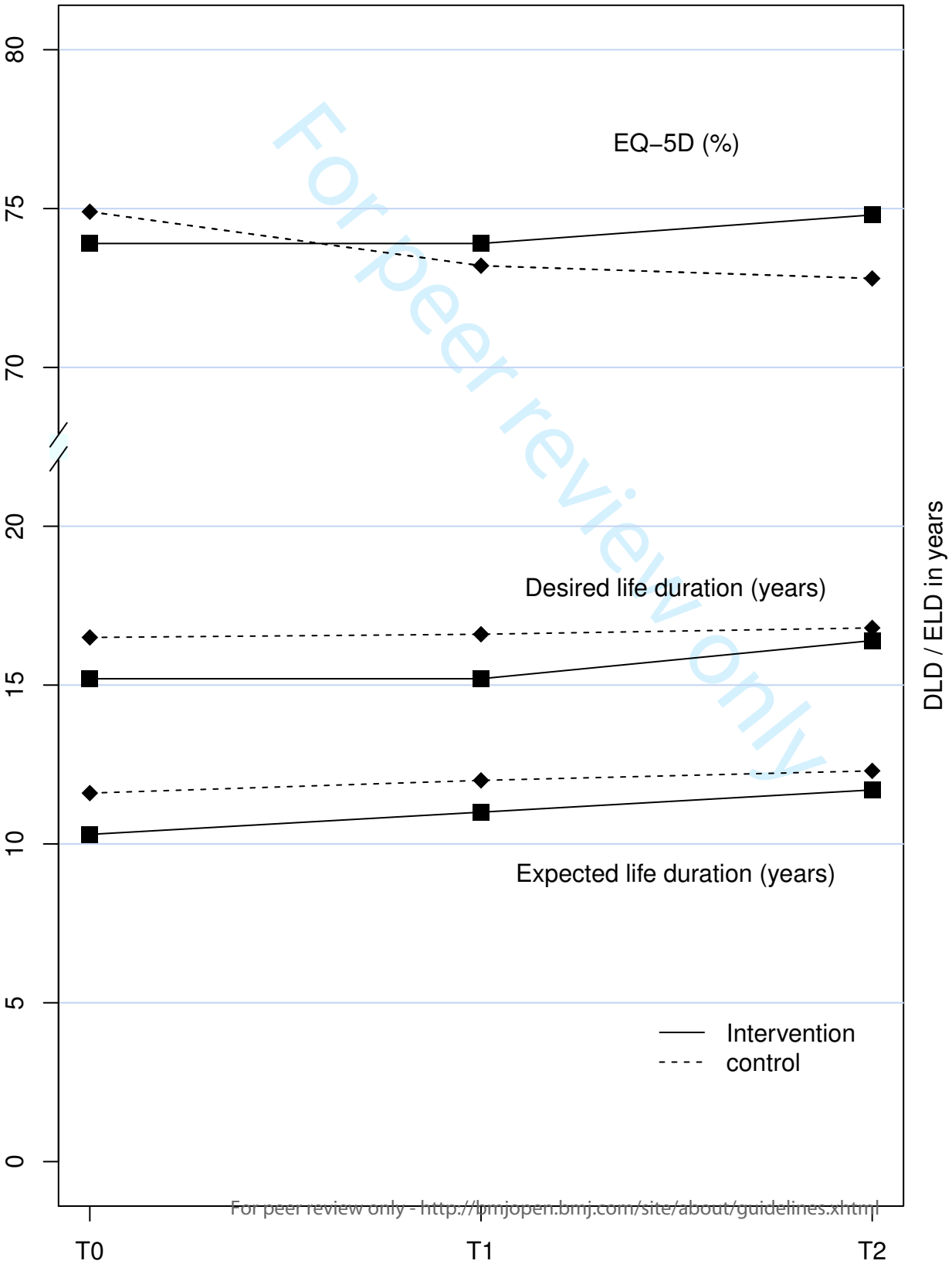

Title:

Prioritising and optimising multiple medications in elderly multi-morbid patients in general practice. - A pragmatic cluster-randomised controlled trial.

[PRIMUM]

PRIoritising ***MU***ltimedication in ***M***ultimorbid patients

Sponsor: **Johann Wolfgang Goethe University Hospital, Frankfurt am Main**

Theodor-Stern-Kai 7
D - 60590 Frankfurt a.M.

The International Standard Randomised Controlled Trial Number (ISRCTN): (follows)

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Sponsor	German Federal Ministry for Education and Research (BMBF) Grant Number: 01GK0702 – Notification of 31.03.2009 and 08.02.2010

1.2 Signature Page

Prioritising and optimising multiple medications in elderly multi-morbid patients in general practice

PRIMUM - PRIoritising MUltimedication in Multimorbid patients [ISRCTN (follows)]

The study protocol (version 1.1, date: 20/07/2010) is approved by the following:

Principal Investigator:

Dr. med. Christiane Muth, MPH

Date	Signature

Co-Investigators:

Prof. Dr. F. Gerlach, MPH:

Date	Signature

Prof. Dr. med. Walter E. Haefeli:

Date	Signature

Prof. Dr. med. Sebastian Harder:

Date	Signature

Study Statistician:

Dipl.-Psych. Justine Rochon, M.Sc. Medical Biometry:

Date	Signature

On behalf of the Scientific Advisory Board:

Date	Signature

1.3 Signature Page for Participating General Practitioners

Prioritising and optimising multiple medications in elderly multi-morbid patients in general practice

PRIMUM - PRIoritising MUltimedication in Multimorbid patients [ISRCTN (follows)]

The study protocol (version 1.1, date: 20/07/2010) is approved by the following:

(to be signed by the investigator of each trial site before commencing the trial)

I herewith confirm that I have read and understood the present protocol and accept it in all its constituent parts. I agree to ensure that all the patients from my trial site who are included in the trial will be treated, observed and documented in accordance with all stipulations of the protocol and in accordance with the principles outlined in the Declaration of Helsinki.

Investigator:

Name, first name: _____

Practice stamp:

_____ _____

Date Signature

1.4 Synopsis of the Protocol

Principal investigator	Dr. Christiane Muth, MD, MPH; Institute for General Practice, Johann Wolfgang Goethe University, Frankfurt / Main
Sponsor	Johann Wolfgang Goethe University, Frankfurt / Main
Title of trial	Prioritising and optimising multiple medications in elderly multimorbid patients in general practice. - A pragmatic cluster-randomised controlled trial.
Abbreviated name of trial	PRIMUM: PRIoritization and optimization of MUltimedication in Multimorbid patients
Indication	Multimedication in elderly, multimorbid patients: Age ≥ 60, ≥ 3 chronic diseases, ≥ 5 long-term prescriptions
Objective	To investigate whether the complex intervention will improve the appropriateness of prescriptions in elderly multi-morbid patients
Intervention	Intervention: Healthcare assistant (HCA) and computer assisted optimization of multi-medication (complex intervention) in accordance with recommended standard[#] Control: Usual care in accordance with recommended standard[#] [#]Recommended standard: clinical practice guideline "Geriatrie" of the guideline group of Hesse (part 1 and 2)[1] Follow-up per patient: 9 months Study duration per patient: 9 months
Rationale	Key problems of multimedication in multimorbidity: 1. Multimorbidity, multimedication and increasing age raise the risk of inappropriate prescriptions and adverse drug reactions, and under-treatment. 2. Multimedication and high complexity of medication reduce adherence among patients. 3. Physician-patient consultations on medication related problems are dominated by doctors in content, focus mostly on effectiveness, and neglect side effects and strategies to manage them. 4. Patients do not generally inform doctors of adverse drug reactions and autonomous decisions to adjust medication dose. Key elements of intervention: Basic assessment of (1) medicines that were actually taken and (2) problems relating to medicines (technical handling, potential adverse drug reactions) and patient's therapeutic aims by HCA provides structured information in the Medication-Monitoring-List (MediMoL) for the general practitioner (GP) and enables patients to discuss their problems with the GP. (3) GP uses a computerized decision support system (pharmaceutical information system, AiD+) to optimize medication (reducing number of inappropriate prescriptions, e.g. pharmaceutical interactions, renal dose adjustments, duplicate prescriptions) and (4) prioritizes medication in the physician-patient consultation taking into consideration patient's preferences. Desired effects: → Prescriptions become more appropriate → Prescriptions become less complex → Prescriptions take the patient's perspective into account (avoidance of adverse drug reactions and under-treatment, patients' preferences are taken into account and priorised) → Patients are more likely to adhere to the doctor's therapy

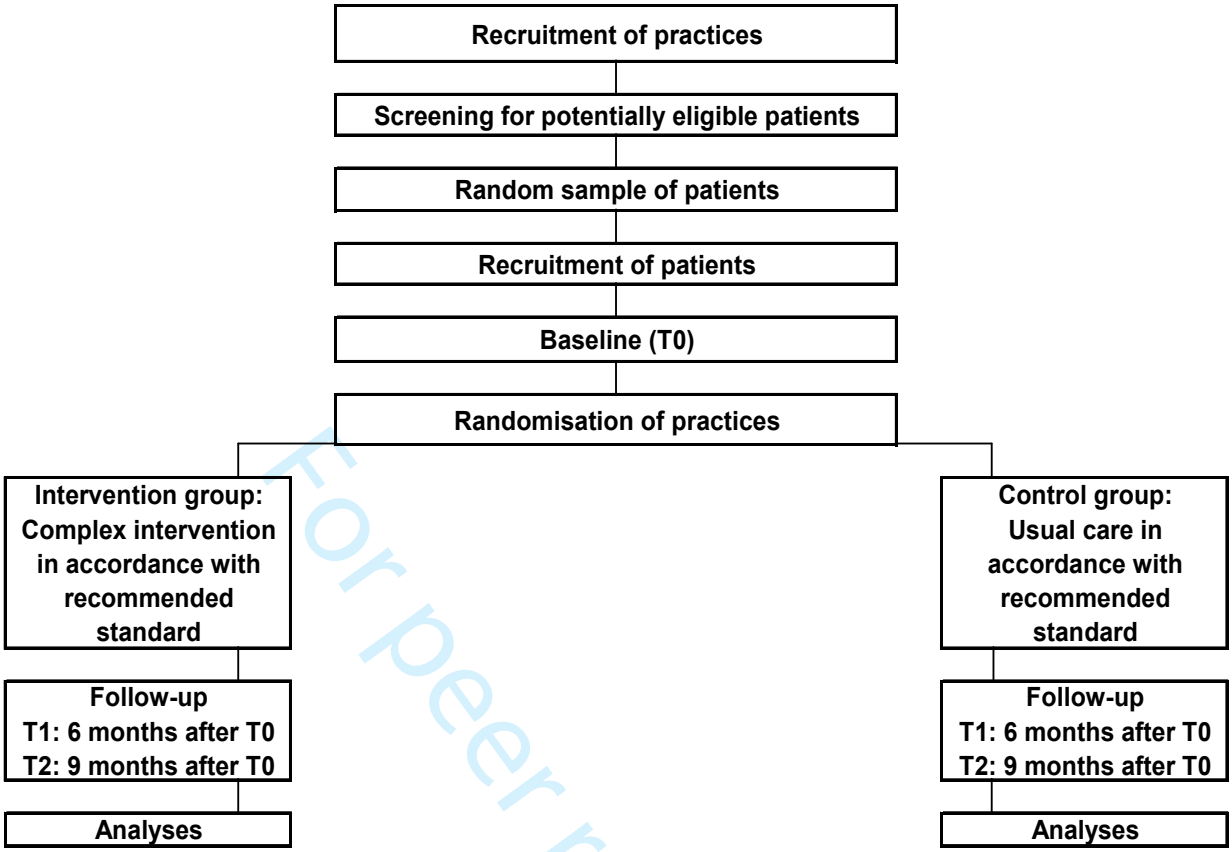
In- and exclusion criteria for trial sites (practices)	Inclusion criteria - General practice cares for patients covered by statutory health insurance and is active in primary care - Specialist doctor for general practice or internal medicine, or doctor with no specialist field. - Practice has internet access - Investigator's agreement to fulfil the contractual obligations arising from the trial - Investigator's agreement to the training of a HCA from the practice for the intervention, as required by the trial Exclusion criteria - Practice focuses on unconventional medical treatments - Practice focuses on special indications (e.g. HIV)
In- and exclusion criteria for patients	Inclusion criteria: - Age ≥ 60 and - ≥ 3 chronic diseases affecting ≥ 2 organ systems, requiring pharmaceutical treatment and - ≥ 5 long-term prescriptions with systemic effects and - Health care provided by GP (at least one contact in most recent quarter) and - Patient is legally competent to sign any documents and - Ability to understand and participate in trial of own free will, to fill out questionnaires and participate in telephone interviews as well as - Written informed consent to participate in trial Exclusion criteria: - Diseases cause life expectancy of < 12 months - Abuse of alcohol or illegal drugs and visible clinical signs or symptoms thereof - Cognitive disability that prevents trial participation (MMSE < 26) - emotional stress that prevents participation in trial - Participation in a clinical investigation within the last 30 days
Outcomes	Primary outcome: difference in Medication Appropriateness Index (MAI)-Score 6 months from baseline minus baseline (MAI T1–T0) Secondary outcomes: MAI T2-T0 and the difference in the following scores 6 and 9 months from baseline minus baseline (T1-T0 and T2-T0): EQ-5D, VES-13, all cause hospitalisation, medication adherence (observed: AS, DS, DoS, RS, self-reported: Morisky-Score), MRCI, BMQ, pain assessment (grade of severity of chronic pain in accordance with M. von Korff, J. Ormel et al. 1992), satisfaction with shared decision making (MSH), patient's future expectation, expected / desired lifetime duration, cognitive dysfunction (VFT), depression (GDS)
Study design	Pragmatic, cluster-randomised controlled trial with the general practice as the unit of randomisation to reduce treatment group contamination. Allocation concealment will be disclosed after baseline but before the intervention on practice level begins. Treatment allocation will be blinded to the pharmacologist (MAI rating) and the statistician. Primary and secondary outcomes will be measured at patient level.
Statistics	The primary analysis will be performed adhering to the intention-to-treat principle and will be based on the change in MAI from baseline (T0) to 6 months after baseline (T1), i.e. MAI T1–T0. Multilevel regression approach will be used to take into account the clustering of patients within practices. Treatment group will be considered fixed factor and variation between practices will be fitted as a random effect. The effect of intervention will be tested at the two-sided significance level of α=0.05. The results will be presented as the mean

	between-group difference in MAI T1–T0 with the corresponding 95% confidence interval. The practice related intracluster correlation coefficient (ICC) will be provided. Results from sensitivity analyses will serve to explain and interpret the results of the primary analysis. The statistical analyses of the secondary endpoints will use the same multilevel approach as the primary analysis. Only the result of the primary efficacy analysis will be interpreted in a confirmatory manner.
Number of trial sites and patients	Number of included general practices: 70 Number of general practices considered in analyses: 62 Number of potentially eligible patients (screening lists): 3.500 Number of included patients: 490 Number of patients considered in analyses: 434
Visits	Visit T0 (baseline), visit T1 (1st follow up 6 months after baseline), visit T2 (2nd follow up 9 months after baseline)
Potentially confounding factors	▪ Age, gender, marital status, lifestyle, socioeconomic status, household composition, housing indicators, house care ▪ Insurance status, participation in disease management programs ▪ Additional prescribers in treatment process ▪ Co-morbidity: Cumulative Illness Rating Scale (CIRS), Charlson-Comorbidity-Index, depression (GDS)
Schedule:	- Pre-phase (development of all trial plans, materials and implemented instruments, ethics vote, study registration): 01/03/2010 to 30/06/2010 - First practice in – last practice out: 01/07/2010 to 30/10/2011 - First patient in – last patient out: 01/08/2010 to 30/10/2011 - Recruitment: a) Practices: 01/07/2010 to 31/12/2010 b) Patients: 01/08/2010 to 31/01/2011 - Database Cleaning, analyses and publication: 01/11/2011 to 29/02/2012 - Total study duration: 01/03/2010 to 29/02/2012

1.5 Key words

Elderly, multimorbidity, polypharmacy, multimedication, medication appropriateness, cluster-randomised controlled trial, pragmatic trial

1.6 Flow chart



2 INTRODUCTION

2.1 Current situation and problem

Chronic conditions accounted for 47% of the global burden of disease in 2002 and are projected to account for about 60% by the year 2020.[2] Along with demographic changes and the change from infectious diseases that are increasingly often cured to chronic diseases the prevalence of multimorbidity increases. Studies carried out in primary care settings found an increase with all age groups from 10% in the 0–19-year-old age group up to 78% in subjects aged 80 and over in the Netherlands, and from 69% in 18–44 year olds up to 98% in those aged over 65 in Canada.[3,4] In 2002 in the U.S., Medicare beneficiaries with five or more chronic conditions accounted for 76% of Medicare expenditures.[5] Therefore, the problems associated with multiple chronic diseases are recognized as a leading healthcare problem.

Multiple disorders in patients are likely to result in multiple drug prescribing but may also result in under-treatment, in particular in the elderly: too little prescriptions or too low dosages have been reported in patients with multimorbidity/polypharmacy, asking for additional prescription(s).[6-10] The potential risks and harmful consequences of polypharmacy, such as drug-drug and drug-disease interactions which potentially cause adverse drug events (ADE), as well as the decreased adherence of patients to complex regimens of multiple medications, are research objectives in pharmacology and geriatrics.[11-13] Several studies investigated inappropriate prescribing and potentially preventable ADE.[14-16] In consequence, guidance on rational prescribing in multimorbid patients recommend a prudent, drug-sparing, and patient centred, not disease-oriented approach: clear therapeutic objectives, prioritisation according to the severity of diseases, efficacy and safety of available therapies, therapeutic individualisation and monitoring, patient implication and attention to their desires and expectations, and avoiding under-treatment.[1,11-13,17,18] Nevertheless, the implementation of these recommendations is still insufficient, as ongoing studies on the prevalence of inappropriate prescribing demonstrate. In our cross-sectional study in 18 general practices and 169 elderly multimorbid adults, patients received a median of 8 drug prescriptions (range 5-16).[19] We found non-considerations of drug-disease interactions in 15%, the necessity of renal dose adjustments in 23%, drug-drug interactions in 25% and an inappropriate choice and dosage of medicines with regard to age in 21% of the patients.[20] Major issues are the often lacking therapeutic goals and their prioritisation as well as inadequate communication with patients.[21,22]

2.2 Background

The risk of inappropriate prescriptions (interactions, non-consideration of renal dose adjustments and contraindications, inappropriate choice of medicines with regard to age and sex and associated discrepancies in terms of pharmacokinetics and -dynamics) rises with increasing age, multimorbidity and multimedication.[6,8,10,23] Inappropriate prescriptions are determining factors for adverse drug events, especially in the aged.[7] At the same time, the risk of under-prescribing rises in patients on multimedication regimes, and this should be avoided if the therapy is to be optimised.[9]

Multimedication and highly complex medication regimes are associated with poor therapy adherence among patients, whereby Horne et al. differentiate between unintended (e.g. technical problems with the intake of medicine, forgetting to take medicine – cognition) and

intended non-adherence (e.g. a lack of information about the aim of the prescribed medicine, attitude towards illness and medication, such as a general rejection of pharmacotherapy). Depression is also linked to non-adherence to medical prescriptions.[24]

Discussions between physician and patient concerning medication are generally initiated by the doctor who tends to control the content to a large degree, focusing on therapeutic benefits and frequently avoiding a discussion of risks, adverse drug reactions and necessary precautionary measures, and rarely checks how much of the content of the consultation has been understood by the patient. Patients often fail to inform their doctor when they have changed the doses of a medicine autonomously, or if they have ceased taking a prescribed medicine.[21,22]

Evidence from previous studies shows benefits from certain strategies in order to avoid inappropriate prescriptions: [22,25,26]

- Regular checks of which drugs have been taken
- The use of computerised decision support systems (CDSS), which automatically generate alerts in case of potentially inappropriate prescriptions and present suitable strategies to prevent them.
- Communication between doctor and patient is more likely to cover problems concerning medication when patients feel at ease to discuss these in pre-consultation interviews with medical assistants (non-physicians). This effect could also be demonstrated for interventions carried out for elderly patients. As a result patients showed higher medication and appointment adherence.

2.3 Rationale

Considering that

1. Multimorbidity, multimedication and increasing age increase the risk of inappropriate prescriptions, adverse drug events, and under-treatment,
2. Multimedication and high medication complexity reduce patient adherence,
3. Consultations between doctor and patient on medication-related problems generally focus on the benefit of a therapy and are dominated by the doctor, and
4. Patients do not usually inform their doctor about changes they make in their medication intake

an intervention was developed that includes the following components:

(1) A medication reconciliation by a general practice based healthcare assistant (HCA),

(2) The systematic assessment of medication-related problems (technical handling, symptoms of potential adverse drug reactions, adherence, patient preferences) by means of a checklist (MediMoL) in a pre-consultation interview conducted by a HCA.

(3) The use of a computerised decision support system (internet based medication information system, AiD+)

(4) Physician-patient consultation on medication-related problems.

The basic assessment in (1) and (2) provide the GP with structured information. This can then be checked by means of the AiD+ to alert the doctor of potentially inappropriate prescriptions, the need for renal dose adjustments and of unintended duplicate prescriptions.

The pre-consultation interview with the HCA should enable patients to discuss their problems with the GP and to tell him about their expectations, wishes, fears, concerns etc.

The GP and patient then discuss necessary changes in the therapy and decide on a new medication. We expect that after taking into consideration the AiD+ alerts and the patients' problems taking the medicine, as well as their dislikes and preferences, the adapted medication will be more suitable, leading to a reduction in potentially inappropriate prescriptions, under-treatment and medication complexity. Furthermore, we expect that a prioritisation of the medication will take place as a result of directly asking and taking into account the patient's perspective.

In consequence, it can be expected that patients are more likely to adhere to the doctor's instructions. Patient health can be improved through the avoidance of under-treatment in pain therapy and possibly through a reduction in adverse drug reactions and associated events. As a result, patient's functional situation, generic quality of life and the desired lifetime duration should be improved.

3 STUDY OBJECTIVES

(1) Primary objective of this trial is to investigate whether the complex intervention will improve the appropriateness of prescriptions in elderly multi-morbid patients six months after baseline as compared to usual care.

(2) Secondary objectives of this study are:

- to ascertain whether the complex intervention will improve the appropriateness of prescriptions in elderly multi-morbid patients nine months after baseline as compared to usual care.
- to assess whether the complex intervention will improve the generic health related quality of life, the functional disability, the desired lifetime duration, the all-cause hospitalisation, and the medication adherence of elderly multimorbid patients six and nine months after baseline.

(3) The following secondary objectives will be investigated to explain the mechanism of the intervention effects at six and nine months after baseline:

a. Patients' beliefs about their medication, since negative attitudes toward medication are associated with non-adherence[27]

b. Medication complexity, as a high complexity is correlated with reduced adherence[24]

c. Severity of chronic pain to ascertain whether this intervention leads to an optimised pain therapy. Results will support the interpretation of intervention effects on health related quality of life and functional disability.

d. Satisfaction with shared decision making to investigate whether the complex intervention leads to a higher patient's satisfaction with involvement[28,29]

e. Depressive symptoms, since depression is associated with reduced adherence[24]

f. Cognitive dysfunction to investigate whether the intervention effects are modified by patient's individual cognitive performance

4 STUDY DESIGN

PRIMUM is scheduled as a pragmatic, cluster-randomised controlled trial with the general practice as the unit of randomisation. A clustered design (practices as clusters) was chosen to reduce treatment group contamination, since HCA and GP trained in the intervention will plausible not be able to provide usual care.

Allocation concealment will be disclosed after completion of the baseline documentation for all study patients within a practice but before the intervention begins. Intervention will take place on practice level.

Due to the type of intervention, neither GPs and their patients nor the PRIMUM study team will be blinded to the treatment allocation. However, allocation will neither be revealed to the pharmacologist who is responsible for the MAI rating nor to the study statistician who is responsible for the statistical analyses.

To reduce the contamination of the control group only general information of the treatment in the intervention group is provided in the regular study protocol (a complex intervention including a checklist based pre-consultation interview by the HCA and the use of an internet based CDSS). Detailed information about the intervention treatment is provided only to the intervention group as an appendix to the study protocol in the intervention training.

All primary and secondary outcomes will be measured at patient level at baseline (T0), and at follow-up: 6 months after baseline (T1) and 9 months after baseline (T2).

5 SETTING AND TRIAL POPULATION

5.1 Setting

The trial will be conducted in general practices of the state of Hesse, Germany.

5.2 In- and exclusion criteria

5.2.1 Criteria for trial sites (General practices)

Inclusion criteria:

- Practice provides health services to persons with German statutory health insurance
- GP practice
- Physician specialises in general practice, internal medicine or has no specialist area
- Practice has internet access which can be used by healthcare assistant
- Investigating physician agrees to the contractual obligations of the trial
- Investigating physician agrees to train a healthcare assistant from the practice as part of the trial for intervention.

Exclusion criteria:

To avoid selection bias for rare diseases and unconventional treatments the following practices are excluded:

- Practice specialises in unconventional medical treatments
- Practice specialises in special indications (e.g. HIV)

5.2.2 Criteria for healthcare assistants (HCA)

Inclusion criteria:

- Written agreement to complete the necessary qualification measures and to perform the tasks associated with the trial.

5.2.3 Patient criteria

Inclusion criteria:

- At least 60 years of age
- Multimorbidity, defined as the existence of at least three chronic diseases, which:
    - Affect at least two different organ systems
    - Require pharmaceutical treatment
    - Represent a disease entity, i.e. arthritis affecting different joints (arthritis of the knee, arthritis of the hip, etc.) is counted as one disease "polyarthritis", irrespective of the location
    - Are not coded in the International Classification of Diseases, version 10 (ICD-10, 2010) in the chapter "H" (diseases of the eye and adnexa, or of the ear and mastoid process) or in the chapters "E00" to "E04" (diseases of the thyroid gland: congenital iodine-deficiency syndrome, iodine-deficiency-related thyroid disorders and allied conditions, subclinical iodine-deficiency hypothyroidism, other hypothyroidism and other non-toxic goitre), since the latter require substitution of iodine and/or thyroxine, only.
- Multimedication, defined as follows: Regularly takes at least five medicines (long-term medication) with systemic effects.
- Care is provided by a GP working at a trial site (at least one contact in most recent quarter).
- Patient is legally competent to sign any documents,
- Patient is capable to give a free and written informed consent to participate in the trial, to fill in questionnaires and to participate in telephone interviews.

Exclusion criteria:

- Diseases that result in an estimated patient's life expectancy under 12 months
- Alcohol or illegal drug abuse with recognisable clinical signs or symptoms
- Cognitive impairment (MMSE < 26), that would prevent participation in the trial
- Emotional stress that would prevent participation in the trial
- Participation in a clinical trial within the last 30 days.

5.3 Recruitment

5.3.1 Recruitment of practices

General practices in the state of Hesse and up to 200 kilometres away from Frankfurt are invited to participate in the study. For this purpose about 1.600 practice addresses provided by the Association of Statutory Health Insurance Physicians of Hesse will be contacted by mail – among them not only active general practitioners. Of those who are interested, the in- and exclusion criteria are checked by phone and a date for an initiating visit is agreed. Of those who decline to participate the reasons for refusal and the in- and exclusion criteria are questioned by phone as far as possible. Of those who do not respond a 10% random sample

is contacted by phone and asked for participation, fulfilment of in- and exclusion criteria and their reasons for denial as well.

5.3.2 Recruitment of patients

HCA or GP creates a list of patient-IDs per practice from the practice computer (systematic query on patients born before 1950, who had a practice contact in the most recent quarter, whose treatment costs accounted for more than € 100 per quarter, sorted by costs). The top five patient-IDs on the list are cancelled to avoid a selection bias for rare diseases with extraordinary treatment costs. From the remaining list all patient IDs are cancelled who do not fulfil the in- and exclusion criteria until a screening list of 50 potentially eligible patient-IDs results. The screening list of pseudonymous patient-IDs is sent to the study centre (Institute for General Practice, Frankfurt, IGP) by telefax. The IGP selects a random sample of the 15 patient IDs (via random numbers by Microsoft Excel©) and sends them (the random list) back to the practice. The 15 patients of the random list are invited to participate in the study consecutively, until 7 patients are included in the study. For each of the 15 patients of the random list, basic characteristics (age, gender, fulfilment of in- and exclusion criteria, exclusive the MMSE score) are documented pseudonymously in a registration form. Only after the written informed consent of the patient the MMSE is conducted by the HCA, its sum score and the personal data (name and telephone number) are also documented. For those patient-IDs which are not related to patients taking part in the study the reasons are documented (reasons for refusal vs. the achievement of the recruitment goal). All written informed consents and registration forms are sent to the IGP via telefax.
This recruitment strategy was found to be feasible in the pilot study.

5.4 Information for participants

5.4.1 Investigator information and training

At the initiating visit at the trial site, both GP and one HCA per practice, are trained in documentation. HCA will participate in order to be in a position to support data documentation and to carry out the Mini-Mental Status Test (MMSE). GP will be informed about the study protocol, ethical considerations and the recommended standard, and will be trained in the use of the Cumulative Illness Rating Scale (CIRS).

Content:

1. Introduction to the PRIMUM trial
2. Introduction to the execution of the trial
3. Introduction to “recommended standards“ (Geriatrics guideline, parts I and II by the Hesse guideline group[1])
4. Explanation of patient clarification, information and declaration of consent
5. Training in execution of MMSE and CIRS-appraisals
6. Introduction to trial documentation including CRFs
7. Content and execution of patient survey
8. Data monitoring, query management and reminder mechanism

9. Presentation of exact trial procedure including timeline
10. Investigators' participation agreement

5.4.2 Patient information and declaration of consent

When the patients in the random list appear in the practice, the GP in person will conduct a patient briefing with them with the help of the patient information sheet prepared for the trial. Patients are to be informed of the aims and the content of the trial, the times, the methods and the content of data collection, the random selection either for the intervention or the control group, of the intervention itself, and on data protection. The patient will be expressly advised of the fact that participation is voluntary and on the possibility to withdraw ones consent. Consent to participate in the trial, as well as the declaration on data protection should be signed and dated by the patient himself. The originals will be sent to the IGP via telefax and archived in the investigator's file. In addition to the time, date and duration of the briefing, the trial number and trial abbreviation should also be entered into the patient's medical records. The patient will receive the patient information sheet and dated and signed copies of his declaration of consent and declaration on data protection.

6 RANDOMISATION AND ALLOCATION CONCEALMENT

Practices will be randomly allocated to the complex intervention or control arm in the ratio of 1:1. Block randomisation with randomly varying block sizes will be used to provide treatment groups of approximately equal size. Randomisation lists will be provided by the Institute of Medical Biometry and Informatics at the University of Heidelberg, using computer generated numbers. Practice allocation to treatment groups will be performed by central randomisation by a study-independent researcher at the IGP after registration of the first patient per practice. Once a practice has been randomised, all the patients recruited for the practice will be deemed intervention or control depending on which arm of the study each practice was allocated. After completion of the baseline documentation of all study patients per practice, the study-independent researcher at the IGP will inform the study team at the IGP about the practice status as either intervention or control. The study team will send a fax with the randomisation result to the practice.

7 TREATMENT PLAN FOR INTERVENTION AND CONTROL GROUPS

7.1 Description of trial treatment in the intervention arm

For detailed intervention see appendix B (handed out merely to the intervention group at the time of the intervention training to avoid contamination of the control group).

As a "recommended standard", the practices in the intervention group will receive the short form of the current geriatrics guideline, parts I and II, published by the Hessen guideline group.[1]

7.2 Description of treatment in the control arm

For the duration of the trial, the patients in the control group will continue to receive the usual treatment from their GP.

As a "recommended standard", the practices in the control group will receive the short form of the current geriatrics guideline, parts I and II, published by the Hessen guideline group.[1]

8 OUTCOME ASSESSMENT

8.1 Outcome measures

8.1.1 Primary Outcome

The primary outcome is the change in the appropriateness of prescriptions after 6 months follow-up measured as a difference in the Medication Appropriateness Index (MAI)-Score 6 months from baseline minus baseline (MAI T1–T0).

The criterion appropriateness of the medication will be calculated and evaluated on the basis of the *Medication Appropriateness Index* (MAI).[30,31]

- The MAI by Hanlon et al. consists of 10 items: (1) Is there an indication for the drug?, (2) Is the medication effective for the condition?, (3) Is the dosage correct?, (4) Are the directions correct?, (5) Are the directions practical?, (6) Are there clinically significant drug-drug interactions?, (7) Are there clinically significant drug-disease/condition interactions?, (8) Is there unnecessary duplication with other drug(s)?, (9) Is the duration of the therapy acceptable?, (10) Is this drug the least expensive alternative compared to others of equal utility? The rating will take place on a three point scale whereby "1" represents the best rating (expressed as correct, practicable etc. depending on the question), "3" the worst rating (incorrect, impracticable etc. depending on the question) and "2" a middle rating. As an alternative, it is also possible to respond with "not applicable" or "unknown".
- The MAI will be used in the following modifications that are comparable to modifications by others:[30,32-34]
    - Item (10) will not be rated, since this is not possible under the current conditions of discount contracts between pharmaceutical industries and different statuatory health insurance companies in Germany. They are based on § 78 Abs. 3 Arzneimittelgesetz (A) and § 130a Absatz 8 SGB V (B). Both paragraphs describe the possibility to offer discounts on official prices of pharmaceuticals by pharmaceutical industry. In conclusion "best prices" vary between health insurance companies and over time.
    - Ratings are specifically defined for each item, e.g. items (5) and (6) are limited to the most commonly observed combinations of drug-drug and drug-disease interactions, and current symptoms (taken from the telephone interview) will be considered for assignment. Operationalisation is summarised in a referenced manual (Appendix A).
- The MAI showed good intra-rater reliability for well-experienced pharmacologists.[30,33,35-37] In Prof. Harder's trial group, an MAI Rating will be carried out independently

of the project and blinded for the patient's group allocation (intervention vs. control). In a random sample of about 20% of the cases an independent second MAI rating will be carried out.

Changes of the medication regime (1) are recommended stepwise[38] and (2) are assumed to be in primary care not always realised by the patient immediately (pers. comm. practice advisory board). Reasons for the delay of changes in the medication taken by the patients probably rely on the prescribing behaviour for the chronically ill (large package sizes) and on financial constraints of the patients (extra out-of-pocket payments per package). Based on (1) and (2) an estimated delay of three months to implement prescriptions into taking is reasonable. To ascertain the effectiveness of the intervention the MAI should be appraised at least three months after intervention, therefore.

8.1.2 Secondary Outcomes

(1) Change in the appropriateness of prescriptions after 9 months follow-up measured as the difference in the Medication Appropriateness Index (MAI)-Score 9 months from baseline minus baseline (MAI T2–T0): To study late intervention effects a second interval will be measured for the medication appropriateness at T2 (9 months after baseline). Furthermore, treatment effects on each MAI item will be determined.

The following parameters will be determined in order to identify treatment effects on patient related outcomes:

(2) Change in generic health related quality of life measured as the difference in the EQ-5D-Score[39,40] 6 months from baseline minus baseline (T1–T0) and 9 months from baseline minus baseline (T2–T0): To ascertain whether the intervention improves the generic health related quality of life the EuroQuoL (EQ-5D) will be used.[39,40] The EQ-5D was feasible in the pilot study and detects even relatively small changes.[41,42]

(3) Change in functional disability measured as the difference in the VES-13-Score[43] 6 months from baseline minus baseline (T1–T0) and 9 months from baseline minus baseline (T2–T0): To ascertain whether the intervention improves functional disability, the activities of daily living will be assessed. In the pilot study the WHO DAS-II was found not to be feasible. In the main study the Vulnerable Elderly Survey, 13 items (VES-13) will be used.[43] The VES-13 predicts death and functional decline in vulnerable elderly patients,[43-45] encompasses physical and instrumental activities of daily living and is feasible to use (pers. comm. Dr. U. Thiem, geriatrician, VES-13 use in the German PRISCUS-project; pers. comm. M. v. d. Akker: VES-13 use in the Maastricht multimorbidity project).

(4) Change in all cause hospitalisation: To ascertain whether the intervention improves all cause hospitalisation of patients, hospital days are counted irrespectively of reasons for admission.

(5) Change in medication adherence: To determine whether the intervention improves the medication adherence the following outcomes will be measured:

- Change in observed adherence measured as the difference between intake (*patient's interview*) and prescribed medication (CRF reported by physician's) 6 months from baseline minus baseline (T1–T0) and 9 months from baseline minus baseline (T1–T0)

- Discrepancy score, DS (Sum of all differences in drug, time of intake, frequency and dose) / Sum of all prescriptions, AS<0.8 or >0.2=1
- Drug Score (DS, Sum of all drugs taken/sum of all prescriptions), DS<0.8 or DS>1.2=1[46]
- Dose Score, (DoS, Sum of all daily doses taken/sum of all prescriptions), DoS<0.8 or DS>1.2=1[46]
- Regimen Score (RS, actual frequency of intake per day / prescribed frequency per day), RS<0.8 or DS>1.=1[46]

- Change in self-reported adherence measured as the difference in the Morisky-Score[47] 6 months from baseline minus baseline (T1–T0) and 9 months from baseline minus baseline (T2–T0)

5) Change in perceived future life expectancy reflects concepts of will to life or years of desired life [YDL] measured as the difference of the three items future expectation / expected lifetime duration / desired lifetime duration in the interval 6 months from baseline minus baseline (T1–T0) and 9 months from baseline minus baseline (T2–T0): Desired and expected life time duration are considered to be sensitive for personal experiences and scientific influences,[48] as well as indicating well being and positive life evaluation.[49] Moreover it is argued that YDL itself reflects mortality on the long run. Thus, if our intervention effects change in YDL, one might argue that participants consider the intervention as relevant in relation to their own life expectancy and life quality.

8.1.3 Secondary outcomes to explain the intervention mechanisms

1) Change in complexity of medication measured as the difference 6 months from baseline minus baseline (T1–T0) and 9 months from baseline minus baseline (T2–T0) in terms of

- Total number of prescriptions
- Number of single doses / day
- Medication Regimen Complexity Index (MRCI),[50]

since a high complexity is associated with a reduced adherence.[24]

2) Change in health and illness beliefs and attitudes measured as the difference in the Beliefs about Medicines Questionaire (BMQ) score[27] 6 months from baseline minus baseline (T1–T0) and 9 months from baseline minus baseline (T2–T0), since denial of illness and / or medication in general might explain non-adherence.[24]

3) Change in severity of chronic pain measured as the difference in *Characteristic Pain Intensity score,* the *Disability Score,* in *Disability Points* and the resulting *Grades of chronic pain severity* in accordance with M. von Korff, J. Ormel[51] et al. in the interval 6 months from baseline minus baseline (T1–T0) and 9 months from baseline minus baseline (T2–T0):

Prevalence of chronic or persistent pain in elderly ranges between 25 and 50%. Nevertheless, under-assessment and under-treatment of pain is frequent in the elderly.[52] Undertreatment is often associated with polypharmacy,[9] and is not adequately captured by MAI

appraisal. Therefore, pain is hypothesised as a surrogate for under-treatment[a] and will be assessed to reveal possible negative intervention effects (i.e. a reduction of polypharmacy at a cost of an impaired pain management). The different scores to grade the severity developed by von Korff, Ormel et al. have been modified for, integrated in the German pain inventory (Deutscher Schmerzfragebogen – questions 11 a-c, and 12 a-d) and validated in a German population.[51,53,54]

4) Change in satisfaction with shared decision making measured as the difference in the *Man Son Hing* scale (MSH)[28,29] interval 6 months from baseline minus baseline (T1–T0) and 9 months from baseline minus baseline (T2–T0): For an appropriate prescription in elderly multimorbid patients a patient centred rather than a disease centred approach is recommended. MSH scale measures the satisfaction with the shared decision making process. It was found feasible, showed high reliability and sensitivity of change and acceptable validity in the German "arriba"-study conducted in primary care practices.[28]

8.2 Timing of outcome assessment

Study visits: at baseline (T0), 6 months (T1) and 9 months (T2) after baseline. Each time the HCA makes a practice appointment with the patient, and measures body height and weight. Patients fill out a questionnaire in the practice and reply it to the HCA in a closed envelope before leaving. HCA and GP fill out a paper based case report form (CRF). At the end of each visit the HCA sends a control sheet by telefax to the IGP to inform that the visit has taken place. The completed CRF and patient questionnaire are sent by mail to the IGP. Immediately after the receipt of the control sheet trained members of the study team conduct the telephone interview with the patient.

Table 1: Study visits

Month	**Before trial begins**	**0**	**6 (+/- 1)**	**9 (+/- 1)**
Visits		**T0**	**T1**	**T2**
Trial measures for *control and intervention group*				
Documentation training, GP and HCA	•			
Profile of practices participating in trial	•			
Sociodemographics of GP				
Sociodemographics of HCA	•			
Identification of potentially eligible patients – screening lists	•			
Random lists	•			
Patient registration sheet (In- and exclusion criteria, reasons for non-participation of patients; for included patients with written informed	•			

[a] Additional searches should reveal literature, where a direct association between polypharmacy and under-treatment of pain is shown (references are welcome). Otherwise we will get the prevalence of severe pain in our population at baseline.

Month	**Before trial begins**	**0**	**6 (+/- 1)**	**9 (+/- 1)**
Visits		**T0**	**T1**	**T2**
consent also: name, first name, telephone number, MMSE score)				
CRF, practice documentation				
• Detailed sociodemographics, patient incl. Disease Management Program (DMP) status		•		
• Patient's current diagnoses		•	•	•
• Patient's current medication		•	•	•
• Height and weight of patient		•	•	•
• Laboratory test results of patient, if available (serum electrolytes K, Na, serum creatinine)		•	•	•
• Degree of patient's multimorbidity (CIRS)		•	•	•
• Existing co- and multimorbidity of patient (Charlson Comorbidity Index)		•	•	•
• Hospital stays (duration, reason)		•	•	•
• Consultation of specialists		•	•	•
Patient questionnaire:				
• Sociodemographics incl. best school leaving certificate and professional certificate, household composition, housing indicators, house care		•		
• Lifestyle		•		
• Generic health related quality of life (EuroQuoL, EQ-5D))		•	•	•
• Functional disability (Vulnerable Elderly Survey, VES-13)		•	•	•
• Attitude of patients to medicinal therapy (Beliefs about Medicines Questionnaire, BMQ)		•	•	•
• Severity of chronic pain in accordance with M. v. Korff, J. Ormel et al. 1992		•	•	•
• Satisfaction with shared decision making (Man-Sin-Hong scale)		•	•	•
• Future expectation, expected / desired lifetime duration		•	•	•
Telephone interview with patient				
• Sociodemographics		•		
• Current patient medication (incl. National drug code: PZN)		•	•	•
• Symptoms for adverse drug reactions		•	•	•
• Infirmity index (Sherbrooke Questionnaire)		•	•	•

Month	**Before trial begins**	**0**	**6 (+/- 1)**	**9 (+/- 1)**
Visits		**T0**	**T1**	**T2**
• Depression (Geriatric Depression Scale, GDS)		•	•	•
• Cognitive dysfunction (Verbal Fluency Test)		•	•	•
• Self reported adherence of patient (Morisky)		•	•	•
Measures for *intervention group only*				
• Intervention: Training for GP's and HCA's		•[#]		

[#]After baseline completion

9 POST-RECRUITMENT RETENTION STRATEGIES

Co-ordinating Centre responsibilities of the IGP:

- Provide study materials incl. self-addressed envelopes which will be supplied to the trial sites in sufficient quantities and postage will be paid by the recipient
- Help ensure complete data collection at baseline, at six months and at nine months
- Respond to any questions (e.g. from practices) about the trial via telephone and telefax (regular office hours Mon. to Fri. 9:00 a.m. to 5:00 p.m.), or mobile phone (Mon. till Fri. between 9:00 a.m. and 7:00 p.m., Sat. & Sun. between 10:00 a.m. and 6:00 p.m.), or email

10 SAFETY MONITORING AND ADVERSE EVENTS

No safety monitoring nor adverse events reporting will be conducted, since worse treatment than previous to the trial is not possible. The study team of the trial (Institute for General Practice, Johann Wolfgang Goethe-University, Frankfurt am Main, IGP) has no influence on the diagnostic-therapeutic decision-making of the GPs and their patients.

11 REGISTRATION, DATA COLLECTION AND MANAGEMENT

11.1 Registration of participants

Practice registration: takes place during the initiation visit by a trained study team member. The participating practices give written informed consents of a general practitioner (GP) and a healthcare assistant (HCA) to participate in the study and to implement the study protocol (centre registration form).

Patient registration: at the IGP the incoming telefaxes of registration forms and signed informed consents are controlled (patient ID is consistent with the patient ID of the random list, signature of the patient, fulfilment of in- and exclusion criteria) and patient registration is confirmed to the practice by telefax.

11.2 Data collection

11.2.1 Data collection of participating HCA and GP

First documentation takes place at the initiating visit at the trial site: social demography of HCA and GP and practice characteristics as well are documented in paper based forms (each one per HCA and GP and practice).

11.2.2 Data collection of participating patients

Examinations and documentation of the patient related data take place regularly during the aforementioned visits 1-3. Visits 1-3 take place in months 0, 6 and 9 (+/- one month) following the inclusion of the patient in the trial. An overview of the individual examinations is given in table 1 (see pp 23). The content of the individual examinations to be documented is described in detail in section 11.3 (see below). At each visit the following documents are collected:

- The patient registration document (T0) and control sheets (T1, T2) filled in by HCA and GP are sent to the IGP via telefax at the day of the patient's visit to the practice.
- The paper based case report form (CRF) completed by the HCA and GP. Every CRF includes information on filling in the form. Necessary correction to the CRF must take place in the following manner: invalid data should be crossed out whereby crossed-out details should be authorised with the date and the investigator's initials.
- The completed patient questionnaire (paper based as well): The patient questionnaires, including an envelope, will be issued by the HCA. The patients fill in the questionnaires in the practice and put them in the envelopes which they then seal themselves (confidentiality of information with respect to trial site). If necessary, the HCA provides help filling in the patient questionnaires and keeps an eye on the return of the completed documents.

The completed CRFs and the sealed envelope with the completed patient questionnaire will be put in the return envelopes (no stamp required) at the trial site and promptly returned to the IGP by mail.

Within five working days as after arrival of the patient registration document / control sheets, trial employees will contact the patient to conduct the telephone interview. Information from these interviews will be entered directly into the entry mask of an SQL data bank (Access©). If the interviewer cannot reach the patient, further attempts to do so will be made on the following days. After the fifth unsuccessful attempt, the responsible practice will be contacted by the trial assistant and asked for information on the whereabouts of the patient. If the attempts to contact the patient fail within one month, the telephone interview for this visit is considered as missing.

11.2.3 Data collection of non-participating patients

If a patient from the random list (see 5.3.2) does not agree to participate, or is not included for any other reason (e.g. the recruitment goal per practice is already fulfilled), then the following data will be documented on the patient registration form pseudonymously – age, gender, in- and exclusion criteria (without MMSE score), reason for non-inclusion. The documentation of further data and especially personal data such as name, date of birth or telephone

number is not permitted. The patient registration forms for those patients who are not included will also be faxed to the IGP and the originals will remain on the files of the GP and checked by the monitor after completion of the trial.

11.3 Description of data sets

11.3.1 Data set to determine practice profile

- Single-handed practice / group practice (incl. ambulatory healthcare centre, with the number of physicians and the question for additional general practitioners),
- Location: Big town (> 100.000 inhabitants) / middle size town (20.000 to 100.000) / small town (5.000 to 20.000) / rural area (< 5.000 inhabitants)
- Clinical specialisation of practice
- Number of registered patients in most recent quarter [in categories: 0 – 499, 500 – 999, 1000 – 1499, 1500 – 1999, 2000 and over]
- Quality management system used in practice
- (Brand name of practice EDV to provide any necessary support for the study by the IGP

11.3.2 Data set to determine profile and sociodemographics of the GP

- Practice-ID as provided by the IGP, GP-ID (consecutively for each participating GP)
- Age, gender of GP
- GPs professional practice experience (year doctor commenced private practice)
- Years of clinical experience in total
- GP: Specialist in primary care, specialist in internal medicine, GP / doctor with no specialist area
- Previous participation in a former clinical trial and name of trial

11.3.3 Data collection to determine profile and sociodemographics of the HCA

- Practice-ID as provided by the IGP, HCA-ID (consecutively for each participating HCA)
- Age, gender of HCA
- School leaving certificate, professional and additional qualifications
- Years of professional experience as health care assistant and at trial site
- Type of employment
- Previous participation in a former clinical trial and name of trial

11.3.4 Patient registration form

Registration form for every patient on random list with

- Practice-ID as provided by the IGP, GP-ID, patient-ID as used in practice computer, month and year of birth, age, gender
- Checklist for in- and exclusion criteria (items to be marked with a cross, exclusive MMSE score)
- Decision not to participate (if possible with reasons)
  vs. patient not approached (as recruitment target already reached)
  vs. readiness to participate (patient's written informed consent is on hand)
- If written informed consent on hand:

- Name, first name, patient's phone number
- MMSE Score

11.3.5 Case report forms (see prototype in appendix)

Sociodemographics and basic clinical data: insurance status (private, statutory or differing), name of insurance company, participation in one of the disease management programs (diabetes mellitus I/II, coronary artery disease, breast cancer, COPD, asthma), home care situation and assessment of quality of care, height (measured), weight (measured), current diagnoses, allergies / intolerances, consultations with specialists (specialisation of physician) and hospital stays during the last six months (date of admission to / release from hospital; inpatient, day hospital care, outpatient, inpatient rehabilitation; reason for treatment).

Laboratory: Laboratory values for serum electrolytes (sodium and potassium) and serum creatinine that are already available in the practice. The most recent values should be taken along with the date of the test, but should not be more than 12 months prior to patient inclusion in the trial.

Current medication: trade name, strength, application, dosage, indication, duration of therapy at time of documentation (more or less than three weeks) and estimated importance of the particular medicine within the concept of the therapy as a whole (4-point Likert scale: very important – important – of little importance – not important).

Current diagnoses: all active diseases of the patient at the time of documentation (acute and chronic diseases) and treatable conditions (e.g. hypertension without end organ failure, positive medical history for gastric ulcer)

Modified Cumulative Illness Rating Scale (CIRS): Assessment of organs / organ systems / areas (15 items in total) according to severity of impairment (5-point Likert scale: no impairment to extreme impairment),[55-57] with one supplementary item "chronic pain syndrome" and one supplementary response category entitled "not applicable" if the named organ (system) is not affected.

Expanded Charlson Comorbidity Index: List of underlying diseases in the Charlson Comorbidity Index[58] plus relevant diseases and situations that often result in contraindications to specific medication.

11.3.6 Patient questionnaires (see prototype in appendix)

Sociodemographics: marital status, number of persons living in the household (i.e. household composition), home care, socioeconomic status (best school leaving certificate, professional training), housing indicators (population size: big town [>100.000 inhabitants] / middle size town [20.000 to 100.000] / small town [5.000 to 20.000] / rural area [<5.000]; housing tenure [home ownership]; place attachment [home / neighbourhood]).

Generic health related **quality of life** (EuroQoL, EQ-5D),[39,40] maintenance of **functional status** (Vulnerable Elderly Survey, VES-13),[43] **Beliefs about Medicines** Questionnaire (BMQ),[27] **severity of chronic pain** (in accordance with M. v. Korff, J. Ormel et al.),[51] satisfaction with shared decision making (Man-Son-Hing scale),[29] future life expectancy (future expectation / expected lifetime duration / desired lifetime duration).[48,49]

11.3.7 Telephone interview with patients

At each visit a trained employee from IGP conducts interviews with patients using an interview guide (see appendix) and enters the answers directly into an Access-data base.

Medication incl. OTC drugs and supplements (trade name, National Drug Code, dose, prescribed by whom, duration of intake more or less than three weeks) currently being taken on a regularly basis; medication to be taken as needed, including OTC drugs (in case of what symptoms, single dose, total maximum dose); autonomous preparation and intake of medication vs. support from third parties, known allergies, symptoms for potentially adverse drug reactions.

Consultation of other healthcare providers: Other healthcare providers consulted during the last six months (name, location, profession/specialisation, number of consultations, reason(s) for consultation, and referral by GP vs. direct access).

Sherbrooke Questionnaire: Five items to identify positive predictors (lives alone, uses a walker, self-reported visual, hearing and memory impairment, sixth item already one of inclusion criteria: more than three long-term medicines daily).[59]

Use of medical aids and special therapeutic measures: Use of visual and/or hearing aids, use of home oxygen therapy, participation in dialysis therapy, ask about implant devices (pacemaker, defibrillator)

Patient interview on depression (Geriatric depression scale, GDS)[60,61]

Patient interview on adherence (Self reported adherence according to Morisky)[47]

Verbal fluency test: Patients are asked to tell as many animals as possible within one minute.[62] Answers are audiotaped and time is controlled by a stop watch. After the interview is finished, the interviewer transcripts the audiotape into the database and deletes the tape soon after.

11.3.8 Documentation of intervention

After completion of the trial the data from the completed intervention tools (MediMoL, AiD+) will be analysed (intervention group only).

11.4 Data management

The responsible trial employee will check all incoming post is complete and confirm receipt by marking it (date of receipt, date of check, initials - tracking). The due dates for sending the documentation is described in a guideline on data flow in the investigator's file. Missing information will be collected in preparation for the following query management (see below).

After confirmed reception of data it will be entered into an SQL trial database (Access©) by one of the trial employees. A data check will take place of this database according to predefined trial rules (range-, validity, and consistency checks according to defined SOPs developed during the course of the trial and documented in the TMF). Queries for the investigators that may crop up as a result of this data check will be formulated by the IGP (see below, Query management). Sending, collecting and processing patient data will always take place under the patient identification number (Pat.-ID) pseudonym.

Coding will be used for some of the data, partly when the data is entered. In retroactive processing steps, some free text information will be encoded into new variables. The encryption specifications will be deposited in the TMF.

11.5 Data Validation (Query management)

Data recognized as missing during the confirmation of receipt check will be collected for each practice using the patient IDs and then faxed to the trial sites as a written request for completion. These fax requests will be filled in and signed by the investigator and then faxed back to the IGP. The receipt of the returned faxes will then be confirmed and the process continued until all missing data have been collected. The checked data will then be forwarded and entered into the database, as described above.

Follow-up enquiries resulting from the data plausibility check will also be collected for each practice and formulated as a written fax request using the patient identification number. They will then be dealt with in the same way as described under (missing data).

If possible, query management will be undertaken during regular practice visits in order to limit the number of fax requests. However, timely query management has first priority.

All CRFs, patient questionnaires, queries and answers will be kept at the IGP in paper-form. Changes to the Access database will be documented in an audit trail. The necessary programming instructions will be developed along with the data management concept.

11.6 Quality control and quality assurance

The study team of the IGP guarantees that all processes in the trial will comply with the Good Clinical Practice (GCP) guidelines, the legal requirements and the SOPs of the IGP. General practitioners and healthcare assistants of the trial sites will be educated on the trial requirements during the investigators' training at the initiating practice visit.

Monitoring: The IGP will be responsible for monitoring the trial. A study employee will regularly visit the trail sites (at least two visits per practice) to ensure that

- the rights of the trial participants are protected,
- the study data are documented completely and in a correct manner and can be verified for defined variables in the source data (selection of appropriate variables will be defined in the data management and validation plan of the trial)
- the trial is conducted in accordance with the study protocol (and its amendments where required) and complies with GCP and legal requirements at the trial site.

Scientific Advisory Board: The board gives scientific advice in questions on planning, conducting and analysing the trial.

11.7 Archiving

The trial documents are to be archived for 15 years. The trial sites will be responsible for archiving their documents (contents of the investigator's file, especially the list of patients, patients' declaration of consent). The IGP will archive the central trial documents, the original CRF (including patient questionnaires, the final report and further reports where necessary).

11.8 End of Trial

11.8.1 Regular / premature end of trial

The **regular end** of the trial is reached when the documentation of the study visits is over for all patients participating in the trial.

The **premature end** of trial can be decided by the principal investigator after the consultation with the scientific advisory board, when recruitment of practices or patients does not meet the recruitment goals, when the number of practices or patients with a premature withdrawal from trial or a permanent violence against the study protocol is expected to avert a successful regular end of trial.

11.8.2 End of trial participation

11.8.2.1 End of trial participation for practices

The **regular end** of the trial participation for a practice is reached when a) the documentation of the study visits is over and b) the treatment in accordance for determined practice status is completed for all patients participating in the trial.

The **premature end** of the trial participation for a practice is reached when the GP withdraws his/her agreement to participate in the trial protocol, or when the principal investigator decides to withdraw a trial site (GP practice) from the trial. Withdrawal has to be done in a written reasoned form. The principal investigator can decide to withdraw a trial site from the trial if:

- It does not satisfy the protocol's technical requirements (e.g. organisational problems in implementing the protocol))
- The implementation of the trial is inadequate for the trial
- The quality of the data is inadequate

11.8.2.2 End of trial participation for patients

The **regular end** of patient's trial participation is reached when documentation of the last planned visit has been completed (T2).

The **premature end** of patient's trial participation is reached

- In cause of death for any reason before the end of trial. If possible, the date and the circumstances of the death (cause of death, location) should be documented.
- In cause of hospitalisation for any reason before the last planned visit has been completed (T2) and before the end of trial.
- In cause of GP decision: The GP can elect to remove a patient from the trial
    - If following the protocol would represent unacceptable stress for the patient because of his situation (that may have to do with the development of his disease),
    - If the patient moves to a nursing home and it is technically or organisationally no longer possible to conduct further telephone interviews
    - If the patient changes to another GP and leaves the trial site.

If the course of events is foreseeable or can be planned a follow-up survey should be brought forward.

- In cause of patient's decision: Patients have the right to discontinue the trial without giving reasons at any time and without losing the right to further treatment from the GP. If a patient does not arrive to an appointment, the GP must follow up the case until he has found out why the patient did not turn up. The GP must try to complete and document all the examinations designated in the protocol.

The IGP must be informed of the premature end by fax and will confirm it. In case of a withdrawal, the reasons/circumstances and the most recent status must be documented. If the patient does not withdraw his declaration of consent, his survival status or a hospital stay should be documented at the end of the regular observation period.

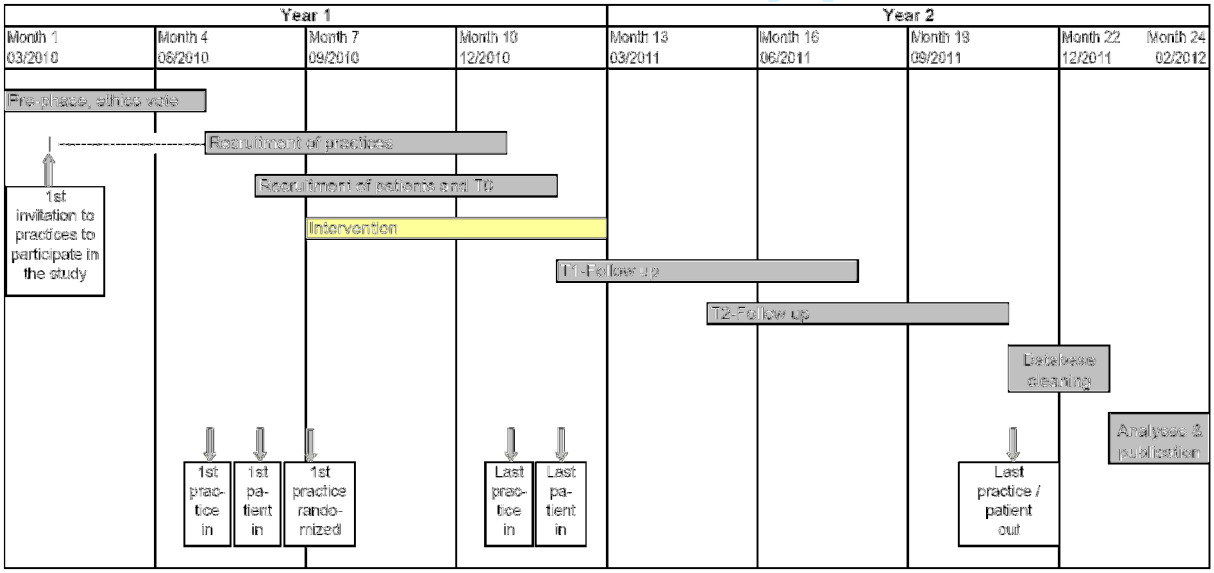
11.8.3 End of treatment

For patients of the control group no regular end of treatment has to be defined, since they are treated as usual.

For patients of the intervention group the **regular end** of treatment is reached when all components of the complex intervention are administered in accordance with the protocol.

For patients of the intervention group the **premature end** of treatment is reached when one or more components are lacking: Patients have the right to discontinue the treatment without giving reasons at any time and without losing the right to further treatment from the GP. If a patient does not arrive to an appointment, the GP must follow up the case until he has found out why the patient did not turn up. The GP must try to complete and document all the components of the complex intervention designated in the protocol. The documentation will continue in accordance with the protocol (intention-to-treat principle) accept the patient withdraws his/her written informed consent in the documentation of his/her data.

11.9 Schedule and expected duration of trial



- Pre-phase (development of all trial plans, materials and implemented instruments, ethics vote, study registration): 01/03/2010 to 30/06/2010
- First practice in – last practice out: 01/07/2010 to 30/10/2011

- First patient in – last patient out: 01/08/2010 to 30/10/2011
- Recruitment:
  a) Practices: 01/07/2010 to 31/12/2010
  b) Patients: 01/08/2010 to 31/01/2011
- Database Cleaning, analyses and publication: 01/11/2011 to 29/02/2012
- Total study duration: 01/03/2010 to 29/02/2012

12 STATISTICAL CONSIDERATIONS

A detailed description of the statistical methods of this study will be provided in a Statistical Analysis Plan (SAP). Data analysis will be done blinded to treatment arm allocation (i.e. the treatments will be identified as 1 and 2 until analysis is complete). The primary analysis will be based on the 6-month follow-up data (T1).

12.1 Populations for analysis

The Intention-to-treat (ITT) population will consist of all randomised practices and their patients. Following the ITT principle, practices and their patients will be analysed in the treatment arms to which they were originally randomized, regardless of whether they refused or discontinued treatment, or whether other protocol deviations are known.

The Per-protocol (PP) population will consist of those ITT practices and patients with no major protocol violations. The criteria for the exclusion of practices or patients from the PP population will be determined by the study team at the latest before database lock.

12.2 Statistical hypotheses, methods, and analyses

The primary objective of this study is to determine the effectiveness of a complex intervention compared to usual care in multimorbid elderly patients, and to show that the complex intervention improves the appropriateness of prescriptions, as compared to usual care. The primary efficacy endpoint is the change in MAI score from baseline (T0) to 6 months after baseline (T1), i.e. the difference MAI T1–T0. The study objective will be statistically formulated as a test of the null hypothesis H0: $\mu 1 = \mu 2$ (the mean difference MAI T1–T0 is equal in the two groups) against the alternative hypothesis H1: $\mu 1 \neq \mu 2$ (the mean MAI T1–T0 are different in the two groups). The null hypothesis will be tested at the two-sided significance level of $\alpha=0.05$.

Because of the cluster randomisation, the primary efficacy analysis will use a multilevel regression approach with patients at level one and practices at level two. The primary model will include treatment group as fixed factor and practice as random factor. The results will be presented as the mean between-group difference in MAI T1–T0 with the corresponding 95% confidence interval. The associated Cohen's effect size d will be calculated. In addition, the practice related intracluster correlation coefficient (ICC) will be estimated. To support the primary analysis, all potentially relevant baseline characteristics at practice level (e.g. practice status) and baseline characteristics at patient level (e.g. MAI score at T0) will be added as covariates to the model in sensitivity analyses. Further sensitivity analysis of the primary endpoint will include an unadjusted two-sample *t*-test on change in MAI from baseline to 6 months after baseline. Results from these sensitivity analyses will serve to explain and interpret the results of the primary analysis.

The primary analysis will be performed adhering to the intention-to-treat principle. An additional sensitivity analysis will be conducted on a per-protocol analysis set.

Baseline characteristics of participating practices and patients will be described by treatment arm. Categorical data will be presented as frequencies and percentages. For continuous data, N, mean, standard deviation, median, inter-quartile range (IQR), minimum, and maximum will be provided.

The statistical analyses of the secondary endpoints will use the same multilevel approach as the primary analysis. All statistical tests will be two-sided at the significance level of α=0.05. Because no adjustments for multiple endpoints are planned, findings will be interpreted with caution in view of the number of statistical tests undertaken. Only the result of the primary efficacy analysis will be interpreted in a confirmatory manner. Confirmatory subgroup analyses are not planned. No interim analysis with regard to efficacy will be done.

A complete case analysis will be performed. If any practices or patients are lost to follow-up, analyses will be done replacing the missing follow-up data with the last available or baseline data carried forward for that practice or patient.

12.3 Sample size

Sample size was calculated using the primary endpoint, the change in MAI score from baseline (T0) to 6 months after baseline (T1), i.e. MAI T1–T0. Because high MAI scores indicate inappropriate prescriptions, a negative difference MAI T1–T0 indicates an improvement in the appropriateness of prescriptions for the target population. The MAI T1–T0 difference is assumed to be normally distributed in each treatment arm population and the variances of the group specific differences T1–T0 are assumed to be equal. In the preliminary analysis of PRIMUM pilot with a total of 60 patients from 12 practices, a mean MAI of 4.2 was observed at baseline. Three months later (i.e. 6 weeks after the intervention), the MAI in the intervention group decreased by 0.9 units, while the MAI in the control group decreased by 0.5 units. Thus, the resulting between-group difference was 0.4 in favour of the complex intervention. In a previous study of a similar patient population, between-group differences of 3 and 4 for changes in MAI from baseline to 3 and 12 months after randomisation were reported.[32] However, the intervention in that study was even more intense than the intervention planned in PRIMUM. Thus, in the present study, a difference in the change values (MAI T1–T0) of at least 2 units between the treatment groups will be considered clinically relevant. In the PRIMUM pilot study, a pooled standard deviation of the MAI T1–T0 difference of 5.2 was observed. However, T1 was defined as 3 months from baseline, whereas in the present study, T1 is measured 6 months after baseline. Consequently, a greater standard deviation is expected for the MAI T1–T0 difference. Using the conservative assumption that the MAI scores at T0 and T1 are uncorrelated, we expect a standard deviation for MAI change of approximately 6 units. With this standard deviation, a between-group difference of 2 units corresponds to Cohen's effect size of d=0.3 and represents a small effect size.[63] Assuming an intracluster correlation coefficient (ICC) of 0.03 at practice level (which is also a conservative assumption because the ICC is assumed to be 0.01 in general practice setting[64]) and assuming an average cluster size of 7 patients, we estimated a design effect of DEFF = 1 + (7 – 1) x 0.03 = 1.18. Taking this design effect into consideration, a total of 62 practices and 434 patients (31 practices and 217 patients per treatment arm) will be required to detect a Cohen's d of 0.3 with a power of 1–β = 0.80 using a two-sample *t*-test at a two-sided significance level of α=0.05. The sample size calculation was performed using NCSS PASS 2008,

Inequality Tests for Two Means in a Cluster Randomised Trial. Assuming a drop-out rate of approximately 10%, the sample size was adjusted to a total of 70 practices and 490 patients (35 practices and 245 patients in each treatment group).

13 ETHICAL AND REGULATORY REQUIREMENTS

13.1 Ethical fundamentals

The project will be carried out in conformation with the Medical Association's code of conduct and good clinical practice (GPC) in line with the World Medical Association Declaration of Helsinki".[65] The trial will be checked and approved by the ethics commission of Frankfurt University Hospital. The original vote by the ethics commission will be kept in the Trial Master File at the Institute for General Practice. In addition, every participating practice will receive a copy to be kept in the investigator's file.

The voluntary participation of doctors and patients in the trial will be recorded in writing following an informed decision to do so. Patients in intervention practices who do not wish to participate will be treated without intervention and in accordance with usual care.

Data protection will be guaranteed for all person-related data: the data will be collected and stored separately from the other individual data in the trial, and deleted at the end of it. Participating patients will be separately informed about data protection in the trial and will give their consent by signing and dating a declaration to that effect. For data analyses, patient identifiers will be kept confidential and the data stored in a separate data base from the personalized one. The trial team are the only persons with access to trial data. Practice teams are also bound by the legal requirement to treat data confidentially.

The present trial will take ICH-GCP criteria into account, and all participants have undertaken an obligation to respect the Declaration of Helsinki and its amendments

The Ethics Commission is to be informed of all changes to the protocol and its renewed approval is to be sought if necessary.

Changes linked to the following points are regarded as requiring renewed approval:

- Necessary changes to the therapy regime, in particular:
  1. Intensification of intervention that is a burden to the patient or could be felt to be a burden by him,
  2. Reduction in intensity of intervention, in view of which a discussion on the likelihood of success must takes place,
  3. Inclusion of further elements in the intervention program about which the patient has not yet been informed,
  4. Changes in the therapy regime of the control arm,
  5. Revision in the risk estimate for participating patients;
  6. Additional examinations, data collection or analyses that necessitate a change in patient information and/or the consent form.

13.2 Subsequent changes to protocol

Changes to protocol may only occur with the prior agreement of all co-operation partners. All participating practices in the trial must be informed of such changes in written form. Changes must be dated and deposited in the Trial Master File.

If in the course of the trial it becomes clear that changes or additions must be made to the present trial protocol, then these must be laid down in the form of an amendment and signed by the principal investigator, the investigators and by those responsible for approving the trial protocol.

Changes to the timetable that may influence the safety of trial participants or the scientific analysis of the trial necessitate renewed approval by the responsible Ethics Commission. The Commission is to be informed of changes to the trial protocol that occur solely for logistical or administrative reasons.

13.3 Trial registration

The trial has been registered as a clinical, scientific based non-AMG-non-MPG-trial in the international trial register "The Current Controlled Trials (CCT)" (URL: http://controlled-trials.com) and - as far as possible - at the German Register of Clinical Trials (DRKS; http://www.germanctr.de) before it begins. The registration notice will be kept in the Trial Master File (TMF) in the IGP.

13.4 Finance and Insurance

No patient insurance is necessary for this trial, as it represents no health risk to patients.

13.5 Responsibility for preparing reports to the funding organization

Joint reports were agreed upon due to the networked nature of the project structure (PRIMUM trial and sub project E within a joint research project). The coordinator of the joint research project and head of the IGP, Prof. Ferdinand M. Gerlach, MPH, will be responsible for the coordination and composition of the reports in a standard format. To this end he will receive the full support of all participants in the project and the co-investigators will provide all required information in a timely fashion.

The reporting process includes

(1) Interim reports to the funding organisation about the trial management in April 2010, and 2011.

(2) A final report following the completion of the trial.

13.6 Publication agreements

The specifications laid down in the CONSORT Statement for cluster-randomised trials must be taken into account when the results of the trial are published.[66]

In principle, the publication should adhere to the suggestions made by the German Research Community (Deutsche Forschungs-Gemeinschaft DFG) to ensure good scientific practice, January 1998 which correspond to the uniform requirements for manuscripts submitted to biomedical journals, NEJM 336: 309 ff, 1977:

"Authorship credit should be based only on substantial contributions to (a) conception and design, or analyses and interpretation of data; and to (b) drafting the article or revising it critically for important intellectual content.; and on (c) final approval of the version to be published"

Conditions (a), (b), and (c) must all be met.

- Names and the sequence of authors' names will be determined collectively for every publication, and by means of asterisks, all particpating persons and their functions will be named at the end of each article.

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15 APPENDIX A

15.1 Abbreviations

ADR	Adverse Drug Reaction
AMG	Medication law
AS	Discrepancy score
BMQ	Beliefs about Medicines Questionnaire
CDSS	Computerized Decision Support System
CIRS	Cumulative Illness Rating Scale
CR	Center registration
CRF	Case Report Form
DEGAM	German Society of General Practice and Family Medicine
DS	Drug Score
DoS	Dose Score
GCP	Good Clinical Practice
GDS	Geriatric Depression Scale
GP	General Practitioner
HCA	Health Care Assistant
ICC	Intra-Cluster Correlation-coefficient
ICH	International Conference on Harmonisation
ID	Identifier
IGP	Institute for General Practice, Goethe university Frankfurt, Coordinating centre of the study
ITT	Intention To Treat
MAI	Medication Appropriateness Index
MSH	Man-Son-Hing scale
MediMoL	Medication Monitoring List
MMSE	Mini Mental Status Exam
MRCI	Medication Regimen Complexity Index
OTC	Over The Counter
PP	Per Protocol
PZN	National Drug Code
RS	Regimen Score

SOP	Standard Operating Procedure
SPSS	Statistical Package for Social Sciences (Software)
TMF	Trial Master File
VES-13	Vulnerable Elderly Survey, 13 items
VFT	Verbal Fluency Test
VRS	Verbal Rating Scale on pain

15.2 Instructions on the content of the investigators file

- Trial protocol (plan) incl. all data collection instruments (sample)
- Geriatrics Guideline from the Hesse Guideline Group (short versions parts 1 and 2)
- Copy of the Ethics Commission vote
- Center Registration (CR)
- Screening list
- Random list
- Original of the signed patient information and consent form to the trial
- Original of the signed data protection declaration
- Patient registration form
- Flow chart on the trial
- Guideline on data flow

Intervention group only:

- Appendix B of the study protocol
- Medication Monitoring List
- AiD+ user manual
- Training material for intervention

15.3 MAI manual

(follows)

16 APPENDIX B

16.1 Description of the intervention (for intervention group, only)

The intervention in the PRIMUM trial is a complex intervention and consists of the following elements:

1. Pre-consultation interview of the HCA with the patient based on a checklist (Medication Monitoring List, MediMoL)
2. Brown bag review: medication reconciliation by the HCA of what drugs are taken by the patient
3. Use of an internet-based, user-initiated computerised decision support system 'AiD+', which alerts in case of
   - discount contracts,
   - duplication with other drugs,
   - drug-drug interactions,
   - renal dose adjustments
   - incompatibilities of parenteral applied drugs

   and provides further information on divisibility of tablets, medication regimen complexity, and maximal dosage
4. Physician-patient-consultation on medication related problems

16.1.1 Intervention – Tools

- Web-based pharmaceutical information system: AiD+ (further information materials will be distributed during intervention training)
- Checklists to track medication-related problems and patients therapeutic aims: Medication-Monitoring-Lists (MediMoL, will be issued during intervention training)

16.1.2 AiD+ development for use in the trial

AiD+ has been developed on the basis of the existing AiD clinic by the Department of Clinical Pharmacology and Pharmacoepidemiology, Heidelberg, for use in the PRIMUM trial, whereby the functionality of AiD+ has been agreed upon with the Institute for General Practice, Frankfurt. With the exception of the features "medication regimen complexity", and "maximal dosage" AiD+ has been tested in the pilot study and has shown a suitable feasibility. The new features have been developed prior to the start of the trial in the practices. All further changes of the functionality of AiD+ will take place after agreement between IGP and AiD developers.

For each trial site, a study employee of the IGP will set up 15 patient files using the patient identification codes from the random list in the password-protected area of the system. If the trial site demands a second random list then the IGP will set up a further 15 patient files.

16.1.3 Schedule of the intervention

In the intervention arm, patients will be looked after by the GP and a trained HCA from the general practice. The practices in the intervention group will receive the simplified version of parts I and II of the latest geriatrics guideline from the Hessen guideline group as a "recommended standard".[1] All study patients from the intervention group will receive the following structured intervention:

	Procedural step	Content
1	HCA arranges appointment	The HCA arranges an appointment with the patient to visit the practice. The patient will be asked to bring all drugs to the appointment that he or she takes, whether occasionally or regularly (also including OTC drugs phytopharmaceuticals and nutrition supplements) including the original packaging wherever possible.
2	HCA enters patient's core data and "practice medication" into Medibox 1 (AiD+)	The HCA logs into the web-based AiD+ (Internet address and password for the protected area are kept in the investigator file. On the trial site's page she calls up the patient by entering the patient's ID and compares the patient's reference code with that of the practice EDP. She confirms that the written declaration of informed consent is dated, has been signed personally and is present in the investigator file. She enters the date of birth, size and weight and the most current laboratory values (serum-potassium, -sodium and -creatinine) in the core data page of AiD+. Then she enters the prescribed medication from the most current therapy plan into AiD+, (entered in practice software) (Medibox 1: "practice medication"). After entering the data she logs out of AiD+.
3	HCA interviews patient on basis of checklist (MediMoL)	The patient arrives at the practice at the arranged time with all the drugs currently being taken. The HCA systematically asks the patient on the basis of a checklist (Medication Monitoring List, MediMoL) about pain, common symptoms of ADRs, need for information on the drugs, reasons for not taking drugs (including technical reasons such as the need to split tablets), adherence aspects such as neglecting to take long-term medication, objections to specific medication and about preferred therapy goals. The MediMoL includes the possibility to answer in free text as well as in pre-provided response categories that take the form of a traffic light pattern, enabling quick comprehension, and more sophisticated reactions according to severity: · Red response category ("Emergency"): in case of this answer, the interview with the patient will be interrupted and the HCA will contact the GP immediately who will then decide how to proceed. · Orange response category ("potentially serious and with a high probability of a clinically relevant problem"): the interview with the patient will be continued as planned. The HCA will inform the GP of the findings on the same day (at the latest within the next 24

	Procedural step	Content
		hours). The GP will decide what to do next. ▪ Yellow response category (’*potentially* a clinically relevant problem’): the interview is continued as planned. If the category yellow is the most serious answer the HCA puts the MediMoL into the general findings tray that is looked at by the GP. ▪ Green response category (’no problem’): the GP is informed of the MediMoL by means of the general findings tray.
4	HCA enters “house medication“ into Medibox 2 *brown bag review*	The HCA logs into the password protected area of AiD+ and opens the patient’s file (compare patient ID and date of birth with the data in the investigator’s file). The HCA enters all drugs (regular medication, medication to be taken as needed, prescriptions from co-treating doctors, OTC products including phytopharmaceuticals and nutrition supplements) using its trade name, the name of the active ingredient or National Drug Code. In addition she records the dosage. After entering the information she stores it under home medication (Medibox 2).
5	GP checks the medication and problems associated with the medication with the support of AiD+ and MediMoL	The GP logs into the password protected area of AiD+ and opens the patient’s file. He checks AiD+, “home medication” and “practice medication” for agreement in terms of the active ingredient (on the ATC code level) and dose. Both home and practice medication appear in a shared AiD+ window (Medibox 3: “coordinated medication”, sorted according to ATC group (groups of active ingredients), whereby the origin of the medication – whether home or practice medication – can be recognized by the coloured background. Thus if there is total agreement between home and practice medication (the prescribed medication is the same as the medication actually taken), Medibox 3 will contain drug pairs with identical active ingredients. The GP then deletes the drug pairs and checks the warnings (drug interactions, duplication with other drugs) and pointers (renal dose adjustment, tablet divisibility, exceeding maximal dose) for clinical relevance. He identifies patient problems using MediMoL. He prepares necessary therapy adjustments in „Medibox 3“.
7	Consultation between GP and patient on medication	The GP discusses the identified problems and any necessary changes in the medication with the patient. He saves the prescription plan he has discussed with the patient in the practice computer and makes a note of other arrangements (further appointments, transfer to a specialist etc.) on the MediMoL. He ends the interview with the patient and gives the MediMoL back to the HCA.
8	HCA ends the intervention	The HCA prints out the updated prescription plan and gives it to the patient. She follows any other instructions that have been made on MediMoL by the GP (e.g. makes an appointment for further interviews, laboratory checks, transfers to a specialist).

Medication Monitoring List (MediMoL)

PRIMUM

Date of interview

Name of the patient ..... ID .....

Name of health care assistant .....

	Contact GP	Follow-up consultation within	Report to the GP	Normal findings

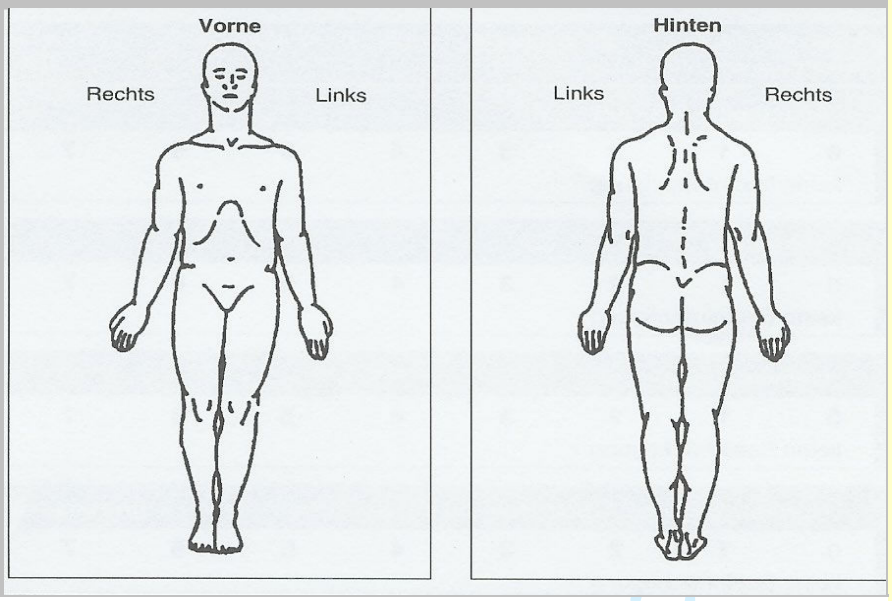
Pain: potential underuse?

1. Did you suffer from pain during the past 2 weeks?

Please take the time frame into consideration! If the patient reports pain, let him/her show the area that hurts. Circle all the aching regions on the map. If more than one area hurts, ask where the pain is most severe and mark the respective circle with an additional arrow.

Yes

Where?



Please present the verbal rating scale (VRS) to the patient and ask him/her about the intensity of the pain. If the patient reports pain in more than one place, ask him/her to describe the intensity at the location where it is most severe.

How intense was the pain during the past week?

Worst imaginable pain	■			
Severe pain		24h		
Moderate pain			■	
Mild pain				■
No pain				■

Did the pain limit your ability to perform activities of daily living (e.g. shopping, gardening, etc.)?

Yes			■	
No				■

No ■

Potential ADR

2. Did you suffer from the following complaints/symptoms during the past 2 wks?

Please take the time frame into consideration!

2.1 Nausea or vomiting? *Please underline as applicable.*

Yes	Almost every day		24h	
	On a number of days			■
	Once				■
No	Never				■

Did you suffer from the following complaints or symptoms during the past two weeks? (cont.)

Potential adverse drug reactions (ADR) or symptoms of underlying diseases

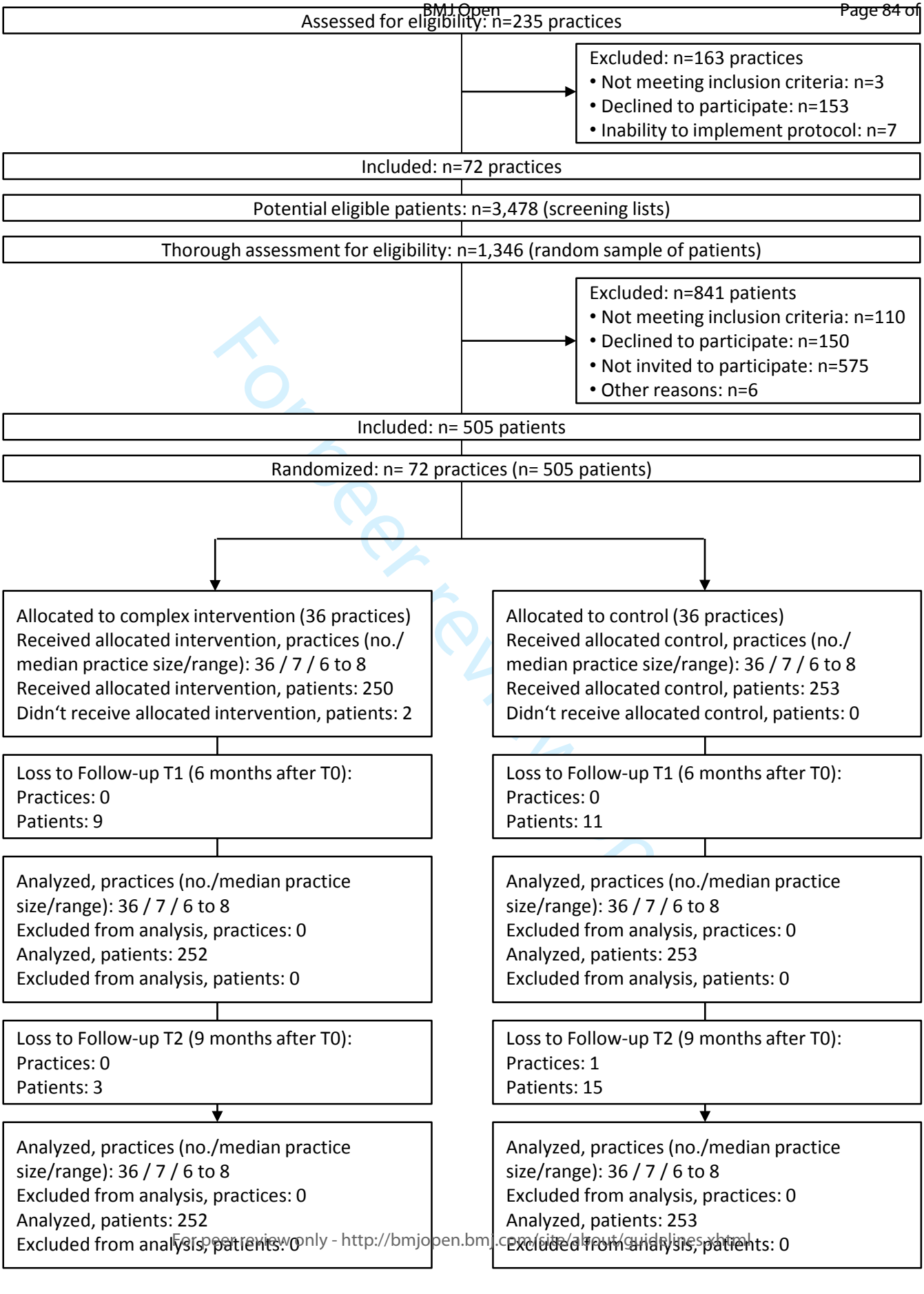
		Contact GP	Follow-up consultation within	Report to the GP	Normal findings
2.2 Dizziness?					
Yes	Almost every day		24h		
	On a number of days				
	Once				
No	Never				
2.3 Shortness of breath?					
Yes	Almost every day		24h		
	On a number of days				
	Once				
No	Never				
2.4 Abnormally rapid heart rate or irregular heartbeat? *Please underline as applicable.*					
Yes	Almost every day		24h		
	On a number of days				
	Once				
No	Never				
2.5 Swollen legs / edema?					
Yes					
No					
2.6 Do you think, your tendency to bleed has increased?					
Yes	Did you suffer from one of the following **more than once** during the past two weeks?				
	Bleeding gums?				
	Nosebleed?				
	Prolonged bleeding after a mild injury (e.g. when shaving or after a light cut)?				
	You have bruises that are more than 3 cm in diameter but you do not remember bumping yourself?				
	None of these problems.				
No					
2.7 Did you notice any black feces / melena during the past three months?					
Please take the time frame into consideration!					
Yes	Did the feces really look black and "tarry" (like tar) or was it just dark?				
	Yes, black and tarry. When did you last notice it?				
	Within the past three days				
	Within the past three weeks but not the past three days		24h		
	More than three weeks ago				
	No, only dark				
No					
Was the green box selected to answer questions 2.1 to 2.7? If so, go to question 3. If a different colored box was chosen to answer at least one question, go to question 2.8.					
2.8 Do you think your symptoms/complaints are caused by your medication?					
Yes	What makes you think so?				
	_____				
	_____				
No					

		Contact GP	Follow-up consultation within	Report to the GP	Normal findings
Information	**3. Do you need more information on your medication?**				
	Yes What in particular would you like to know? _____			☐	
	No				☐
Problems to take medicines in	**4.1 Did you have any of the following problems handling your medication during the past two weeks?**				
	Getting medicine out of the box or blister pack?				
	Yes Which drugs? _____			☐	
	No				☐
	Splitting, crushing or dissolving tablets?				
	Yes Which drugs? _____			☐	
	No				☐
	Counting the drops of a solution or applying plasters?				
	Yes Which drugs? _____			☐	
	No				☐
	Inserting suppositories?				
	Yes Which drugs? _____			☐	
	No				☐
	Administering inhalers or nebulizers?				
	Yes Which drugs? _____			☐	
	No				☐
	4.2 Did you have any difficulties swallowing a medicine during the past two weeks?				
	Yes The medicine is too large			☐	
	The taste is bad			☐	
	I have always had difficulties swallowing tablets			☐	
	Other reasons: _____			☐	
	No				☐
Adherence	**5.1 Did you try a medicine which was recommended by relatives, friends, neighbors etc. during the past two weeks ?**				
	Yes Which drugs?			☐	
	No				☐
	5.2 During the past two weeks, did you only take certain medicines when you felt worse?				
	Yes Which drugs? _____			☐	
	No				☐
	5.3 During past two weeks, did you neglect to take your prescribed medicine now and then?				
	Yes Which drugs? _____				
	When do you neglect to take your medicine?				
	_____			☐	
	No				☐
	5.4 Would you like to take fewer medications?				
	Yes Would you like to discuss this with your physician?				
	Yes Anything in particular?			☐	
	No				☐
	No				☐

		Contact GP	Follow-up consultation within	Report to the GP	Normal findings
Adherence	**5.5 Do you take a medicine that you would prefer not to take?**				
	Yes — Which medicine?			☐	
	What don't you like about it?				
	I can't tolerate it.			☐	
	I don't believe it is effective.			☐	
	It is too expensive			☐	
	Because I have to take so many other medications.			☐	
	Other reasons: _____			☐	
	No				☐
Patientent's preferences & treatment goals	**6.1 What are your medications supposed to achieve in your current situation?**				
	Please answer by ticking the blue boxess. ***Several answers possible*** *.*				
	☐ Prolonged survival?			☐	
	☐ Fewer hospitalizations?			☐	
	☐ Less pain?			☐	
	☐ Improved functional status (e.g., able to go shopping)			☐	
	☐ More enjoyment of life?			☐	
	☐ Others: _____			☐	
	6.2 What is most important to you?				
	Please tick one of the yellow boxes above (6.1). *Please note:* ***one answer only!***				
Communication within the practice team	**7. Making an appointment for a consultation with the physician (depending on find**				
	If you ticked any orange boxes, please inform the patient that after checking with the GP, you may well call him up and ask him to come to the practice. If you ticked only yellow and / or green boxes: please follow the procedure you have agreed upon in your practice for dealing with study patients.				
	Date of appointment with the physician: ..... **End of interview**				
	8. Health care assistant's assessment				
	Was there anything striking about the patient, e.g., exceptional circumstances or conflicts?				
	9. Information provided to the health care assistant by the physician after the physician-patient consultation on medication-related problems				
	Order lab tests: _____				
	☐ Electrolytes, creatinine				
	☐ Blood count				
	☐ Others				
	☐ Referral				
	☐ No changes to treatment				
	Treatment changes:				
	☐ Changes in medication				
	☐ Others				
	☐ Next consultation (follow up)				
	☐ Others				

Acknowledged:

Date Physician ..... Date Health care assistant .....



Characteristics of non-responding practices

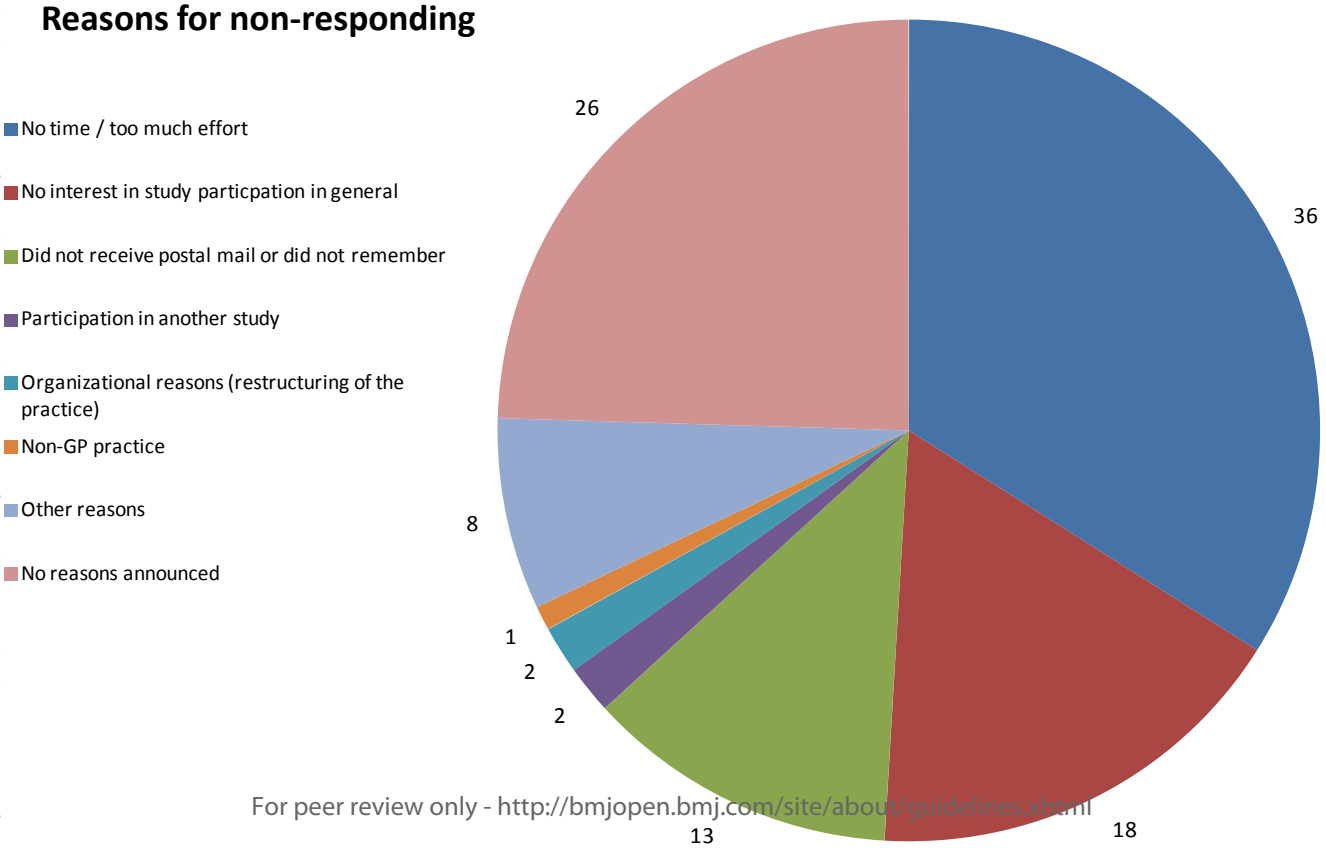
In total, 132 practices were called up to three times, of them 6 did not answer the phone.

107/126 were active general practices, 7 were not, and 12 practices did not provide information about it at the phone.

55/107 (51%) of the general practices had internet access, 50/107 had not, 2 did not provide details.

	Participating practices (total)	Non-responding practices
Practices	**N=72**	**N=132**
Location: no. (%)	N=72	N=132
City (>100,000 inhabitants)	22 (31%)	46 (35%)
Middle size town (20,000 to 100,000)	16 (22%)	37 (28%)
Small town (5,000 to 20,000)	25 (35%)	47 (36%)
Rural area (<5,000 inhabitants)	9 (13%)	2 (2%)
Practice type: no. (%)	**N=72**	**N=126**
Single handed practices	41 (57%)	75 (60%)
Group practice	27 (38%)	27 (21%)
Practice community	4 (6%)	6 (5%)
Not announced	-	18 (14%)

Reasons for non-responding



Effectiveness of a complex intervention on PRIoritising MUltimedication in Multimorbidity (PRIMUM) in primary care: results of a pragmatic cluster-randomised controlled trial.

Christiane Muth, Lorenz Uhlmann, Walter E. Haefeli, Justine Rochon, Marjan van den Akker, Rafael Perera, Corina Güthlin, Martin Beyer, Frank Oswald, Jose M. Valderas, André Knottnerus, Ferdinand M. Gerlach, Sebastian Harder

Web-appendix 4:

Table 1: Intention to treat analysis of primary and secondary outcomes and sensitivity analyses

Table 2: Symptoms for potential adverse drug reactions (ADR) - descriptive analysis

Table 1: Intention to treat analysis of primary and secondary outcomes and sensitivity analyses

	Control group		Intervention group				
	n_c	Mean (SD)	n_i	Mean (SD)	Adjusted difference (95% CI)	ICC/ICC_{adj}	P
Medication appropriateness index (MAI)							
MAI, Baseline (T0)	253	4.6 (5.8)	252	4.8 (5.4)	-	-	-
Primary outcome							
MAI, 6 months (T1)	243	3.8 (4.3)	241	4.6 (5.5)	0.7 (-0.2 to 1.6)*	0.016/0.017	0.137
Secondary outcome							
MAI, 9 months (T2)	228	3.9 (4.9)	238	4.8 (5.2)	0.6 (-0.5 to 1.7)*	0.000/0.000	0.272
Sensitivity analysis							
DMP non-participants:							
MAI, baseline	114	4.1 (5.2)	99	3.8 (3.8)	-	-	-
MAI, 6 months	110	3.5 (4.2)	92	4.2 (4.7)	0.7 (-0.4 to 1.9)*	0.000/0.000	0.200
MAI, 9 months	103	4.5 (5.7)	91	4.5 (5.1)	0.1 (-1.5 to 1.6)*	0.000/0.000	0.939
DMP participants:							
MAI, baseline	139	5.1 (6.2)	153	5.4 (6.1)	-	-	-
MAI, 6 months	133	4.0 (4.5)	149	4.8 (5.9)	0.7 (-0.6 to 1.9)*	0.006/0.010	0.295
MAI, 9 months	125	3.5 (4.0)	147	4.9 (5.3)	1.1 (0.0 to 2.2)*	0.000/0.000	0.049
Secondary outcomes on quality of life-related measures, functional status, pain, and hospitalisation							
EQ-5D:							
Baseline	240	74.9 (23.0)	241	73.9 (24.4)	-	-	-
6 months	225	73.2 (24.8)	229	73.9 (23.8)	1.4 (-2.5 to 5.3)	0.080/0.082	0.471
9 months	214	72.8 (25.1)	222	74.8 (23.4)	2.3 (-1.6 to 6.2)	0.049/0.048	0.247
Expected life duration:							
Baseline	200	11.6 (6.9)	209	10.3 (6.9)	-	-	-
6 months	200	12.0 (7.1)	202	11.0 (7.3)	0.0 (-1.1 to 1.1)	0.000/0.000	0.987
9 months	184	12.3 (7.0)	195	11.7 (7.9)	0.5 (-1.3 to 2.4)	0.185/0.192	0.588
Desired life duration:							
Baseline	207	16.5 (9.1)	218	15.2 (8.9)	-	-	-
6 months	196	16.6 (9.1)	200	15.2 (8.7)	-0.4 (-1.6 to 0.7)*	0.000/0.000	0.423
9 months	180	16.8 (9.2)	195	16.4 (9.8)	0.5 (-0.9 to 1.8)	0.078/0.081	0.479

	Control group		Intervention group				
	n_c	Mean (SD)	n_i	Mean (SD)	Adjusted difference (95% CI)	ICC/ICC_{adj}	P
Functional status (VES-13):							
Baseline	228	3.0 (2.9)	223	2.6 (2.7)	-	-	-
6 months	217	3.0 (2.9)	222	2.6 (2.8)	0.1 (-0.3 to 0.5)	0.000/0.000	0.681
9 months	199	2.7 (2.8)	204	2.8 (2.8)	0.4 (0.0 to 0.8)	0.051/0.043	0.047
Pain (von Korff index):							
Baseline	197	1.7 (1.3)	204	1.7 (1.2)	-	-	-
6 months	184	1.7 (1.4)	198	1.8 (1.2)	0.2 (-0.1 to 0.4)*	0.000/0.000	0.135
9 months	168	1.6 (1.2)	194	1.7 (1.2)	0.0 (-0.2 to 0.3)	0.004/0.006	0.782
Number of hospital stays:							
Baseline	40	1.4 (0.7)	42	1.7 (1.0)	-	-	-
6 months	45	1.4 (0.7)	34	1.4 (0.5)	1.2 (0.6 to 2.3)‡	0.000 / -	0.646
9 months	25	1.2 (0.4)	28	1.3 (0.6)	1.0 (0.3 to 3.1)‡	0.000 / -	0.949
Number of days spent in							
hospital:	40	14.9 (12.9)	42	19.0 (12.2)	-	-	-
Baseline	45	13.1 (11.5)	34	9.8 (8.9)	1.1 (0.5 to 2.3)‡	0.894 / -	0.850
6 months	25	9.7 (8.2)	28	28 (11.6)	0.4 (0.1 to 2.8)‡	0.859 / -	0.336
9 months							
Secondary outcomes of adherence and related measures							
Self-reported adherence:							
Baseline	252	3.7 (0.8)	250	3.7 (0.6)	-	-	-
6 months	238	3.8 (0.5)	237	3.6 (0.8)	-0.1 (-0.2 to 0.0)	0.005/0.002	0.044
9 months	225	3.7 (0.6)	231	3.7 (0.7)	0.0 (-0.2 to 0.1)	0.005/0.007	0.629
Drug score:#							
Baseline	251	101 (40.2%)	250	87 (34.8%)	-	-	-
6 months	237	101 (42.6%)	237	78 (32.9%)	0.7 (0.5 to 1.0)†	0.000/0.000	0.051
9 months	224	88 (39.3%)	231	85 (36.8%)	0.9 (0.6 to 1.4)†	0.010/0.009	0.736
Dose score:#							
Baseline	251	125 (49.8%)	248	134 (54%)	-	-	-
6 months	235	128 (54.5%)	236	136 (57.6%)	1.1 (0.7 to 1.6)†*	0.000/0.000	0.756
9 months	222	121 (54.5%)	229	145 (63.3%)	1.4 (0.9 to 2.0)†*	0.013/0.005	0.119

	Control group		Intervention group				
	n_c	Mean (SD)	n_i	Mean (SD)	Adjusted difference (95% CI)	ICC/ICC_{adj}	P
Regimen score:[#]							
Baseline	251	124 (49.4%)	249	131 (52.6%)	-	-	-
6 months	235	117 (49.8%)	236	134 (56.8%)	1.3 (0.8 to 2.0)†*	0.057/0.051	0.297
9 months	222	114 (51.4%)	229	137 (59.8%)	1.4 (0.9 to 2.1)†*	0.050/0.042	0.148
Number of prescriptions:							
Baseline	253	8.0 (2.4)	252	8.1 (2.8)	-	-	-
6 months	242	7.8 (2.3)	241	8.4 (3.0)	1.0 (1.0 to 1.1)‡*	0.097 / -	0.183
9 months	227	7.8 (2.2)	238	8.4 (3.2)	1.0 (1.0 to 1.1)‡*	0.100 / -	0.310
Number of single doses:							
Baseline	253	9.2 (3.5)	252	9.4 (4.1)	-	-	-
6 months	242	8.9 (3.3)	241	9.4 (4.1)	1.0 (1.0 to 1.1)‡*	0.183/-	0.573
9 months	227	9.0 (3.6)	238	9.4 (4.4)	1.0 (0.9 to 1.1)‡*	0.212/-	0.761
MRCI:							
Baseline	253	26.9 (12.3)	252	28.4 (14.3)	-	-	-
6 months	242	26.3 (12.2)	241	28.6 (14.3)	0.7 (-0.7 to 2.1)*	0.030/0.032	0.308
9 months	227	26.3 (11.9)	238	29.1 (15.6)	1.0 (-0.6 to 2.5)*	0.042/0.042	0.212
Man Song Hing scale:							
Baseline	241	8.4 (3.4)	246	8.6 (3.4)	-	-	-
6 months	233	8.6 (3.2)	233	8.4 (3.4)	-0.1 (-0.7 to 0.5)	0.047/0.050	0.789
9 months	219	8.8 (3.5)	231	8.7 (3.7)	-0.2 (-1.0 to 0.5)	0.041/0.041	0.519
BMQ, specific necessities:							
Baseline	233	22.1 (3.3)	240	22.1 (3.1)	-	-	-
6 months	219	22.0 (2.9)	230	21.8 (3.5)	-0.2 (-0.8 to 0.4)	0.043/0.046	0.557
9 months	207	21.6 (3.6)	226	21.9 (3.4)	0.3 (-0.4 to 1.0)	0.000/0.000	0.349
BMQ, specific concerns:							
Baseline	229	13.4 (5.2)	238	13.4 (5.2)	-	-	-
6 months	223	13.1 (4.8)	227	12.8 (4.8)	-0.2 (-1.0 to 0.7)	0.021/0.023	0.714
9 months	211	12.6 (5.0)	226	12.5 (5.1)	0.1 (-0.8 to 1.0)	0.044/0.047	0.838
BMQ, general overuse:							

	Control group		Intervention group				
	n_c	Mean (SD)	n_i	Mean (SD)	Adjusted difference (95% CI)	ICC/ICC_{adj}	P
Baseline	237	10.5 (3.5)	241	10.5 (3.7)	-	-	-
6 months	229	10.4 (3.6)	226	10.4 (3.4)	-0.2 (-0.8 to 0.5)	0.048/0.050	0.637
9 months	213	10.5 (3.6)	225	10.6 (3.6)	0.0 (-0.7 to 0.6)	0.054/0.057	0.917
BMQ, general harms:							
Baseline	239	8.0 (3.0)	245	7.9 (3.0)	-	-	-
6 months	229	7.9 (2.8)	234	7.9 (3.2)	0.1 (-0.4 to 0.6)	0.000/0.002	0.631
9 months	214	8.2 (3.1)	232	8.0 (3.2)	-0.2 (-0.8 to 0.4)	0.045/0.047	0.602

n_c / n_i – number of patients in control group / intervention group; SD - standard deviation. Adjusted differences are adjusted for clustering effects and baseline. If not stated otherwise, they are provided as mean differences between groups with 95% confidence intervals (CI), adjusted for clustering effects and baseline. ICCs are provided as crude values and adjusted for group. P-values are adjusted for cluster effects and baseline. [#]Discrepancies between prescriptions and intake provided in terms of no. and percentage of deviating patients, [†]effects are provided as estimated Odds Ratios with 95% CI adjusted for clustering effects and baseline. [‡]Effects are provided as estimated risk ratios for group with 95% CI adjusted for clustering effects and baseline. *The trend was in favour of the control group.

Abbreviations: BMQ – Beliefs about Medicine Questionnaire, CIRS - Cumulative Illness Rating Scale, DMP – Disease Management Program, EQ-5D – EuroQuol, MAI – Medication Appropriateness Index, MRCI – Medication regimen Complexity Index, VES-13 – Vulnerable Elderly Survey-13 items,

Table 2: Symptoms for potential adverse drug reactions (ADR) – descriptive analysis

Symptom[†] *(number, percentage)*	T0		T1		T2	
	Control group (n=253)	Intervention group (n=252)	Control group (n=237)	Intervention group (n=238)	Control group (n=225)	Intervention group (n=231)
Bleeding diathesis[#]	44 (17)	33 (13)	28 (12)	43 (18)	34 (15)	39 (17)
Ankle edema	78 (31)	84 (33)	79 (33)	87 (37)	67 (30)	90 (39)
Dizziness[#]	54 (21)	54 (21)	61 (26)	52 (22)	59 (26)	46 (20)
Dyspnea[#]	86 (34)	70 (28)	62 (26)	68 (29)	55 (24)	53 (23)
Difficulties urinating	51 (20)	64 (25)	56 (24)	54 (23)	43 (19)	47 (20)
Abdominal pain[#]	36 (14)	37 (15)	29 (12)	24 (10)	38 (17)	30 (13)
Tachycardia or palpitation[#]	36 (14)	36 (14)	28 (12)	26 (11)	21 (9)	21 (9)
Nausea or vomiting[#]	16 (6)	11 (4)	22 (9)	10 (4)	8 (4)	15 (6)

[†]for details see Figure 1, item "h", [#]symptoms appeared on at least several or almost every day

Manuscript: "Effectiveness of a complex intervention on PRIoritising MUltimedication in Multimorbidity (PRIMUM) in primary care: results of a pragmatic cluster-randomised controlled trial."

Table 1: CONSORT 2010 checklist of information to include when reporting a cluster randomised trial

Section/Topic	Item No	Standard Checklist item	Extension for cluster designs	Page No *
Title and abstract				
	1a	Identification as a randomised trial in the title	Identification as a cluster randomised trial in the title	✓
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)[i,ii]	See table 2	✓
Introduction				
Background and objectives	2a	Scientific background and explanation of rationale	Rationale for using a cluster design	7 Introduction section for scientific background
	2b	Specific objectives or hypotheses	Whether objectives pertain to the the cluster level, the individual participant level or both	7
Methods				
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	Definition of cluster and description of how the design features apply to the clusters	7
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons		**none**
Participants	4a	Eligibility criteria for participants	Eligibility criteria for clusters	7, 8
	4b	Settings and locations where the data were collected		7
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Whether interventions pertain to the cluster level, the individual participant level or both	8-9 plus PaTplot (figure 1, icons "2" to "5" and "j" to "k"), provision of an instrument (web-appendix 2)
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	Whether outcome measures pertain to the cluster level, the individual participant level or both	9-10 plus PaTplot (figure 1, icons "f" to "h")
	6b	Any changes to trial outcomes after the trial commenced, with reasons		**none**
Sample size	7a	How sample size was determined	Method of calculation, number of clusters(s) (and whether equal or unequal cluster sizes are assumed), cluster size, a	10-11

			coefficient of intracluster correlation (ICC or *k*), and an indication of its uncertainty	
	7b	When applicable, explanation of any interim analyses and stopping guidelines		n.a.
Randomisation:				
Sequence generation	8a	Method used to generate the random allocation sequence		8 plus PaTplot (figure 1: icon "i")
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Details of stratification or matching if used	8 plus PaTplot (figure 1: icon "i")
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Specification that allocation was based on clusters rather than individuals and whether allocation concealment (if any) was at the cluster level, the individual participant level or both	8
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Replace by 10a, 10b and 10c	
	10a		Who generated the random allocation sequence, who enrolled clusters, and who assigned clusters to interventions	8 plus PaTplot (figure 1: icon "i")
	10b		Mechanism by which individual participants were included in clusters for the purposes of the trial (such as complete enumeration, random sampling)	PaTplot (figure 1: icons "c" to "e")
	10c		From whom consent was sought (representatives of the cluster, or individual cluster members, or both), and whether consent was sought before or after randomisation	PaTplot (figure 1: icons "a", "b", "e")
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how		8
	11b	If relevant, description of the similarity of interventions		8-9 (both groups received practice guidelines for older adults)

Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	How clustering was taken into account	11
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses		11
Results				
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	For each group, the numbers of clusters that were randomly assigned, received intended treatment, and were analysed for the primary outcome	Web-appendix 3 (Flow chart)
	13b	For each group, losses and exclusions after randomisation, together with reasons	For each group, losses and exclusions for both clusters and individual cluster members	11-12 plus web-appendix 3
Recruitment	14a	Dates defining the periods of recruitment and follow-up		PaTplot (figure 1)
	14b	Why the trial ended or was stopped		N.a., trial was completed.
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Baseline characteristics for the individual and cluster levels as applicable for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	For each group, number of clusters included in each analysis	Table 1; web-appendix 3 (flow chart), table 1 and 2; web-appendix 4,
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Results at the individual or cluster level as applicable and a coefficient of intracluster correlation (ICC or k) for each primary outcome	Web-appendix 4, table 1 and 2; web appendix 3, flow chart
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended		n.a.
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory		Figure 2 (2a and 2b)
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms[iii])		n.a.
Discussion				
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses		14-15
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	Generalisability to clusters and/or individual participants (as relevant)	22
Interpretation	22	Interpretation consistent with results, balancing		23

		benefits and harms, and considering other relevant evidence	
Other information			
Registration	23	Registration number and name of trial registry	4
Protocol	24	Where the full trial protocol can be accessed, if available	Web-appendix 1
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	17

** Note: page numbers refer to the numbers within the original WORD file*

Table 2: Extension of CONSORT for abstracts[i,ii] to reports of cluster randomised trials

Item	Standard Checklist item	Extension for cluster trials
Title	Identification of study as randomised	**Identification of study as cluster randomised** ✓
Trial design	Description of the trial design (e.g. parallel, cluster, non-inferiority)	✓
Methods		
Participants	Eligibility criteria for participants and the settings where the data were collected	**Eligibility criteria for clusters** We did not apply inclusion criteria of major relevance for practices and provided this information with main text.
Interventions	Interventions intended for each group	✓
Objective	Specific objective or hypothesis	**Whether objective or hypothesis pertains to the cluster level, the individual participant level or both** ✓
Outcome	Clearly defined primary outcome for this report	**Whether the primary outcome pertains to the cluster level, the individual participant level or both** ✓
Randomization	How participants were allocated to interventions	**How clusters were allocated to interventions** ✓
Blinding (masking)	Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment	✓
Results		
Numbers randomized	Number of participants randomized to each group	**Number of clusters randomized to each group** ✓
Recruitment	Trial status[1]	N.a.
Numbers analysed	Number of participants analysed in each group	**Number of clusters analysed in each group** ✓
Outcome	For the primary outcome, a result for each group and the estimated effect size and its precision	**Results at the cluster or individual participant level as applicable for each primary outcome**

[1] Relevant to Conference Abstracts

		✓
Harms	Important adverse events or side effects	n.a.
Conclusions	General interpretation of the results	✓
Trial registration	Registration number and name of trial register	✓
Funding	**Source of funding**	Due to the word limit, we provided the source of funding with the plain text

The TIDieR (Template for Intervention Description and Replication) Checklist*:

Information to include when describing an intervention and the location of the information

Item number	Item	Where located **	
		Primary paper (page or appendix number)	Other † (details)
	BRIEF NAME		
1.	Provide the name or a phrase that describes the intervention.	The title: "complex intervention in PRIoritising MUltimedication in Multimorbidity (PRIMUM) in primary care"	_____
	WHY		
2.	Describe any rationale, theory, or goal of the elements essential to the intervention.	Abstract: objectives Main text: introduction (p. 6-7)	Pilot study [iv]
	WHAT		
3.	Materials: Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (e.g. online appendix, URL).	Abstract: interventions Main text: p. 8, last paragraph Figure 1 (icons "j" and "3" to "5") web-appendices 1 (study protocol) and 2 (checklist MediMoL)	_____
4.	Procedures: Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities.	Abstract: interventions Main text: p. 8-9 Figure 1 (icons "j" and "3" to "5") web-appendices 1 (study protocol) and 2 (checklist MediMoL)	_____
	WHO PROVIDED		
5.	For each category of intervention provider (e.g. psychologist, nursing assistant), describe their expertise, background and any specific training given.	Abstract: interventions Main text: methods section; for expertise and background of health care assistants (introduction: p. 6, last paragraph); Figure 1	_____

		(icon "j" for intervention training)	
	HOW		
6.	Describe the modes of delivery (e.g. face-to-face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group.	Figure 1 (icons "j" and "3" to "5")	_____
	WHERE		
7.	Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features.	Figure 1 (icons "j" and "3" to "5")	_____
	WHEN and HOW MUCH		
8.	Describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity or dose.	Methods section p. 8, last paragraph	_____
	TAILORING		
9.	If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how.	N/A	_____
	MODIFICATIONS		
10.‡	If the intervention was modified during the course of the study, describe the changes (what, why, when, and how).	N/A - the intervention was not modified during the study.	_____
	HOW WELL		
11.	Planned: If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them.	N/A	_____
12.‡	Actual: If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned.	N/A	_____

** **Authors** - use N/A if an item is not applicable for the intervention being described. **Reviewers** – use '?' if information about the element is not reported/not sufficiently reported.

† If the information is not provided in the primary paper, give details of where this information is available. This may include locations such as a published protocol or other published papers (provide citation details) or a website (provide the URL).

ǂ If completing the TIDieR checklist for a protocol, these items are not relevant to the protocol and cannot be described until the study is complete.

* We strongly recommend using this checklist in conjunction with the TIDieR guide (see *BMJ* 2014;348:g1687) which contains an explanation and elaboration for each item.

* The focus of TIDieR is on reporting details of the intervention elements (and where relevant, comparison elements) of a study. Other elements and methodological features of studies are covered by other reporting statements and checklists and have not been duplicated as part of the TIDieR checklist. When a **randomised trial** is being reported, the TIDieR checklist should be used in conjunction with the CONSORT statement (see www.consort-statement.org) as an extension of **Item 5 of the CONSORT 2010 Statement.** When a **clinical trial protocol** is being reported, the TIDieR checklist should be used in conjunction with the SPIRIT statement as an extension of **Item 11 of the SPIRIT 2013 Statement** (see www.spirit-statement.org). For alternate study designs, TIDieR can be used in conjunction with the appropriate checklist for that study design (see www.equator-network.org).

REFERENCES

[i] Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG, et al. CONSORT for reporting randomised trials in journal and conference abstracts. *Lancet* 2008, 371:281-283

[ii] Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG at al (2008) CONSORT for reporting randomized controlled trials in journal and conference abstracts: explanation and elaboration. *PLoS Med* 5(1): e20

[iii] Ioannidis JP, Evans SJ, Gotzsche PC, O'Neill RT, Altman DG, Schulz K, Moher D. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Ann Intern Med* 2004; 141(10):781-788.

[iv] Muth C, Harder S, Uhlmann L, Rochon J, Fullerton B, Guthlin C, et al. Pilot study to test the feasibility of a trial design and complex intervention on PRIoritising MUltimedication in Multimorbidity in general practices (PRIMUMpilot). BMJ Open 2016;6(7):e011613.

BMJ Open

Effectiveness of a complex intervention on PRIoritising MUltimedication in Multimorbidity (PRIMUM) in primary care: results of a pragmatic cluster-randomised controlled trial.

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Primary Subject Heading:	Patient-centred medicine
Secondary Subject Heading:	General practice / Family practice, Health services research, Medical management, Research methods, Geriatric medicine
Keywords:	Multimorbidity, Multiple Chronic Conditions, polypharmacy, medication reconciliation, drug therapy, computer-assisted, medication appropriateness index

Effectiveness of a complex intervention on PRIoritising MUltimedication in Multimorbidity (PRIMUM) in primary care: results of a pragmatic cluster-randomised controlled trial.

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Key words:

Multimorbidity; Multiple Chronic Conditions[MeSH]; comorbidity [MeSH]; polypharmacy [MeSH]; complex intervention; medication reconciliation [MeSH]; drug therapy, computer-assisted [MeSH]; medication appropriateness index; primary care [MeSH]; general practice [MeSH]

WORD COUNT: (aim but not strictly limited: ≤4,000 – currently: 4,589)

Abstract: (305 words)

Objectives: Investigate the effectiveness of a complex intervention aimed at improving the appropriateness of medication in older patients with multimorbidity in general practice.

Design: Pragmatic, cluster-randomised controlled trial with general practice as unit of randomisation.

Setting: 72 general practices in Hesse, Germany.

Participants: 505 randomly sampled, cognitively intact patients (≥60 years, ≥3 chronic conditions under pharmacological treatment, ≥5 long-term drug prescriptions with systemic effects); 465 patients and 71 practices completed the study.

Interventions: Intervention group (IG): The health care assistant conducted a checklist-based interview with patients on medication-related problems and reconciled their medications. Assisted by a computerised decision-support system, the general practitioner optimized medication, discussed it with patients and adjusted it accordingly. The control group (CG) continued with usual care.

Outcome measures: The primary outcome was a modified medication appropriateness index (MAI, excluding item 10 on cost effectiveness), assessed in blinded medication reviews and calculated as the difference between baseline and after 6 months; secondary outcomes after six- and nine-months follow-up: quality of life, functioning, medication adherence etc.

Results: At baseline, a high proportion of patients had appropriate to mildly inappropriate prescriptions (MAI 0-5 points: n=350 patients). Randomisation revealed balanced groups (IG: 36 practices/252 patients; CG: 36/253). Intervention had no significant effect on primary outcome: mean MAI sum scores decreased by 0.3 points in IG and 0.8 points in CG, resulting in a non-significant adjusted mean difference of 0.7 (95% CI -0.2 to 1.6) points in favour of CG. Secondary outcomes showed non-significant changes (quality of life slightly improved in IG but continued to decline in CG) or remained stable (functioning, medication adherence).

Conclusions: The intervention had no significant effects. Our ability to detect effects was limited by outcomes that did not adequately measured undertreatment and the high proportion of participants receiving appropriate prescriptions and enjoying good quality of life and functional status at baseline.

Trial registration: Controlled Trials: ISRCTN99526053 - August 31, 2010 - http://www.controlled-trials.com/ISRCTN99526053 and ClinicalTrials.gov: NCT01171339 - July 27, 2010 - http://clinicaltrials.gov/ct2/show/NCT01171339?term=PRIMUM&rank=1

"Strengths and limitations of this study"

- The PRIMUM intervention was developed and piloted in accordance with the latest MRC guidance on complex interventions.
- The effectiveness of the PRIMUM intervention was evaluated in a rigorously conducted cluster-randomised trial that involved random sampling of patients, disclosure of treatment allocation after baseline completion, and adherence to the protocol.
- To evaluate the generic patient-centred strategy of applying PRIMUM, we used the commonly used medication appropriateness index (MAI), as this implicit measure allows individualized assessments.
- We blinded both the assessment of the primary outcome MAI and the statistical analyses.
- Key limitations were that the baseline values of MAI and the secondary outcomes did not provide enough scope for improvement, and that medication underuse in polypharmacy was not sufficiently reflected in our outcome measures.

Introduction:

The prevalence of multimorbidity, i.e. the co-occurrence of multiple chronic or acute diseases and medical conditions in one person,[1] increases with age, and most primary care consultations currently involve patients with multiple conditions.[2-4] Multiple disorders in patients are likely to result in multiple drug prescriptions. This increases the risk of drug-drug and drug-disease interactions, inappropriate dosages or drug selection, and non-adherence of patients. They may, however, also result in undertreatment.[5-10] Inappropriate prescriptions may result in hospitalisations, falls and related injuries, decreased quality of life, cognitive and physical dysfunction, loss of autonomy, and increased mortality, particularly in the elderly.[6-8, 11-14] Negative health outcomes caused by inappropriate polypharmacy are responsible for high outlays for hospital treatment, home care and nursing homes.[15-17] Much morbidity and many costs may be preventable – for instance 20% to 50% of medication-related hospitalisations on internal wards have been estimated to be avoidable.[13, 16, 18-20] Recently, Dreischulte and co-researchers observed a reduction in hospital admission rates for gastrointestinal ulcers or bleeding in their trial evaluating a complex intervention addressing nine specific high-risk prescribing patterns such as nonsteroidal anti-inflammatory drugs (NSAIDs) in renal failure, or in combination with oral anticoagulants.[21] Further trials also evaluated interventions addressing safety indicators and achieved a reduction in high-risk prescribing through adherence to explicit criteria that are relevant to public health.[22, 23] However, 'the range of reported effect sizes was modest, and it is unclear whether such interventions can result in clinically significant improvements in patient outcomes'.[24]

Furthermore, considering there are more than 10,000 known diseases, the number of possible interactions between diseases and treatments in patients with multimorbidity is vast, and patients may not be able to cope with the treatment burden.[25] Generic patient-centred strategies to assess potential interactions and to prioritise and individualise management in accordance with patients' preferences and shared treatment goals have been recommended for patients with multimorbidity and polypharmacy.[26-32] In these patients, evidence of interventions with proven effectiveness on clinical outcomes remains scarce. However, recent Cochrane reviews have identified strategies that appear to be beneficial in terms of reducing inappropriate prescribing.[33, 34] Based on promising strategies to combat inappropriate polypharmacy and in accordance with guiding principles to manage patients with multimorbidity, we developed and piloted a complex intervention.[35] As the prevalence of multimorbidity and polypharmacy in older people is high, they made up the target population. To reduce the workload on the General Practitioner (GP), the intervention also involved a health care assistant (HCA) from the practice.[35] In Germany, HCAs receive less training than nurses and are comparable to certified medical assistants in the USA. In usual care, HCAs work as

receptionists, assist GPs (e.g. in diagnostic procedures or wound management) and conduct, for instance, dietary counselling. On many occasions, HCAs have successfully participated in chronic care interventions where they have, for example, surveyed patients by following protocols with fixed interview questions for conditions such as osteoarthritis, major depression, and chronic heart failure, under the supervision of GPs.[36-40]

In accordance with Medical Research Council (MRC) guidance on developing and evaluating complex interventions, we tested the feasibility of the complex intervention in a pilot study.[35] On the basis of overall feasibility findings, we improved the intervention and trial design. To compare the effectiveness of the complex PRIMUM intervention with usual care in older patients with multimorbidity and polypharmacy in general practice, we used the medication appropriateness index (MAI) as primary outcome. This implicit (non-criteria-based) measure allows an individualized assessment of medication appropriateness.[41-43] We investigated whether the appropriateness of drug prescriptions changed after 6 months follow-up measured as a difference in the MAI-Score 6 months from baseline minus baseline (MAI T1–T0).

Methods:

Study design

The study was a pragmatic, cluster-randomised controlled trial with the general practice as the unit of randomisation. To further reduce contamination of the control group and unlike the pilot study, detailed information on the intervention treatment was only provided to the intervention group.[35] Primary and secondary outcomes were measured at patient level (**Figure** 1[44-69] and web-appendix 1: study protocol).

[About here: Figure 1. PaT plot [70] of the PRIMUM trial.]

Setting and participants

General practices in the German state of Hesse were eligible if they provided primary care under the German statutory health insurance system, and if at least one of the HCA staff members was able to access the internet in the practice. Practices specializing in unconventional treatments or in special indications (e.g. HIV) were excluded. To recruit practices, we sent letters to about 1,600 practice addresses provided by the Association of Statutory Health Insurance Physicians of Hesse –

addressees were not exclusively active general practitioners. We checked inclusion and exclusion criteria for those who were interested by phone and agreed upon a time for investigator training (**Figure 1**: icon "1"). In both groups, GPs and HCAs received a lump-sum of €300 in recompense for the work involved in documenting results. In the intervention group, GPs and HCAs received an additional €150 for the extra work that the intervention entailed.

GPs that did not respond to the original letter received a reminder phone call. We phoned a random 10% sample of those who did not respond to either the letter or the reminder up to three times in order to collect data on inclusion and exclusion criteria, practice characteristics, and reasons for non-participation.

Patients: A random sample of seven patients per practice were included (**Figure 1**, patient recruitment, icons "c" to "e"). Patients were required to be≥ 60 years old, have ≥ 3 chronic conditions under pharmacological treatment, ≥ 5 long-term prescriptions of drugs with systemic effects (the medication regimen may have included drugs with local effects but these did not fulfil the inclusion criterion), have made ≥ 1 practice visit during the past quarter, and be able to fill in questionnaires and participate in telephone interviews. To include a greater number of patients at risk of (manageable) interactions than in the pilot study,[35] patients had to have diseases affecting at least two different organ systems operationalized as two different chapters of ICD-10. The chapters "H" (diseases of the eyes and ears) and "E00" to "E04" (diseases of the thyroid gland without hyperthyroidism) were not counted because their potential for systemic interactions was considered to be low. We excluded patients with dementia and cognitive impairment (Mini-Mental Status Examination, MMSE < 26),[47] because we designed our intervention for cognitively intact patients and did not target caregivers. Further exclusion criteria were a life expectancy ≤ 12 months, alcohol and drug abuse (based on the GP's assessment), or participation in another clinical trial 30 days prior to inclusion.

Randomisation, allocation concealment, and blinding

The first patient from each practice served as the basis for randomisation (**Figure 1**, icon "i"). Patients registered thereafter were treated according to practice status (control or intervention), which was assigned in an allocation ratio of 1:1 using a block randomisation of variable block length. At the study centre, an external researcher generated the allocation sequence using the random number generator of Microsoft EXCEL. Treatment allocation was disclosed to the practice after baseline completion. Owing to the nature of the intervention, it was not possible to blind GPs, HCAs, patients, and the study team. Treatment allocation was blinded to the clinical pharmacologist conducting

medication reviews for the primary outcome (MAI - medication appropriateness index) and to the statistician.

Intervention and control groups

Intervention group

The PaTplot [70] (**Figure 1**, icons "j" and "3" to "5") shows the four elements of the complex intervention. It consists of (1) a brown bag review and (2) a checklist-based pre-consultation interview with the patient that is conducted by the HCA (**web-appendix 2**), (3) a CDSS-assisted medication review carried out by the GP and (4) a GP-patient consultation to optimise and prioritise medication. GPs had the option to use the CDSS to help prepare the medication review with the patient, and during the consultation itself. Trained HCAs and GPs (**Figure 1**, item "2") implemented the intervention on a single occasion, which took the GP and the HCA a per-patient average of 35 and 45 minutes respectively.[35] The practice team for the intervention group received the GP guidelines for ambulatory geriatric care prepared by the Hesse Guideline Group (**Figure 1**, item "k"). Recommendations in the guideline focus on primary and secondary prevention (e.g. physical exercise, fall assessment and prevention).[46]

Control group

The control group continued to receive usual care but the practice team also received the GP guidelines for ambulatory geriatric care (**Figure 1**, item "k")[46] to harmonize usual care in both groups.

Outcomes

The *primary outcome* was the difference in MAI sum score [41, 71] at 6 months minus the corresponding baseline score (MAI T1–T0). The MAI is commonly used in RCTs[42, 43] and consists of ten items: indication, effectiveness, correctness of dosage, correctness of direction, practicality of direction, drug–drug interactions, drug-disease interactions, unnecessary drug duplications, correctness of treatment duration, and costs. The MAI item on cost was omitted because variable discount contracts between pharmaceutical companies and statutory health insurers preclude cost comparisons in Germany. The medication reviews were conducted by the same clinical pharmacologist (SH) that performed the pilot study. He rated nine items per prescription from '1'

(appropriate) to '3' (inappropriate) where '2' represents a middle rating of uncertain appropriateness in a blinded chart review. In line with the piloted procedures,[35] he coded the MAI according to the GP's prescriptions, renal function, electrolytes, multimorbidity (diagnoses, Cumulative Illness Rating Scale—CIRS)[44, 45] (Figure 1, icon f) and symptoms of adverse drug reactions (Figure 1, icon h). Phytopharmaceuticals, homeopathic and other complementary and alternative medicine products were excluded from the rating. MAI sum scores for the entire medication regimen were calculated on the basis of these ratings. Based on the intra-rater reliability of the MAI ratings in the pilot study (B-statistics: the intra-rater reliability for the nine MAI items ranged from 0.90 to 0.99 and was slightly better than inter-rater reliability),[35] we did not perform a duplicate MAI rating. MAI ratings were transformed by subtracting 1 from the original rating, resulting in values ranging from '0' (best rating) to '2' (worst rating), and summed to give an MAI score per prescription (theoretically ranging from 0 to 18) and across the entire medication regimen of the patient. Lower MAI sum scores denoted better prescribing appropriateness. A negative difference in MAI sum scores (MAI T1-T0) therefore reflected an improvement in prescribing quality.

Secondary outcomes (6 vs. 9 months): we measured the change in the MAI score after 9 months (MAI T2–T0). On the assumption, improved medication appropriateness would result in improved health-related quality of life and functional status, we measured the differences in the EQ-5D index score,[48, 49] changes in perceived future life expectancy (a quality of life-related concept indicating wellbeing and positive life evaluation measured in years of expected and desired lifetime duration),[52, 53] functional status (differences in vulnerable elderly survey, VES-13),[50] all-cause hospitalisation and severity of chronic pain (von Korff-Index)[51] after six and nine months (T1-T0 and T2-T0).

To explain intervention effects, we also measured changes in satisfaction with shared decision making (Man Son Hing scale, MSH)[54, 55] and medication adherence after six and nine months (T1-T0 and T2-T0). We investigated a) self-reported adherence in accordance with Morisky (low scores indicating good adherence);[62] b) "observed adherence" measured in terms of discrepancies between medicines actually taken (reported during patient interviews) and medicines prescribed (reported by GP), as expressed in the three scores developed by Barat et al.[72] The scores were based on ratios calculated as follows:

(1) The drug score (DS) representing the ratio of the number of drugs reported by the patients to the number of drugs reported by the GP,

(2) The dose score (DoS=d1(a1)+d2(a2)+d3(a3)+…/n), where d_i is the drug used by the patients (value 0 or 1), n is the number of drugs in the GP's report, and a_i is the dose-

deviation ratio calculated by dividing the patient's reported daily dose by the daily dose prescribed by the GP, and

(3) The regimen score (RS=d1(b1)+d2(b2)+d3(b3)+…/n), where b_i is the regimen-deviation ratio and calculated by dividing the patient's reported daily intake frequency (once daily, twice daily, etc.) by the corresponding frequency prescribed by the GP.[72]

Scores outside an interval of 0.8–1.2 were considered to be divergent.

Further adherence-related measures assessed the complexity of the medication (total number of prescriptions, number of single doses/day, and Medication Regimen Complexity Index, MRCI),[73] patients' beliefs and attitudes toward medication (Beliefs about Medicine Questionnaire, BMQ), [56, 57] cognitive function (verbal fluency test, VFT)[59] and depressive symptoms (Geriatric Depression Scale, GDS) [60, 61] – GDS and VFT will be reported elsewhere.

Sample size

Based on the results obtained in previous studies,[35, 74] a difference in the change values (MAI T1–T0) of at least 2 units between the treatment groups was considered clinically relevant. Based on the pilot study, a standard deviation of 6 units was expected, resulting in a Cohen's effect size d of 0.3 and representing a small effect size.[75] Assuming an intra-cluster correlation coefficient (ICC) of 0.03 at practice level [76] and an average cluster size of 7 patients, a total of 62 practices and 434 patients (31 practices and 217 patients per treatment arm) were required to detect such an effect with 80% power using a two-sample t-test at a two-sided significance level of α=0.05. The sample size calculation was performed using NCSS PASS 2008 (Inequality Tests for Two Means in a Cluster Randomised Trial). On the basis of an assumed drop-out rate of approximately 10%, the sample size was adjusted to a total of 70 practices and 490 patients (35 practices and 245 patients in each treatment group).

Statistical analysis

We performed descriptive analyses of the primary endpoint, the secondary endpoints, and all patient and practice characteristics (separately for patients in both groups) and calculated mean and standard deviation for continuous variables, and relative and absolute frequencies for categorical data.

In the primary analysis and using a two-sided significance level of α=0.05, we tested the null hypothesis H0: $\mu1 = \mu2$ (the mean difference MAI T1–T0 is the same in both groups) against the

alternative hypothesis H1: μ1 ≠ μ2 (the mean MAI T1–T0 differs). Because of cluster randomisation, we used a multilevel regression approach with patients at level one and practices at level two. The primary model included treatment group and MAI baseline as fixed factors and practice as a random factor. In a mixed model, estimates are adjusted for the correlation of observations on the same level, whereby a specific structure has to be chosen. We applied the compound symmetry correlation structure on the assumption that a correlation exists between patients from the same practice and that a specific numerical value can be attached to this correlation. We assumed the value was 0 for the correlation with patients from other practices. The results are presented as the adjusted mean between-group difference in MAI T1–T0 with the corresponding 95% confidence interval. In addition, the practice-related ICC was estimated. The primary analysis was performed in accordance with the intention-to-treat principle,[77] and additional sensitivity analyses were conducted on a per-protocol analysis set. In the multilevel approach, we made use of the missing at random assumption that the baseline or the treatment variable can explain missing data in the response. No additional imputation of missing data was conducted. In a sensitivity analysis, we replaced missing values for the primary endpoint using the baseline observation carried forward (BOCF) approach. The statistical analyses of the secondary endpoints used the same multilevel approach as the primary analysis. A linear, binary or Poisson mixed model was fitted in accordance with the scaling of the considered endpoint. The obtained p-values in the secondary analyses are only interpreted exploratively. All evaluations were carried out using software package R (version 2.15.0 and higher),[78] in combination with the R-packages xtable,[79] nlme,[80] lme4,[81] multilevel,[82] and psychometric[83].

Results:

Participant flow and non-responders

Of the 1,662 practice addresses we sent letters to (1,332 of them also received a phone call reminder), 1,325 did not reply at all, 102 answered but were not interested in further information, and 235 general practices asked for further details and were assessed for eligibility. Of those, 153 practices finally declined to participate, three did not meet inclusion criteria, and seven were not able to create screening lists using their practice computer. Of the 72 included practices, 3,478 IDs for potentially eligible patients were provided, from which a random sample of 1,346 IDs was drawn at the study centre and sent to the practices. In total, 505 patients were consecutively included from the random sample and 465 completed the study (intervention group 238/252, control group 227/253) (flow chart: **web-appendix 3**).

Of the 1,325 practices that did not reply, we called 132 randomly selected practices. Six practices did not answer the phone, 51 were willing to answer all questions, and 75 provided partial information. Sixty-one interviewed practices (48%) were not eligible (seven were not active GPs; 51 had no internet access, and three declined to say). Practice characteristics and reasons for not responding are provided in **web-appendix 3**.

Baseline characteristics of participants

Most practices were single-handed (57%), medium-sized (64%), and located in small to mid-sized towns (57%). Slightly more male GPs (57%) participated; they were either specialists in general practice (83%) or in internal medicine. On average, they were 51 years of age, had more than 23 years of clinical experience, and had worked in private practice for about 15 years. With one exception, HCAs were female. They averaged about 40 years of age, had about 17 years of clinical experience, and had worked in the practice at various employment levels (49% less than full time) for an average of 10 years. About three-quarters were qualified HCAs. Patients were slightly more often female (52%), had a median age of 72 years, and averaged eight prescriptions in nine single doses per day. Almost all patients were covered by statutory health insurance (96%), and looked after themselves (94%). 58% participated in one of the national disease management programs (DMP). Overall, baseline characteristics were well balanced in both groups (**Table 1**).

[About here: Table 1: Baseline characteristics of practices and patients]

Outcomes

Our study found the intervention to have no significant effect. The mean MAI sum scores had decreased minimally in both groups six months after baseline – by 0.3 points in the intervention group and 0.8 points in the control group – revealing a non-significant adjusted mean difference of 0.7 (95% CI -0.2 to 1.6) points in favour of the control group (ITT, per protocol analysis and BOCF approach did not differ). To control for the effects of oversampled patients registered in a DMP, we compared DMP participants with non-participants, which revealed no effects on MAI. Furthermore, socio-demographic factors did not have an influence (**Table 2**).

[About here: Table 2: Intention to treat analysis of primary and secondary outcomes and sensitivity analyses]

To explore our results, we conducted additional, non-prespecified analyses. As the sample size was not sufficiently large to perform subgroup analyses, we calculated multilevel models, which revealed strong effects of the baseline values of MAI sum scores on the primary outcome MAI T1-T0 ($p < 0.001$) (**Figure 2a**)**.** The figure also shows the low proportion of patients with high inappropriateness at baseline, and the size and direction of the MAI changes in both groups after six months. To explain the relationship between the number of prescriptions and MAI values, we conducted exploratory regression analysis, which approximately revealed a square function (**Figure 2b**).

[About here:

Figure 2 – Distribution and changes in the medication appropriateness index (MAI) using baseline values and number of prescriptions

Figure 2a (upper image): Changes in MAI scores in intervention and control groups six months after baseline compared to baseline values (absolute numbers of study participants and boxes and whiskers per subgroup are provided)

Figure 2b (lower image): MAI scores at baseline in terms of the number of prescriptions (higher diameters of drops represent higher numbers of study participants)]

Secondary outcomes showed small, non-significant changes. In the intervention group, patients' self-reported quality of life improved minimally (about 2.3% in EQ-5D, 0.5 years in both expected and desired lifetime) after six and nine months, whereas it continued to decline in the control group (**Figure 3**). Additionally, in the intervention group the mean number of hospital stays decreased and the mean number of days spent in hospital had dropped by half after six months, but in both groups the event rate was too small to show significant differences (intention-to-treat analyses of the primary and secondary outcomes: **Table 2**, descriptive analysis of symptoms for potential adverse drug reactions (ADR): **Web-appendix 4**).

[About here: Figure 3: Secondary outcomes related to patients' self-reported quality of life measures]

Discussion:

Key findings of the study

This study found the complex PRIMUM intervention to have no significant effects in older patients with multimorbidity and polypharmacy in general practice. At baseline, many patients already received appropriate prescriptions and enjoyed good quality of life and functional status. We can therefore conclude that in our study, there was not enough scope for improvement.

Strengths and limitations of study

The systematic development and stepwise evaluation of the PRIMUM intervention in accordance with MRC guidance on complex interventions[84] was a strength as demonstrated by refinements in the design of the main trial, based on the results of pilot testing.[35] Recruitment to target, random sampling of patients, minimal attrition (we lost one cluster to follow-up because the GP moved to another town), and adherence to the protocol are additional strengths when compared with previous studies.[85, 86] However, our study also had several limitations.

Firstly, there is no agreed definition of polypharmacy and patient inclusion at the numerical threshold of ≥5 prescriptions was somewhat arbitrary,[87, 88] but using a higher threshold would have meant losing patients whose medication was highly inappropriate (Figure 2b). Moreover, the association between the number of prescriptions and health outcomes is not linear: Payne and co-authors found only the most extreme levels of polypharmacy to be associated with increased admission rates in patients with multimorbidity,[89] while Gnjidic and her co-researchers identified the best discriminating threshold to be between 4.5 and 6.5 medicines for associations with frailty, disability, mortality, and falls.[90]

Secondly, our study population may limit the generalisability of the results. Our study was population-based and involved no pre-selection, and the response rate of practices was low. We cannot rule out that relatively ambitious GPs volunteered more frequently. As far as the choice of patients is concerned, we took a random sample within each practice and our selection criteria aimed at including a broad range of diseases involving as many organ systems as possible. We

applied the cognition test during recruitment and after consent. As our ultimate aim was to promote regular practice consultations, we excluded patients with dementia. The study required that patients who were unable to fill in questionnaires or to answer telephone calls should not attend (e.g., some nursing home residents and migrants). These groups may therefore have been under-represented. To enable random sampling, we applied a systematic case finding using prescription costs as a proxy but oversampled DMP participants. However, German DMPs do not address multimorbidity or polypharmacy and we did not find any DMP impact on outcomes in our study.

Thirdly, our outcome measures were slightly insensitive. In the intervention group, the increase in the average number of prescriptions indicates that GPs had more often begun to prescribe patients a new medicine. If undertreatment had been a key problem in our study, having the MAI as the main outcome variable would have led us to underestimate its impact, because it does not reliably detect underuse.[42] It is noteworthy that the number of medicines used in intervention and control groups had diverged after 6 and 9 months, with the adjusted mean number of drugs being 1.0 higher in the intervention group (Table 2). Figure 2b shows that the more drugs a physician prescribes, the greater the chance that the MAI score will increase. The intervention may have induced increased prescribing of medicines (e.g. in case of otherwise undetected underuse), which may explain the trend towards smaller reductions of the MAI scores in the intervention group.

Fourthly, our efforts to reduce contamination of controls by using a cluster-randomised design and withholding intervention details may have been substantially offset by a potentially important Hawthorne effect, as has been noted in other studies.[85, 91] GPs and HCAs collected extensive data on medication, diseases and laboratory parameters (see icon 'f' in Figure 1) at each study visit. It can be assumed that data collection will have had the same effect as the structured medication reviews: we also observed improvements in MAI mean values in the control group at the first follow-up (Figure 2a), and a slight decrease in the average numbers of prescriptions. The net effect was that the decrease in MAI scores in the control group was slightly larger than in the intervention group where it had been partly offset by an increase in the number of prescriptions (and higher MAI scores) resulting from identified underuse. However, the differences were very small.

Comparison with other studies

Most primary care studies have investigated pharmacist-led interventions, and have shown inconclusive results in various outcomes.[33, 92-96] However, pharmacist-led interventions may be difficult to implement in health care contexts in which pharmacists have no access to clinical information (e.g. patients' diagnoses, laboratory tests), patients often visit many different

pharmacies, and inter-professional relationships between GPs and pharmacists are not well established, as in Germany.[85, 86] In this context in particular, information technology systems have been identified by European GPs as supporting safer prescribing.[97-99] Further factors that have been addressed include support from other health care professionals such as nurses, systematic medication reviews, and greater involvement of the patient.[97-99] However, the efficacy of these measures is inconclusive: Olsson and co-investigators found that a physician-led medication review had no effect on indicators of high-risk prescribing in older patients with polypharmacy.[100] In contrast, a large-scale cluster-randomised controlled trial achieved reductions in unintentional drug duplications, drug-drug interactions, and new prescriptions of potentially inappropriate medications, but failed to show an impact on the discontinuation of inappropriate medicines.[101]

No evidence yet exists that polypharmacy interventions lead to decrease in mortality and hospitalisations,[94] functional decline and falls,[102, 103] and health-related quality of life[85, 86, 100, 104-107]. A recent meta-analysis revealed a modest reduction in the number of drugs (on average -0.2 in the intervention group vs.+0.2 in controls) but the results of the included studies differed widely [94] and, considering the frequency and potential impact of medication underuse,[6-8] a reduction in net prescription numbers is an ambiguous study endpoint.

Possible explanations and implications of the study

Our study showed the intervention to have no significant effect. We cannot rule out that there was not enough scope for improvement in our study (Figure 2a: the MAI of the patients included in the left two box plots in both groups could not improve). Additionally, there was a relevant Hawthorne effect (Figure 2a: the patients included in the four box plots of the control group on the right hand side also improved). The patients depicted in the four box plots of the intervention group on the right hand side (Figure 2a) improved less than corresponding patients in the control group, which probably reflects the small numbers of patients and the lack of an intervention effect. In addition, given the MAI's inability to detect changes in inappropriate underuse, it may have not been sensitive enough for the purpose of our study. As any newly prescribed drug worsens the MAI score, unless it is completely appropriate, this may at least partially explain the difference. Ongoing process evaluation concerning medication changes may provide further explanations of the outcomes and information on the implications of the study.

Further research is needed to identify patients that stand to benefit significantly from an intervention that aims to support the care of complex patients with multimorbidity and high treatment

burden.[108, 109] Future studies may also benefit from considering a refined choice of outcome measures that adequately takes underuse into account.

Conclusion

We did not find the intervention to have significant effects. The high proportion of participants receiving both appropriate prescriptions and enjoying good quality of life and functional status may have limited our ability to detect a potential effect. Further research should seek to identify groups of patients that are most likely to benefit from such resource-intensive interventions. Outcome measures should be patient-relevant and detect changes in underuse.

(Statements)

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Details of contributors: CM drafted the manuscript, coordinated the study and contributed to the conception, design, data collection and data analyses. SH contributed to the conception and design and conducted the MAI ratings. FMG was the guarantor of the study. JR and LU contributed to the conception, design and conducted data analyses. WEH contributed to the conception and design and provided the study version of CDSS. CG, MB, FO, RP, MvdA, AK, JVM and FMG provided specific advice on the conception, methods, and coordination of the study. All authors critically revised and agreed on the final version of the manuscript.

Ethics approval: The ethics commission of the medical faculty of the Johann Wolfgang Goethe University, Frankfurt / Main approved the study (resolution number E 46/10, file number 123/10, date: 20/05/2010) and all of the participants gave their written informed consent before taking part.

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Transparency declaration: Christiane Muth affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies between information contained in the trial registration and the actual study have been explained.

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- Muth C, Uhlmann L, Haefeli WE, Rochon J, van den Akker M, Beyer M, Perera R, Knottnerus A, Gerlach FM, Harder S (2014) PRIorisierung von MUltimedikation bei Multimorbidität (PRIMUM)* Cluster-RCT in Hausarztpraxen zeigte keine Effekte auf die Angemessenheit der Verschreibung. 48. Kongress der DEGAM, 18.-20.09.2014, Hamburg; Abstractband V3c | 3, S. 88.
- Muth C, Rochon J, Namyst A, Fullerton B, Harder S, van den Akker M, Perera-Salazar R, Gerlach FM, Beyer M. Anwendung der MRC Guidance in der allgemeinmedizinischen Forschung: Ergebnisse aus der PRIMUM-Studie (PRIorisierung von MUltimedikation bei Multimorbidität. Vortrag auf 13. Jahrestagung des Deutschen Netzwerks Evidenzbasierte Medizin, Hamburg, 15.–17.03.2012, Abstractband IV/1a

Table 1: Baseline characteristics of practices and patients

	Control group	Intervention group
Practices	**n=36**	**n=36**
Practice characteristics		
Location (number, percentage):		
City (>100,000 inhabitants)	16 (44)	6 (17)
Mid-sized town (20,000 to 100,000)	6 (17)	10 (28)
Small town (5,000 to 20,000)	10 (28)	15 (41)
Rural area (<5,000 inhabitants)	4 (11)	5 (14)
Single-handed practices (number, percentage)	21 (58)	20 (56)
Panel size‡ (number, percentage):		
Fewer than 1,000	11 (31)	12 (33)
1,000-1,499	14 (39)	11 (31)
1,500 or more	11 (31)	13 (36)
General practitioners		
Age (mean, SD)	50.2 ± 7.6	51.9 ± 7.0
Male sex (number, percentage)	21 (58)	20 (56)
Board certificate GP (number, percentage)	30 (83)	30 (83)
Years of clinical experience (mean, SD)	22.6 ± 8.6	23.3 ± 7.9
Years at practice site (mean, SD)	14.3 ± 9.1	15.7 ± 8.4
Health care assistants		
Age (mean, SD)	40.1 ± 8.8	37.8 ± 12.6
Female sex (number, percentage)	36 (100)	35 (97)
Fully qualified HCA (number, percentage)	25 (69)	27 (75)
Years of professional experience (mean, SD)	18.4 ± 9.3	15.9 ± 10.6
Years at practice site (mean, SD)	10.4 ± 8.2	9.6 ± 8.5
Full-time employment (number, percentage)	17 (47)	20 (56)
Cluster size (median number of patients, range)	7 (6 to 8)	7 (6 to 8)
Patients	**n=253**	**n=252**
Sociodemographics		
Age (mean, SD)	71.7 ± 7.4	72.5 ± 6.5
Female sex (number, percentage)	131 (52)	133 (53)
Covered by statutory health insurance (number, percentage)	243 (96)	243 (96)
Participation in a DMP (number, percentage)	139 (55)	153 (61)
Consultation with specialists in previous six months (number, percentage)	222 (88)	227 (90)
Living with spouse: yes (number, percentage)	166 (67)	152 (61)
Fending for themselves (number, percentage)	236 (94)	237 (94)
Home care situation rated as 'good' or 'very good' in GP assessment (number, percentage)	233 (92)	239 (95)
CASMIN educational classification (number, percentage):		
High	25 (10)	14 (6)
Middle	80 (32)	66 (27)
Low	144 (58)	169 (68)
Morbidity and medication		
Charlson comorbidity score (mean, SD)	3.2 ± 2.4	3.0 ± 2.0

		Control group	Intervention group
	CIRS sum score (mean, SD)	7.3 ± 4.3	8.1 ± 4.8
	CIRS number of affected organ systems (mean, SD)	4.4 ± 2.3	4.6 ± 2.4
	Potential ADR symptoms† (number, percentage):		
	Bleeding diathesis#	44 (17)	33 (13)
	Ankle edema	78 (31)	84 (33)
	Dizziness#	54 (21)	54 (21)
	Dyspnea#	86 (34)	70 (28)
	Difficulties urinating	51 (20)	64 (25)
	Abdominal pain#	36 (14)	37 (15)
	Tachycardia or palpitation#	36 (14)	36 (14)
	Nausea or vomiting#	16 (6)	11 (4)
Others			
	BMI (mean, SD)	30.3 ± 7.5	30.1 ± 5.6
	Geriatric Depression Scale (mean, SD)	2.4 ± 2.3	2.3 ± 2.2
	Verbal Fluency Test (mean, SD)	19.1 ± 5.6	18.6 ± 5.8

‡The number of patient registrations in a practice over a 3-month period, †for details see Figure 1, item "h", #symptoms appeared on at least several or almost every day;
Abbreviations: ADR – adverse drug reaction, BMI – body mass index, CASMIN - Comparative Analysis of Social Mobility in Industrial Nations, CIRS - Cumulative Illness Rating Scale, GP – general practitioner, HCA – health care assistant, SD – Standard Deviation

Table 2: Intention to treat analysis of primary and secondary outcomes and sensitivity analyses

	Control group		Intervention group				
	n_c	Mean (SD)	n_i	Mean (SD)	Adjusted difference (95% CI)	ICC/ICC_{adj}	P
Medication appropriateness index (MAI)							
MAI, Baseline (T0)	253	4.6 (5.8)	252	4.8 (5.4)	-	-	-
No. of prescriptions rated with MAI, Baseline#	253	7.8 (2.3)	252	8.0 (2.6)			
Primary outcome							
MAI, 6 months (T1)	243	3.8 (4.3)	241	4.6 (5.5)	MD: 0.7 (-0.2 to 1.6)*	0.016/0.017	0.137
No. of prescriptions rated with MAI, 6 months#	243	7.6 (2.2)	241	8.1 (2.8)	RR: 1.0 (1.0 to 1.1)	0.067/-	0.354
Secondary outcome							
MAI, 9 months (T2)	228	3.9 (4.9)	238	4.8 (5.2)	MD 0.6 (-0.5 to 1.7)*	0.000/0.000	0.272
No. of prescriptions rated with MAI, 9 months#	228	7.7 (2.3)	238	8.1 (3.0)	RR: 1.0 (1.0 to 1.1)	0.075/-	0.497
Sensitivity analysis							
DMP non-participants:							
MAI, baseline	114	4.1 (5.2)	99	3.8 (3.8)	-	-	-
MAI, 6 months	110	3.5 (4.2)	92	4.2 (4.7)	MD: 0.7 (-0.4 to 1.9)*	0.000/0.000	0.200
MAI, 9 months	103	4.5 (5.7)	91	4.5 (5.1)	MD: 0.1 (-1.5 to 1.6)*	0.000/0.000	0.939
DMP participants:							
MAI, baseline	139	5.1 (6.2)	153	5.4 (6.1)	-	-	-
MAI, 6 months	133	4.0 (4.5)	149	4.8 (5.9)	MD: 0.7 (-0.6 to 1.9)*	0.006/0.010	0.295
MAI, 9 months	125	3.5 (4.0)	147	4.9 (5.3)	MD: 1.1 (0.0 to 2.2)*	0.000/0.000	0.049
Secondary outcomes on quality of life-related measures							
EQ-5D index (percentage)							
Baseline	240	74.9 (23.0)	241	73.9 (24.4)	-	-	-
6 months	225	73.2 (24.8)	229	73.9 (23.8)	MD: 1.4 (-2.5 to 5.3)	0.080/0.082	0.471
9 months	214	72.8 (25.1)	222	74.8 (23.4)	MD: 2.3 (-1.6 to 6.2)	0.049/0.048	0.247

	Control group		Intervention group				
	n_c	Mean (SD)	n_i	Mean (SD)	Adjusted difference (95% CI)	ICC/ICC_{adj}	P
Expected life duration (years)							
Baseline	200	11.6 (6.9)	209	10.3 (6.9)	-	-	-
6 months	200	12.0 (7.1)	202	11.0 (7.3)	MD: 0.0 (-1.1 to 1.1)	0.000/0.000	0.987
9 months	184	12.3 (7.0)	195	11.7 (7.9)	MD: 0.5 (-1.3 to 2.4)	0.185/0.192	0.588
Desired life duration (years)							
Baseline	207	16.5 (9.1)	218	15.2 (8.9)	-	-	-
6 months	196	16.6 (9.1)	200	15.2 (8.7)	MD: -0.4 (-1.6 to 0.7)*	0.000/0.000	0.423
9 months	180	16.8 (9.2)	195	16.4 (9.8)	MD: 0.5 (-0.9 to 1.8)	0.078/0.081	0.479
Secondary outcomes on functional status, pain and hospitalisation							
Functional status (VES-13)							
Baseline	228	3.0 (2.9)	223	2.6 (2.7)	-	-	-
6 months	217	3.0 (2.9)	222	2.6 (2.8)	MD: 0.1 (-0.3 to 0.5)	0.000/0.000	0.681
9 months	199	2.7 (2.8)	204	2.8 (2.8)	MD: 0.4 (0.0 to 0.8)	0.051/0.043	0.047
Pain (von Korff index)							
Baseline	197	1.7 (1.3)	204	1.7 (1.2)	-	-	-
6 months	184	1.7 (1.4)	198	1.8 (1.2)	MD: 0.2 (-0.1 to 0.4)*	0.000/0.000	0.135
9 months	168	1.6 (1.2)	194	1.7 (1.2)	MD: 0.0 (-0.2 to 0.3)	0.004/0.006	0.782
Number of hospital stays							
Baseline	40	1.4 (0.7)	42	1.7 (1.0)		-	-
6 months	45	1.4 (0.7)	34	1.4 (0.5)	RR: 1.2 (0.6 to 2.3)	0.000 / -	0.646
9 months	25	1.2 (0.4)	28	1.3 (0.6)	RR: 1.0 (0.3 to 3.1)	0.000 / -	0.949
Number of days spent in hospital							
Baseline	40	14.9 (12.9)	42	19.0 (12.2)	-	-	-
6 months	45	13.1 (11.5)	34	9.8 (8.9)	RR: 1.1 (0.5 to 2.3)	0.894 / -	0.850
9 months	25	9.7 (8.2)	28	28 (11.6)	RR: 0.4 (0.1 to 2.8)	0.859 / -	0.336
Secondary outcomes of adherence and related measures							
Self-reported adherence							

	Control group		Intervention group				
	n_c	Mean (SD)	n_i	Mean (SD)	Adjusted difference (95% CI)	ICC/ICC_{adj}	P
Baseline	252	3.7 (0.8)	250	3.7 (0.6)	-	-	-
6 months	238	3.8 (0.5)	237	3.6 (0.8)	MD: -0.1 (-0.2 to 0.0)	0.005/0.002	0.044
9 months	225	3.7 (0.6)	231	3.7 (0.7)	MD: 0.0 (-0.2 to 0.1)	0.005/0.007	0.629
Observed adherence: Drug score (no. and percentage of deviating patients)							
Baseline	251	101 (40.2%)	250	87 (34.8%)	-	-	-
6 months	237	101 (42.6%)	237	78 (32.9%)	OR: 0.7 (0.5 to 1.0)	0.000/0.000	0.051
9 months	224	88 (39.3%)	231	85 (36.8%)	OR: 0.9 (0.6 to 1.4)	0.010/0.009	0.736
Observed adherence: Dose score (no. and percentage of deviating patients)							
Baseline	251	125 (49.8%)	248	134 (54%)	-	-	-
6 months	235	128 (54.5%)	236	136 (57.6%)	OR: 1.1 (0.7 to 1.6)*	0.000/0.000	0.756
9 months	222	121 (54.5%)	229	145 (63.3%)	OR: 1.4 (0.9 to 2.0)*	0.013/0.005	0.119
Observed adherence: Regimen score (no. and percentage of deviating patients)							
Baseline	251	124 (49.4%)	249	131 (52.6%)	-	-	-
6 months	235	117 (49.8%)	236	134 (56.8%)	OR: 1.3 (0.8 to 2.0)*	0.057/0.051	0.297
9 months	222	114 (51.4%)	229	137 (59.8%)	OR: 1.4 (0.9 to 2.1)*	0.050/0.042	0.148
Number of prescriptions							
Baseline	253	8.0 (2.4)	252	8.1 (2.8)	-	-	-
6 months	242	7.8 (2.3)	241	8.4 (3.0)	RR: 1.0 (1.0 to 1.1)*	0.097 / -	0.183
9 months	227	7.8 (2.2)	238	8.4 (3.2)	RR: 1.0 (1.0 to 1.1)*	0.100 / -	0.310
Number of single doses:							
Baseline	253	9.2 (3.5)	252	9.4 (4.1)	-	-	-
6 months	242	8.9 (3.3)	241	9.4 (4.1)	RR: 1.0 (1.0 to 1.1)*	0.183/-	0.573

	Control group		Intervention group				
	n_c	Mean (SD)	n_i	Mean (SD)	Adjusted difference (95% CI)	ICC/ICC_{adj}	P
9 months	227	9.0 (3.6)	238	9.4 (4.4)	RR: 1.0 (0.9 to 1.1)*	0.212/-	0.761
MRCI							
Baseline	253	26.9 (12.3)	252	28.4 (14.3)	-	-	-
6 months	242	26.3 (12.2)	241	28.6 (14.3)	MD: 0.7 (-0.7 to 2.1)*	0.030/0.032	0.308
9 months	227	26.3 (11.9)	238	29.1 (15.6)	MD: 1.0 (-0.6 to 2.5)*	0.042/0.042	0.212
Man Song Hing scale							
Baseline	241	8.4 (3.4)	246	8.6 (3.4)	-	-	-
6 months	233	8.6 (3.2)	233	8.4 (3.4)	MD: -0.1 (-0.7 to 0.5)	0.047/0.050	0.789
9 months	219	8.8 (3.5)	231	8.7 (3.7)	MD: -0.2 (-1.0 to 0.5)	0.041/0.041	0.519
BMQ, specific necessities							
Baseline	233	22.1 (3.3)	240	22.1 (3.1)	-	-	-
6 months	219	22.0 (2.9)	230	21.8 (3.5)	MD: -0.2 (-0.8 to 0.4)	0.043/0.046	0.557
9 months	207	21.6 (3.6)	226	21.9 (3.4)	MD: 0.3 (-0.4 to 1.0)	0.000/0.000	0.349
BMQ, specific concerns							
Baseline	229	13.4 (5.2)	238	13.4 (5.2)	-	-	-
6 months	223	13.1 (4.8)	227	12.8 (4.8)	MD: -0.2 (-1.0 to 0.7)	0.021/0.023	0.714
9 months	211	12.6 (5.0)	226	12.5 (5.1)	MD: 0.1 (-0.8 to 1.0)	0.044/0.047	0.838
BMQ, general overuse							
Baseline	237	10.5 (3.5)	241	10.5 (3.7)	-	-	-
6 months	229	10.4 (3.6)	226	10.4 (3.4)	MD: -0.2 (-0.8 to 0.5)	0.048/0.050	0.637
9 months	213	10.5 (3.6)	225	10.6 (3.6)	MD: 0.0 (-0.7 to 0.6)	0.054/0.057	0.917
BMQ, general harms							
Baseline	239	8.0 (3.0)	245	7.9 (3.0)	-	-	-
6 months	229	7.9 (2.8)	234	7.9 (3.2)	MD: 0.1 (-0.4 to 0.6)	0.000/0.002	0.631
9 months	214	8.2 (3.1)	232	8.0 (3.2)	MD: -0.2 (-0.8 to 0.4)	0.045/0.047	0.602

n_c / n_i – number of patients in control group / intervention group; SD - standard deviation; MD – mean differences, OR – Odds Ratio, and RR – Relative Risk are provided with 95% confidence intervals (CI), and adjusted for clustering effects and baseline. ICCs are provided as crude values using a mixed model without any adjustment (either group or baseline). The adjusted values use a mixed model that includes the group variable. P-values are adjusted for cluster effects and

baseline. #Phytopharmaceuticals, homeopathic and other complementary and alternative medicine products were excluded from rating. *control group tended to perform better.

Abbreviations: BMQ – Beliefs about Medicine Questionnaire, CIRS - Cumulative Illness Rating Scale, DMP – Disease Management Program, EQ-5D – EuroQuol five dimensions, MAI – Medication Appropriateness Index, MRCI – Medication regimen Complexity Index, VES-13 – Vulnerable Elderly Survey-13 items

List of Tables and Figures:

Table 1: Baseline characteristics of practices and patients

Legend: ‡The number of patient registrations in a practice over a 3-month period, †for details see Figure 1, item "h", #symptoms appeared on at least several or almost every day;
Abbreviations: ADR – adverse drug reaction, BMI – body mass index, CASMIN - Comparative Analysis of Social Mobility in Industrial Nations, CIRS - Cumulative Illness Rating Scale, GP – general practitioner, HCA – health care assistant, SD – Standard Deviation

Table 2: Intention to treat analysis of primary and secondary outcomes and sensitivity analyses

Legend: n_c / n_i – number of patients in control group / intervention group; SD - standard deviation; MD – mean differences, OR – Odds Ratio, and RR – Relative Risk are provided with 95% confidence intervals (CI), and adjusted for clustering effects and baseline. ICCs are provided as crude values using a mixed model without any adjustment (either group or baseline). The adjusted values use a mixed model that includes the group variable. P-values are adjusted for cluster effects and baseline. #Phytopharmaceuticals, homeopathic and other complementary and alternative medicine products were excluded from rating. *control group tended to perform better.

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Figure 1: PaT plot [70] of the PRIMUM trial.

Abbreviations: GP - general practitioner; HCA - health care assistant; †structured symptoms of side effects: dizziness, dyspnea, tachycardia / palpitations, nausea / vomiting, abdominal pain, bleeding diathesis, difficulties urinating, ankle oedema - frequency expressed as occurrence on one day / several days / almost every day during the past two weeks.

Figure 2: Distribution and changes in the medication appropriateness index (MAI) using baseline values and number of prescriptions

Figure 2a (upper image): Changes in MAI scores in intervention and control groups six months after baseline compared to baseline values (absolute numbers of study participants and boxes and whiskers per subgroup are provided)

Figure 2b (lower image): MAI scores at baseline in terms of the number of prescriptions (higher diameters of drops represent higher numbers of study participants)

Figure 3: Secondary outcomes related to patients' self-reported quality of life measures

Supplemental files:

- Web-appendix 1: study protocol
- Web-appendix 2: Medication Monitoring List (MediMoL) – checklist used by health care assistants
- Web-appendix 3: CONSORT flowchart and practice characteristics of non-responders
- Web-appendix 4: Symptoms for potential adverse drug reactions (ADR) - descriptive analysis
- CONSORT and TIDieR checklists

List of abbreviations

ADR	Adverse Drug Reaction
BMI	Body Mass Index
BMQ	Beliefs about Medicines Questionnaire
CASMIN	Comparative Analysis of Social Mobility in Industrial Nations
CDSS	Computerized Decision Support System
CIRS	Cumulative Illness Rating Scale
CRF	Case Report Form
DS	Drug Score
DoS	Dose Score
GDS	Geriatric Depression Scale
GP	General Practitioner
ICC	Intra-Cluster Correlation-coefficient
ID	Identifier
ITT	Intention To Treat
HCA	Health care assistant
MAI	Medication Appropriateness Index
MediMoL	Medication Monitoring List
MMSE	Mini Mental Status Exam
MRCI	Medication Regimen Complexity Index
RS	Regimen Score
SD	Standard Deviation

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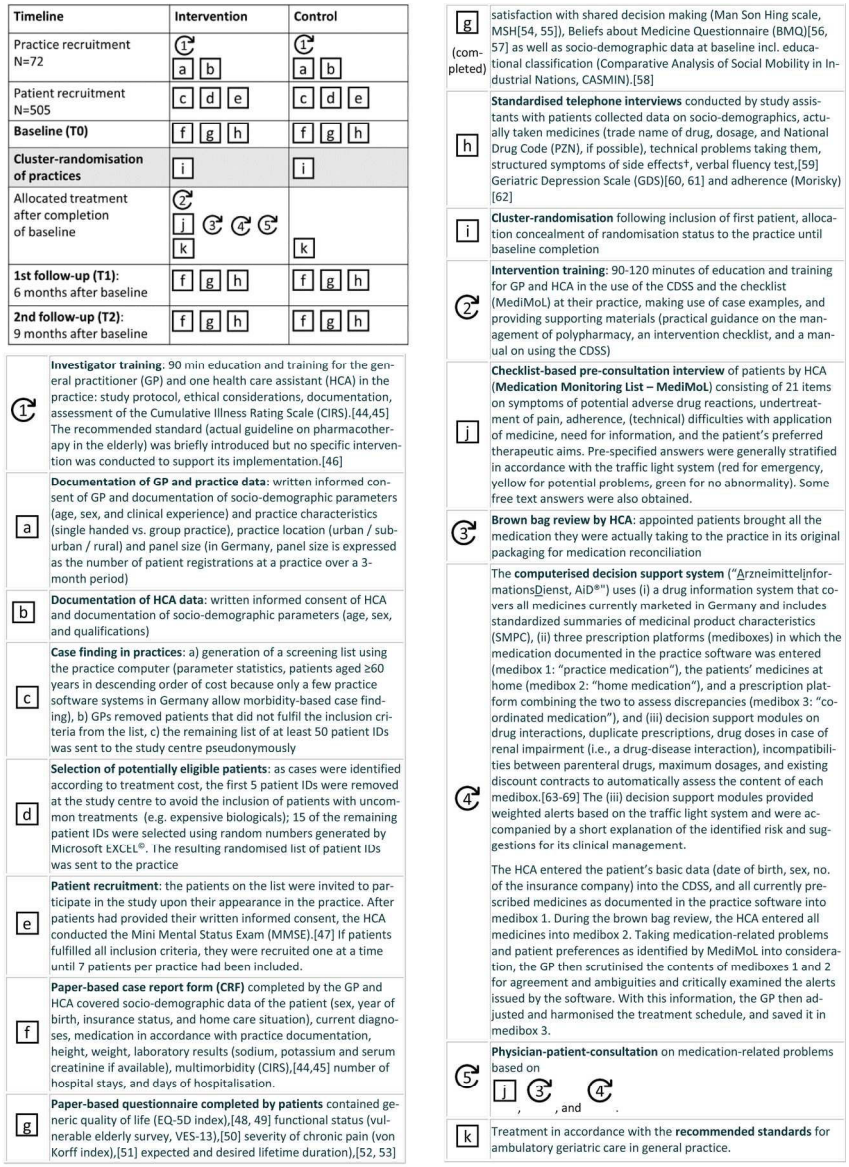

Figure 1: PaT plot [70] of the PRIMUM trial.

164x233mm (300 x 300 DPI)

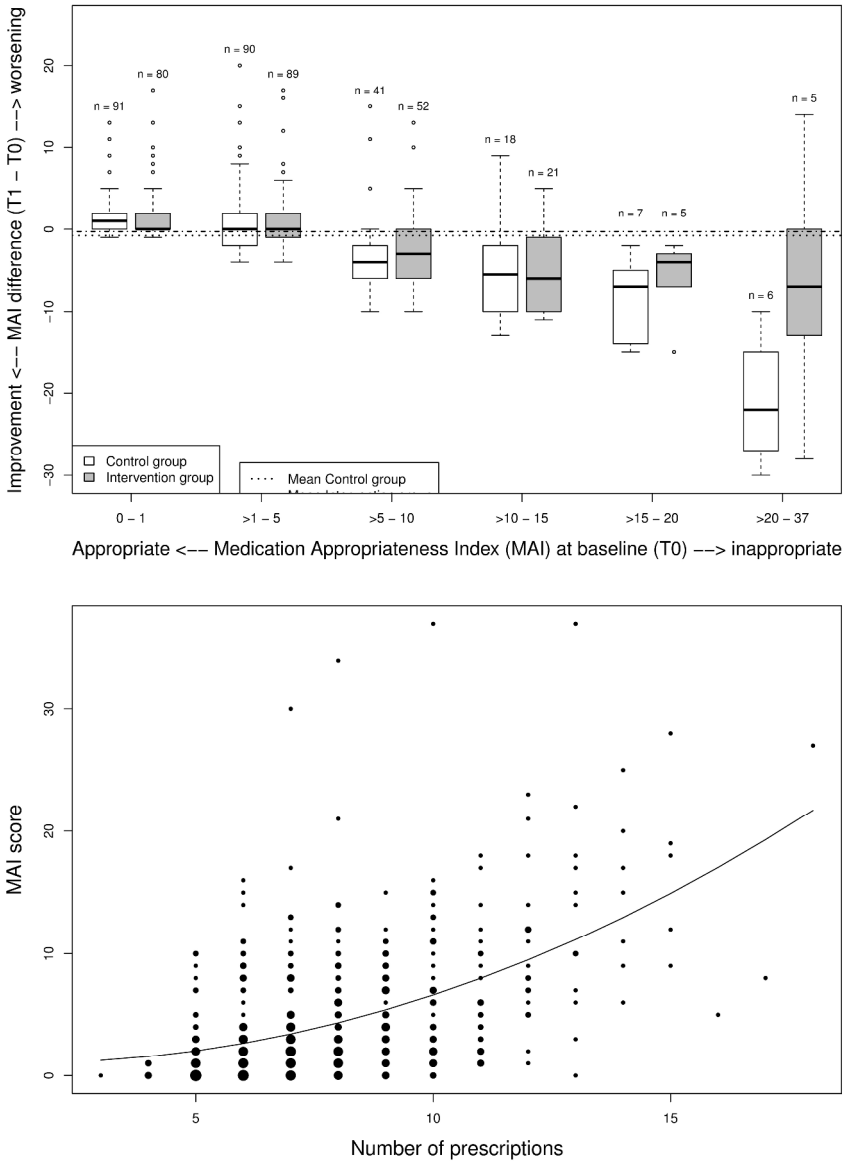

Figure 2: Distribution and changes in the medication appropriateness index (MAI) using baseline values and number of prescriptions

Figure 2a (upper image): Changes in MAI scores in intervention and control groups six months after baseline compared to baseline values (absolute numbers of study participants and boxes and whiskers per subgroup are provided)

Figure 2b (lower image): MAI scores at baseline in terms of the number of prescriptions (higher diameters of drops represent higher numbers of study participants)

381x519mm (300 x 300 DPI)

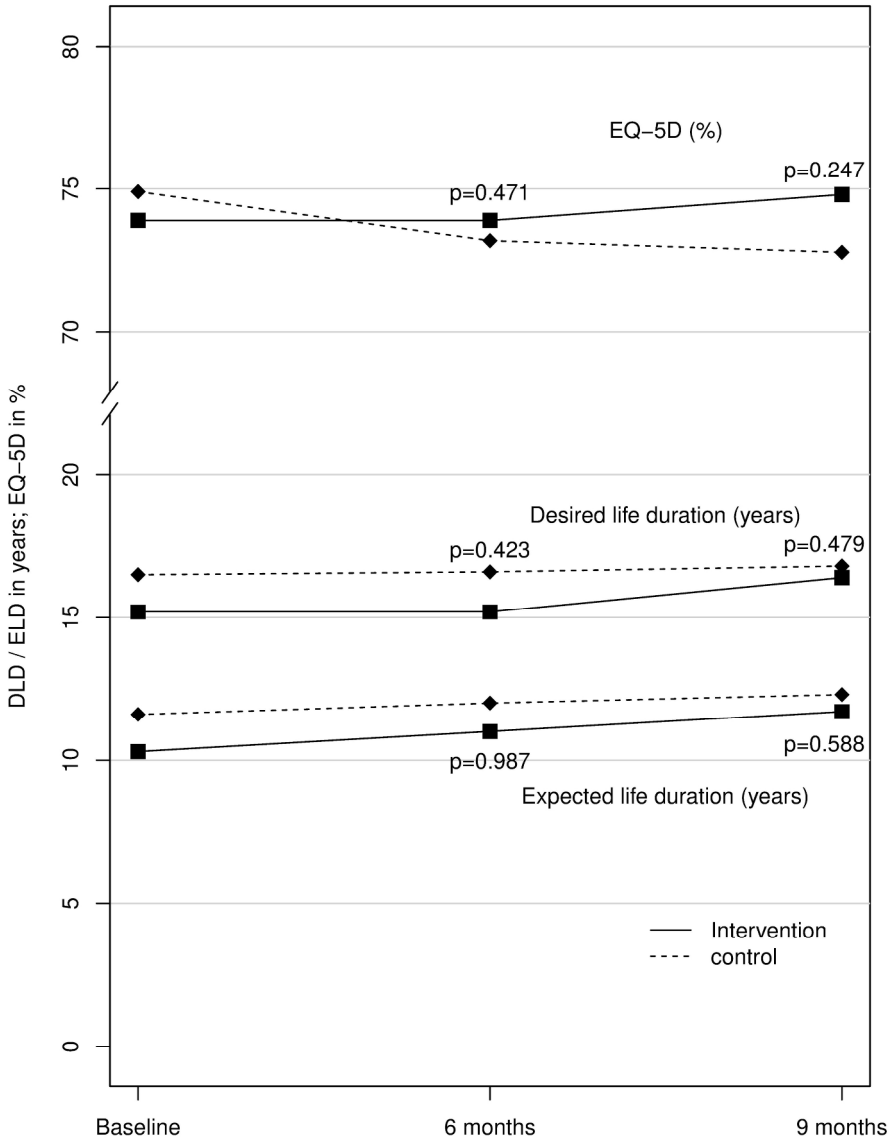

Figure 3: Secondary outcomes related to patients' self-reported quality of life measures

228x293mm (300 x 300 DPI)

Title:

Prioritising and optimising multiple medications in elderly multi-morbid patients in general practice. - A pragmatic cluster-randomised controlled trial.

[PRIMUM]

PRIoritising ***MU***ltimedication in ***M***ultimorbid patients

Sponsor: **Johann Wolfgang Goethe University Hospital, Frankfurt am Main**

Theodor-Stern-Kai 7
D - 60590 Frankfurt a.M.

The International Standard Randomised Controlled Trial Number (ISRCTN): (follows)

Trial administration:

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Sponsor	German Federal Ministry for Education and Research (BMBF) Grant Number: 01GK0702 – Notification of 31.03.2009 and 08.02.2010

1.2 Signature Page

Prioritising and optimising multiple medications in elderly multi-morbid patients in general practice

PRIMUM - PRIoritising MUltimedication in Multimorbid patients [ISRCTN (follows)]

The study protocol (version 1.1, date: 20/07/2010) is approved by the following:

Principal Investigator:

Dr. med. Christiane Muth, MPH

Date	Signature

Co-Investigators:

Prof. Dr. F. Gerlach, MPH:

Date	Signature

Prof. Dr. med. Walter E. Haefeli:

Date	Signature

Prof. Dr. med. Sebastian Harder:

Date	Signature

Study Statistician:

Dipl.-Psych. Justine Rochon, M.Sc. Medical Biometry:

Date	Signature

On behalf of the Scientific Advisory Board:

Date	Signature

1.3 Signature Page for Participating General Practitioners

Prioritising and optimising multiple medications in elderly multi-morbid patients in general practice

PRIMUM - PRIoritising MUltimedication in Multimorbid patients [ISRCTN (follows)]

The study protocol (version 1.1, date: 20/07/2010) is approved by the following:

(to be signed by the investigator of each trial site before commencing the trial)

I herewith confirm that I have read and understood the present protocol and accept it in all its constituent parts. I agree to ensure that all the patients from my trial site who are included in the trial will be treated, observed and documented in accordance with all stipulations of the protocol and in accordance with the principles outlined in the Declaration of Helsinki.

Investigator:

Name, first name: _____

Practice stamp:

_____ _____

Date Signature

1.4 Synopsis of the Protocol

Principal investigator	Dr. Christiane Muth, MD, MPH; Institute for General Practice, Johann Wolfgang Goethe University, Frankfurt / Main
Sponsor	Johann Wolfgang Goethe University, Frankfurt / Main
Title of trial	Prioritising and optimising multiple medications in elderly multimorbid patients in general practice. - A pragmatic cluster-randomised controlled trial.
Abbreviated name of trial	PRIMUM: PRIoritization and optimization of MUltimedication in Multimorbid patients
Indication	Multimedication in elderly, multimorbid patients: Age ≥ 60, ≥ 3 chronic diseases, ≥ 5 long-term prescriptions
Objective	To investigate whether the complex intervention will improve the appropriateness of prescriptions in elderly multi-morbid patients
Intervention	Intervention: Healthcare assistant (HCA) and computer assisted optimization of multi-medication (complex intervention) in accordance with recommended standard[#] Control: Usual care in accordance with recommended standard[#] [#]Recommended standard: clinical practice guideline "Geriatrie" of the guideline group of Hesse (part 1 and 2)[1] Follow-up per patient: 9 months Study duration per patient: 9 months
Rationale	Key problems of multimedication in multimorbidity: 1. Multimorbidity, multimedication and increasing age raise the risk of inappropriate prescriptions and adverse drug reactions, and under-treatment. 2. Multimedication and high complexity of medication reduce adherence among patients. 3. Physician-patient consultations on medication related problems are dominated by doctors in content, focus mostly on effectiveness, and neglect side effects and strategies to manage them. 4. Patients do not generally inform doctors of adverse drug reactions and autonomous decisions to adjust medication dose. Key elements of intervention: Basic assessment of (1) medicines that were actually taken and (2) problems relating to medicines (technical handling, potential adverse drug reactions) and patient's therapeutic aims by HCA provides structured information in the Medication-Monitoring-List (MediMoL) for the general practitioner (GP) and enables patients to discuss their problems with the GP. (3) GP uses a computerized decision support system (pharmaceutical information system, AiD+) to optimize medication (reducing number of inappropriate prescriptions, e.g. pharmaceutical interactions, renal dose adjustments, duplicate prescriptions) and (4) prioritizes medication in the physician-patient consultation taking into consideration patient's preferences. Desired effects: → Prescriptions become more appropriate → Prescriptions become less complex → Prescriptions take the patient's perspective into account (avoidance of adverse drug reactions and under-treatment, patients' preferences are taken into account and priorised) → Patients are more likely to adhere to the doctor's therapy

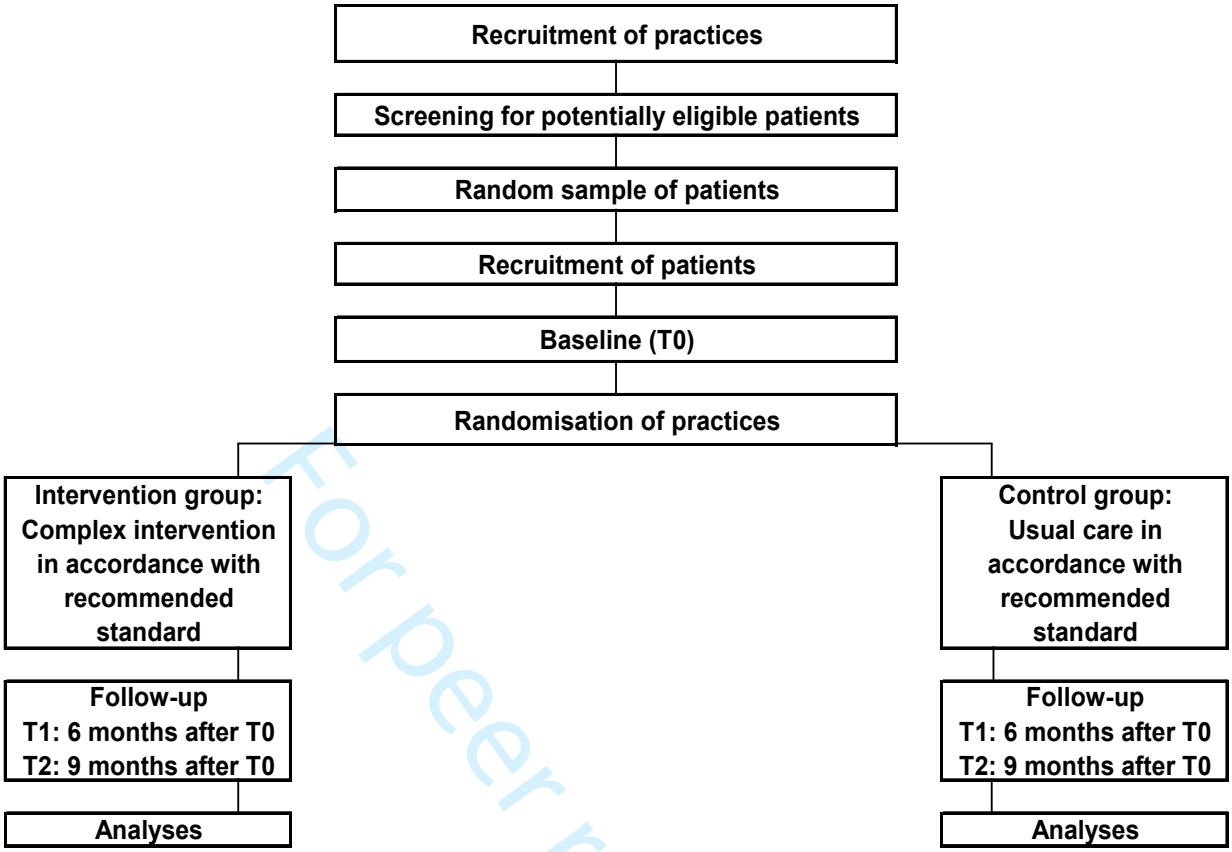
In- and exclusion criteria for trial sites (practices)	Inclusion criteria - General practice cares for patients covered by statutory health insurance and is active in primary care - Specialist doctor for general practice or internal medicine, or doctor with no specialist field. - Practice has internet access - Investigator's agreement to fulfil the contractual obligations arising from the trial - Investigator's agreement to the training of a HCA from the practice for the intervention, as required by the trial Exclusion criteria - Practice focuses on unconventional medical treatments - Practice focuses on special indications (e.g. HIV)
In- and exclusion criteria for patients	Inclusion criteria: - Age ≥ 60 and - ≥ 3 chronic diseases affecting ≥ 2 organ systems, requiring pharmaceutical treatment and - ≥ 5 long-term prescriptions with systemic effects and - Health care provided by GP (at least one contact in most recent quarter) and - Patient is legally competent to sign any documents and - Ability to understand and participate in trial of own free will, to fill out questionnaires and participate in telephone interviews as well as - Written informed consent to participate in trial Exclusion criteria: - Diseases cause life expectancy of < 12 months - Abuse of alcohol or illegal drugs and visible clinical signs or symptoms thereof - Cognitive disability that prevents trial participation (MMSE < 26) - emotional stress that prevents participation in trial - Participation in a clinical investigation within the last 30 days
Outcomes	Primary outcome: difference in Medication Appropriateness Index (MAI)-Score 6 months from baseline minus baseline (MAI T1–T0) Secondary outcomes: MAI T2-T0 and the difference in the following scores 6 and 9 months from baseline minus baseline (T1-T0 and T2-T0): EQ-5D, VES-13, all cause hospitalisation, medication adherence (observed: AS, DS, DoS, RS, self-reported: Morisky-Score), MRCI, BMQ, pain assessment (grade of severity of chronic pain in accordance with M. von Korff, J. Ormel et al. 1992), satisfaction with shared decision making (MSH), patient's future expectation, expected / desired lifetime duration, cognitive dysfunction (VFT), depression (GDS)
Study design	Pragmatic, cluster-randomised controlled trial with the general practice as the unit of randomisation to reduce treatment group contamination. Allocation concealment will be disclosed after baseline but before the intervention on practice level begins. Treatment allocation will be blinded to the pharmacologist (MAI rating) and the statistician. Primary and secondary outcomes will be measured at patient level.
Statistics	The primary analysis will be performed adhering to the intention-to-treat principle and will be based on the change in MAI from baseline (T0) to 6 months after baseline (T1), i.e. MAI T1–T0. Multilevel regression approach will be used to take into account the clustering of patients within practices. Treatment group will be considered fixed factor and variation between practices will be fitted as a random effect. The effect of intervention will be tested at the two-sided significance level of α=0.05. The results will be presented as the mean

	between-group difference in MAI T1–T0 with the corresponding 95% confidence interval. The practice related intracluster correlation coefficient (ICC) will be provided. Results from sensitivity analyses will serve to explain and interpret the results of the primary analysis. The statistical analyses of the secondary endpoints will use the same multilevel approach as the primary analysis. Only the result of the primary efficacy analysis will be interpreted in a confirmatory manner.
Number of trial sites and patients	Number of included general practices: 70 Number of general practices considered in analyses: 62 Number of potentially eligible patients (screening lists): 3.500 Number of included patients: 490 Number of patients considered in analyses: 434
Visits	Visit T0 (baseline), visit T1 (1st follow up 6 months after baseline), visit T2 (2nd follow up 9 months after baseline)
Potentially confounding factors	▪ Age, gender, marital status, lifestyle, socioeconomic status, household composition, housing indicators, house care ▪ Insurance status, participation in disease management programs ▪ Additional prescribers in treatment process ▪ Co-morbidity: Cumulative Illness Rating Scale (CIRS), Charlson-Comorbidity-Index, depression (GDS)
Schedule:	- Pre-phase (development of all trial plans, materials and implemented instruments, ethics vote, study registration): 01/03/2010 to 30/06/2010 - First practice in – last practice out: 01/07/2010 to 30/10/2011 - First patient in – last patient out: 01/08/2010 to 30/10/2011 - Recruitment: a) Practices: 01/07/2010 to 31/12/2010 b) Patients: 01/08/2010 to 31/01/2011 - Database Cleaning, analyses and publication: 01/11/2011 to 29/02/2012 - Total study duration: 01/03/2010 to 29/02/2012

1.5 Key words

Elderly, multimorbidity, polypharmacy, multimedication, medication appropriateness, cluster-randomised controlled trial, pragmatic trial

1.6 Flow chart



2 INTRODUCTION

2.1 Current situation and problem

Chronic conditions accounted for 47% of the global burden of disease in 2002 and are projected to account for about 60% by the year 2020.[2] Along with demographic changes and the change from infectious diseases that are increasingly often cured to chronic diseases the prevalence of multimorbidity increases. Studies carried out in primary care settings found an increase with all age groups from 10% in the 0–19-year-old age group up to 78% in subjects aged 80 and over in the Netherlands, and from 69% in 18–44 year olds up to 98% in those aged over 65 in Canada.[3,4] In 2002 in the U.S., Medicare beneficiaries with five or more chronic conditions accounted for 76% of Medicare expenditures.[5] Therefore, the problems associated with multiple chronic diseases are recognized as a leading healthcare problem.

Multiple disorders in patients are likely to result in multiple drug prescribing but may also result in under-treatment, in particular in the elderly: too little prescriptions or too low dosages have been reported in patients with multimorbidity/polypharmacy, asking for additional prescription(s).[6-10] The potential risks and harmful consequences of polypharmacy, such as drug-drug and drug-disease interactions which potentially cause adverse drug events (ADE), as well as the decreased adherence of patients to complex regimens of multiple medications, are research objectives in pharmacology and geriatrics.[11-13] Several studies investigated inappropriate prescribing and potentially preventable ADE.[14-16] In consequence, guidance on rational prescribing in multimorbid patients recommend a prudent, drug-sparing, and patient centred, not disease-oriented approach: clear therapeutic objectives, prioritisation according to the severity of diseases, efficacy and safety of available therapies, therapeutic individualisation and monitoring, patient implication and attention to their desires and expectations, and avoiding under-treatment.[1,11-13,17,18] Nevertheless, the implementation of these recommendations is still insufficient, as ongoing studies on the prevalence of inappropriate prescribing demonstrate. In our cross-sectional study in 18 general practices and 169 elderly multimorbid adults, patients received a median of 8 drug prescriptions (range 5-16).[19] We found non-considerations of drug-disease interactions in 15%, the necessity of renal dose adjustments in 23%, drug-drug interactions in 25% and an inappropriate choice and dosage of medicines with regard to age in 21% of the patients.[20] Major issues are the often lacking therapeutic goals and their prioritisation as well as inadequate communication with patients.[21,22]

2.2 Background

The risk of inappropriate prescriptions (interactions, non-consideration of renal dose adjustments and contraindications, inappropriate choice of medicines with regard to age and sex and associated discrepancies in terms of pharmacokinetics and -dynamics) rises with increasing age, multimorbidity and multimedication.[6,8,10,23] Inappropriate prescriptions are determining factors for adverse drug events, especially in the aged.[7] At the same time, the risk of under-prescribing rises in patients on multimedication regimes, and this should be avoided if the therapy is to be optimised.[9]

Multimedication and highly complex medication regimes are associated with poor therapy adherence among patients, whereby Horne et al. differentiate between unintended (e.g. technical problems with the intake of medicine, forgetting to take medicine – cognition) and

intended non-adherence (e.g. a lack of information about the aim of the prescribed medicine, attitude towards illness and medication, such as a general rejection of pharmacotherapy). Depression is also linked to non-adherence to medical prescriptions.[24]

Discussions between physician and patient concerning medication are generally initiated by the doctor who tends to control the content to a large degree, focusing on therapeutic benefits and frequently avoiding a discussion of risks, adverse drug reactions and necessary precautionary measures, and rarely checks how much of the content of the consultation has been understood by the patient. Patients often fail to inform their doctor when they have changed the doses of a medicine autonomously, or if they have ceased taking a prescribed medicine.[21,22]

Evidence from previous studies shows benefits from certain strategies in order to avoid inappropriate prescriptions: [22,25,26]

- Regular checks of which drugs have been taken
- The use of computerised decision support systems (CDSS), which automatically generate alerts in case of potentially inappropriate prescriptions and present suitable strategies to prevent them.
- Communication between doctor and patient is more likely to cover problems concerning medication when patients feel at ease to discuss these in pre-consultation interviews with medical assistants (non-physicians). This effect could also be demonstrated for interventions carried out for elderly patients. As a result patients showed higher medication and appointment adherence.

2.3 Rationale

Considering that

1. Multimorbidity, multimedication and increasing age increase the risk of inappropriate prescriptions, adverse drug events, and under-treatment,
2. Multimedication and high medication complexity reduce patient adherence,
3. Consultations between doctor and patient on medication-related problems generally focus on the benefit of a therapy and are dominated by the doctor, and
4. Patients do not usually inform their doctor about changes they make in their medication intake

an intervention was developed that includes the following components:

(1) A medication reconciliation by a general practice based healthcare assistant (HCA),

(2) The systematic assessment of medication-related problems (technical handling, symptoms of potential adverse drug reactions, adherence, patient preferences) by means of a checklist (MediMoL) in a pre-consultation interview conducted by a HCA.

(3) The use of a computerised decision support system (internet based medication information system, AiD+)

(4) Physician-patient consultation on medication-related problems.

The basic assessment in (1) and (2) provide the GP with structured information. This can then be checked by means of the AiD+ to alert the doctor of potentially inappropriate prescriptions, the need for renal dose adjustments and of unintended duplicate prescriptions.

The pre-consultation interview with the HCA should enable patients to discuss their problems with the GP and to tell him about their expectations, wishes, fears, concerns etc.

The GP and patient then discuss necessary changes in the therapy and decide on a new medication. We expect that after taking into consideration the AiD+ alerts and the patients' problems taking the medicine, as well as their dislikes and preferences, the adapted medication will be more suitable, leading to a reduction in potentially inappropriate prescriptions, under-treatment and medication complexity. Furthermore, we expect that a prioritisation of the medication will take place as a result of directly asking and taking into account the patient's perspective.

In consequence, it can be expected that patients are more likely to adhere to the doctor's instructions. Patient health can be improved through the avoidance of under-treatment in pain therapy and possibly through a reduction in adverse drug reactions and associated events. As a result, patient's functional situation, generic quality of life and the desired lifetime duration should be improved.

3 STUDY OBJECTIVES

(1) Primary objective of this trial is to investigate whether the complex intervention will improve the appropriateness of prescriptions in elderly multi-morbid patients six months after baseline as compared to usual care.

(2) Secondary objectives of this study are:

- to ascertain whether the complex intervention will improve the appropriateness of prescriptions in elderly multi-morbid patients nine months after baseline as compared to usual care.
- to assess whether the complex intervention will improve the generic health related quality of life, the functional disability, the desired lifetime duration, the all-cause hospitalisation, and the medication adherence of elderly multimorbid patients six and nine months after baseline.

(3) The following secondary objectives will be investigated to explain the mechanism of the intervention effects at six and nine months after baseline:

a. Patients' beliefs about their medication, since negative attitudes toward medication are associated with non-adherence[27]

b. Medication complexity, as a high complexity is correlated with reduced adherence[24]

c. Severity of chronic pain to ascertain whether this intervention leads to an optimised pain therapy. Results will support the interpretation of intervention effects on health related quality of life and functional disability.

d. Satisfaction with shared decision making to investigate whether the complex intervention leads to a higher patient's satisfaction with involvement[28,29]

e. Depressive symptoms, since depression is associated with reduced adherence[24]

f. Cognitive dysfunction to investigate whether the intervention effects are modified by patient's individual cognitive performance

4 STUDY DESIGN

PRIMUM is scheduled as a pragmatic, cluster-randomised controlled trial with the general practice as the unit of randomisation. A clustered design (practices as clusters) was chosen to reduce treatment group contamination, since HCA and GP trained in the intervention will plausible not be able to provide usual care.

Allocation concealment will be disclosed after completion of the baseline documentation for all study patients within a practice but before the intervention begins. Intervention will take place on practice level.

Due to the type of intervention, neither GPs and their patients nor the PRIMUM study team will be blinded to the treatment allocation. However, allocation will neither be revealed to the pharmacologist who is responsible for the MAI rating nor to the study statistician who is responsible for the statistical analyses.

To reduce the contamination of the control group only general information of the treatment in the intervention group is provided in the regular study protocol (a complex intervention including a checklist based pre-consultation interview by the HCA and the use of an internet based CDSS). Detailed information about the intervention treatment is provided only to the intervention group as an appendix to the study protocol in the intervention training.

All primary and secondary outcomes will be measured at patient level at baseline (T0), and at follow-up: 6 months after baseline (T1) and 9 months after baseline (T2).

5 SETTING AND TRIAL POPULATION

5.1 Setting

The trial will be conducted in general practices of the state of Hesse, Germany.

5.2 In- and exclusion criteria

5.2.1 Criteria for trial sites (General practices)

Inclusion criteria:

- Practice provides health services to persons with German statutory health insurance
- GP practice
- Physician specialises in general practice, internal medicine or has no specialist area
- Practice has internet access which can be used by healthcare assistant
- Investigating physician agrees to the contractual obligations of the trial
- Investigating physician agrees to train a healthcare assistant from the practice as part of the trial for intervention.

Exclusion criteria:

To avoid selection bias for rare diseases and unconventional treatments the following practices are excluded:

- Practice specialises in unconventional medical treatments
- Practice specialises in special indications (e.g. HIV)

5.2.2 Criteria for healthcare assistants (HCA)

Inclusion criteria:

- Written agreement to complete the necessary qualification measures and to perform the tasks associated with the trial.

5.2.3 Patient criteria

Inclusion criteria:

- At least 60 years of age
- Multimorbidity, defined as the existence of at least three chronic diseases, which:
    - Affect at least two different organ systems
    - Require pharmaceutical treatment
    - Represent a disease entity, i.e. arthritis affecting different joints (arthritis of the knee, arthritis of the hip, etc.) is counted as one disease "polyarthritis", irrespective of the location
    - Are not coded in the International Classification of Diseases, version 10 (ICD-10, 2010) in the chapter "H" (diseases of the eye and adnexa, or of the ear and mastoid process) or in the chapters "E00" to "E04" (diseases of the thyroid gland: congenital iodine-deficiency syndrome, iodine-deficiency-related thyroid disorders and allied conditions, subclinical iodine-deficiency hypothyroidism, other hypothyroidism and other non-toxic goitre), since the latter require substitution of iodine and/or thyroxine, only.
- Multimedication, defined as follows: Regularly takes at least five medicines (long-term medication) with systemic effects.
- Care is provided by a GP working at a trial site (at least one contact in most recent quarter).
- Patient is legally competent to sign any documents,
- Patient is capable to give a free and written informed consent to participate in the trial, to fill in questionnaires and to participate in telephone interviews.

Exclusion criteria:

- Diseases that result in an estimated patient's life expectancy under 12 months
- Alcohol or illegal drug abuse with recognisable clinical signs or symptoms
- Cognitive impairment (MMSE < 26), that would prevent participation in the trial
- Emotional stress that would prevent participation in the trial
- Participation in a clinical trial within the last 30 days.

5.3 Recruitment

5.3.1 Recruitment of practices

General practices in the state of Hesse and up to 200 kilometres away from Frankfurt are invited to participate in the study. For this purpose about 1.600 practice addresses provided by the Association of Statutory Health Insurance Physicians of Hesse will be contacted by mail – among them not only active general practitioners. Of those who are interested, the in- and exclusion criteria are checked by phone and a date for an initiating visit is agreed. Of those who decline to participate the reasons for refusal and the in- and exclusion criteria are questioned by phone as far as possible. Of those who do not respond a 10% random sample

is contacted by phone and asked for participation, fulfilment of in- and exclusion criteria and their reasons for denial as well.

5.3.2 Recruitment of patients

HCA or GP creates a list of patient-IDs per practice from the practice computer (systematic query on patients born before 1950, who had a practice contact in the most recent quarter, whose treatment costs accounted for more than € 100 per quarter, sorted by costs). The top five patient-IDs on the list are cancelled to avoid a selection bias for rare diseases with extraordinary treatment costs. From the remaining list all patient IDs are cancelled who do not fulfil the in- and exclusion criteria until a screening list of 50 potentially eligible patient-IDs results. The screening list of pseudonymous patient-IDs is sent to the study centre (Institute for General Practice, Frankfurt, IGP) by telefax. The IGP selects a random sample of the 15 patient IDs (via random numbers by Microsoft Excel©) and sends them (the random list) back to the practice. The 15 patients of the random list are invited to participate in the study consecutively, until 7 patients are included in the study. For each of the 15 patients of the random list, basic characteristics (age, gender, fulfilment of in- and exclusion criteria, exclusive the MMSE score) are documented pseudonymously in a registration form. Only after the written informed consent of the patient the MMSE is conducted by the HCA, its sum score and the personal data (name and telephone number) are also documented. For those patient-IDs which are not related to patients taking part in the study the reasons are documented (reasons for refusal vs. the achievement of the recruitment goal). All written informed consents and registration forms are sent to the IGP via telefax.
This recruitment strategy was found to be feasible in the pilot study.

5.4 Information for participants

5.4.1 Investigator information and training

At the initiating visit at the trial site, both GP and one HCA per practice, are trained in documentation. HCA will participate in order to be in a position to support data documentation and to carry out the Mini-Mental Status Test (MMSE). GP will be informed about the study protocol, ethical considerations and the recommended standard, and will be trained in the use of the Cumulative Illness Rating Scale (CIRS).

Content:

1. Introduction to the PRIMUM trial
2. Introduction to the execution of the trial
3. Introduction to “recommended standards“ (Geriatrics guideline, parts I and II by the Hesse guideline group[1])
4. Explanation of patient clarification, information and declaration of consent
5. Training in execution of MMSE and CIRS-appraisals
6. Introduction to trial documentation including CRFs
7. Content and execution of patient survey
8. Data monitoring, query management and reminder mechanism

9. Presentation of exact trial procedure including timeline
10. Investigators' participation agreement

5.4.2 Patient information and declaration of consent

When the patients in the random list appear in the practice, the GP in person will conduct a patient briefing with them with the help of the patient information sheet prepared for the trial. Patients are to be informed of the aims and the content of the trial, the times, the methods and the content of data collection, the random selection either for the intervention or the control group, of the intervention itself, and on data protection. The patient will be expressly advised of the fact that participation is voluntary and on the possibility to withdraw ones consent. Consent to participate in the trial, as well as the declaration on data protection should be signed and dated by the patient himself. The originals will be sent to the IGP via telefax and archived in the investigator's file. In addition to the time, date and duration of the briefing, the trial number and trial abbreviation should also be entered into the patient's medical records. The patient will receive the patient information sheet and dated and signed copies of his declaration of consent and declaration on data protection.

6 RANDOMISATION AND ALLOCATION CONCEALMENT

Practices will be randomly allocated to the complex intervention or control arm in the ratio of 1:1. Block randomisation with randomly varying block sizes will be used to provide treatment groups of approximately equal size. Randomisation lists will be provided by the Institute of Medical Biometry and Informatics at the University of Heidelberg, using computer generated numbers. Practice allocation to treatment groups will be performed by central randomisation by a study-independent researcher at the IGP after registration of the first patient per practice. Once a practice has been randomised, all the patients recruited for the practice will be deemed intervention or control depending on which arm of the study each practice was allocated. After completion of the baseline documentation of all study patients per practice, the study-independent researcher at the IGP will inform the study team at the IGP about the practice status as either intervention or control. The study team will send a fax with the randomisation result to the practice.

7 TREATMENT PLAN FOR INTERVENTION AND CONTROL GROUPS

7.1 Description of trial treatment in the intervention arm

For detailed intervention see appendix B (handed out merely to the intervention group at the time of the intervention training to avoid contamination of the control group).

As a "recommended standard", the practices in the intervention group will receive the short form of the current geriatrics guideline, parts I and II, published by the Hessen guideline group.[1]

7.2 Description of treatment in the control arm

For the duration of the trial, the patients in the control group will continue to receive the usual treatment from their GP.

As a "recommended standard", the practices in the control group will receive the short form of the current geriatrics guideline, parts I and II, published by the Hessen guideline group.[1]

8 OUTCOME ASSESSMENT

8.1 Outcome measures

8.1.1 Primary Outcome

The primary outcome is the change in the appropriateness of prescriptions after 6 months follow-up measured as a difference in the Medication Appropriateness Index (MAI)-Score 6 months from baseline minus baseline (MAI T1–T0).

The criterion appropriateness of the medication will be calculated and evaluated on the basis of the *Medication Appropriateness Index* (MAI).[30,31]

- The MAI by Hanlon et al. consists of 10 items: (1) Is there an indication for the drug?, (2) Is the medication effective for the condition?, (3) Is the dosage correct?, (4) Are the directions correct?, (5) Are the directions practical?, (6) Are there clinically significant drug-drug interactions?, (7) Are there clinically significant drug-disease/condition interactions?, (8) Is there unnecessary duplication with other drug(s)?, (9) Is the duration of the therapy acceptable?, (10) Is this drug the least expensive alternative compared to others of equal utility? The rating will take place on a three point scale whereby "1" represents the best rating (expressed as correct, practicable etc. depending on the question), "3" the worst rating (incorrect, impracticable etc. depending on the question) and "2" a middle rating. As an alternative, it is also possible to respond with "not applicable" or "unknown".
- The MAI will be used in the following modifications that are comparable to modifications by others:[30,32-34]
    - Item (10) will not be rated, since this is not possible under the current conditions of discount contracts between pharmaceutical industries and different statuatory health insurance companies in Germany. They are based on § 78 Abs. 3 Arzneimittelgesetz (A) and § 130a Absatz 8 SGB V (B). Both paragraphs describe the possibility to offer discounts on official prices of pharmaceuticals by pharmaceutical industry. In conclusion "best prices" vary between health insurance companies and over time.
    - Ratings are specifically defined for each item, e.g. items (5) and (6) are limited to the most commonly observed combinations of drug-drug and drug-disease interactions, and current symptoms (taken from the telephone interview) will be considered for assignment. Operationalisation is summarised in a referenced manual (Appendix A).
- The MAI showed good intra-rater reliability for well-experienced pharmacologists.[30,33,35-37] In Prof. Harder's trial group, an MAI Rating will be carried out independently

of the project and blinded for the patient's group allocation (intervention vs. control). In a random sample of about 20% of the cases an independent second MAI rating will be carried out.

Changes of the medication regime (1) are recommended stepwise[38] and (2) are assumed to be in primary care not always realised by the patient immediately (pers. comm. practice advisory board). Reasons for the delay of changes in the medication taken by the patients probably rely on the prescribing behaviour for the chronically ill (large package sizes) and on financial constraints of the patients (extra out-of-pocket payments per package). Based on (1) and (2) an estimated delay of three months to implement prescriptions into taking is reasonable. To ascertain the effectiveness of the intervention the MAI should be appraised at least three months after intervention, therefore.

8.1.2 Secondary Outcomes

(1) Change in the appropriateness of prescriptions after 9 months follow-up measured as the difference in the Medication Appropriateness Index (MAI)-Score 9 months from baseline minus baseline (MAI T2–T0): To study late intervention effects a second interval will be measured for the medication appropriateness at T2 (9 months after baseline). Furthermore, treatment effects on each MAI item will be determined.

The following parameters will be determined in order to identify treatment effects on patient related outcomes:

(2) Change in generic health related quality of life measured as the difference in the EQ-5D-Score[39,40] 6 months from baseline minus baseline (T1–T0) and 9 months from baseline minus baseline (T2–T0): To ascertain whether the intervention improves the generic health related quality of life the EuroQuoL (EQ-5D) will be used.[39,40] The EQ-5D was feasible in the pilot study and detects even relatively small changes.[41,42]

(3) Change in functional disability measured as the difference in the VES-13-Score[43] 6 months from baseline minus baseline (T1–T0) and 9 months from baseline minus baseline (T2–T0): To ascertain whether the intervention improves functional disability, the activities of daily living will be assessed. In the pilot study the WHO DAS-II was found not to be feasible. In the main study the Vulnerable Elderly Survey, 13 items (VES-13) will be used.[43] The VES-13 predicts death and functional decline in vulnerable elderly patients,[43-45] encompasses physical and instrumental activities of daily living and is feasible to use (pers. comm. Dr. U. Thiem, geriatrician, VES-13 use in the German PRISCUS-project; pers. comm. M. v. d. Akker: VES-13 use in the Maastricht multimorbidity project).

(4) Change in all cause hospitalisation: To ascertain whether the intervention improves all cause hospitalisation of patients, hospital days are counted irrespectively of reasons for admission.

(5) Change in medication adherence: To determine whether the intervention improves the medication adherence the following outcomes will be measured:

- Change in observed adherence measured as the difference between intake (*patient's interview*) and prescribed medication (CRF reported by physician's) 6 months from baseline minus baseline (T1–T0) and 9 months from baseline minus baseline (T1–T0)

- Discrepancy score, DS (Sum of all differences in drug, time of intake, frequency and dose) / Sum of all prescriptions, AS<0.8 or >0.2=1
- Drug Score (DS, Sum of all drugs taken/sum of all prescriptions), DS<0.8 or DS>1.2=1[46]
- Dose Score, (DoS, Sum of all daily doses taken/sum of all prescriptions), DoS<0.8 or DS>1.2=1[46]
- Regimen Score (RS, actual frequency of intake per day / prescribed frequency per day), RS<0.8 or DS>1.=1[46]

- Change in self-reported adherence measured as the difference in the Morisky-Score[47] 6 months from baseline minus baseline (T1–T0) and 9 months from baseline minus baseline (T2–T0)

5) Change in perceived future life expectancy reflects concepts of will to life or years of desired life [YDL] measured as the difference of the three items future expectation / expected lifetime duration / desired lifetime duration in the interval 6 months from baseline minus baseline (T1–T0) and 9 months from baseline minus baseline (T2–T0): Desired and expected life time duration are considered to be sensitive for personal experiences and scientific influences,[48] as well as indicating well being and positive life evaluation.[49] Moreover it is argued that YDL itself reflects mortality on the long run. Thus, if our intervention effects change in YDL, one might argue that participants consider the intervention as relevant in relation to their own life expectancy and life quality.

8.1.3 Secondary outcomes to explain the intervention mechanisms

1) Change in complexity of medication measured as the difference 6 months from baseline minus baseline (T1–T0) and 9 months from baseline minus baseline (T2–T0) in terms of

- Total number of prescriptions
- Number of single doses / day
- Medication Regimen Complexity Index (MRCI),[50]

since a high complexity is associated with a reduced adherence.[24]

2) Change in health and illness beliefs and attitudes measured as the difference in the Beliefs about Medicines Questionaire (BMQ) score[27] 6 months from baseline minus baseline (T1–T0) and 9 months from baseline minus baseline (T2–T0), since denial of illness and / or medication in general might explain non-adherence.[24]

3) Change in severity of chronic pain measured as the difference in *Characteristic Pain Intensity score,* the *Disability Score,* in *Disability Points* and the resulting *Grades of chronic pain severity* in accordance with M. von Korff, J. Ormel[51] et al. in the interval 6 months from baseline minus baseline (T1–T0) and 9 months from baseline minus baseline (T2–T0):

Prevalence of chronic or persistent pain in elderly ranges between 25 and 50%. Nevertheless, under-assessment and under-treatment of pain is frequent in the elderly.[52] Under-treatment is often associated with polypharmacy,[9] and is not adequately captured by MAI

appraisal. Therefore, pain is hypothesised as a surrogate for under-treatment[a] and will be assessed to reveal possible negative intervention effects (i.e. a reduction of polypharmacy at a cost of an impaired pain management). The different scores to grade the severity developed by von Korff, Ormel et al. have been modified for, integrated in the German pain inventory (Deutscher Schmerzfragebogen – questions 11 a-c, and 12 a-d) and validated in a German population.[51,53,54]

4) Change in satisfaction with shared decision making measured as the difference in the *Man Son Hing* scale (MSH)[28,29] interval 6 months from baseline minus baseline (T1–T0) and 9 months from baseline minus baseline (T2–T0): For an appropriate prescription in elderly multimorbid patients a patient centred rather than a disease centred approach is recommended. MSH scale measures the satisfaction with the shared decision making process. It was found feasible, showed high reliability and sensitivity of change and acceptable validity in the German "arriba"-study conducted in primary care practices.[28]

8.2 Timing of outcome assessment

Study visits: at baseline (T0), 6 months (T1) and 9 months (T2) after baseline. Each time the HCA makes a practice appointment with the patient, and measures body height and weight. Patients fill out a questionnaire in the practice and reply it to the HCA in a closed envelope before leaving. HCA and GP fill out a paper based case report form (CRF). At the end of each visit the HCA sends a control sheet by telefax to the IGP to inform that the visit has taken place. The completed CRF and patient questionnaire are sent by mail to the IGP. Immediately after the receipt of the control sheet trained members of the study team conduct the telephone interview with the patient.

Table 1: Study visits

Month	**Before trial begins**	**0**	**6 (+/- 1)**	**9 (+/- 1)**
Visits		**T0**	**T1**	**T2**
Trial measures for *control and intervention group*				
Documentation training, GP and HCA	•			
Profile of practices participating in trial	•			
Sociodemographics of GP				
Sociodemographics of HCA	•			
Identification of potentially eligible patients – screening lists	•			
Random lists	•			
Patient registration sheet (In- and exclusion criteria, reasons for non-participation of patients; for included patients with written informed	•			

[a] Additional searches should reveal literature, where a direct association between polypharmacy and under-treatment of pain is shown (references are welcome). Otherwise we will get the prevalence of severe pain in our population at baseline.

Month	**Before trial begins**	**0**	**6 (+/- 1)**	**9 (+/- 1)**
Visits		**T0**	**T1**	**T2**
consent also: name, first name, telephone number, MMSE score)				
CRF, practice documentation				
• Detailed sociodemographics, patient incl. Disease Management Program (DMP) status		•		
• Patient's current diagnoses		•	•	•
• Patient's current medication		•	•	•
• Height and weight of patient		•	•	•
• Laboratory test results of patient, if available (serum electrolytes K, Na, serum creatinine)		•	•	•
• Degree of patient's multimorbidity (CIRS)		•	•	•
• Existing co- and multimorbidity of patient (Charlson Comorbidity Index)		•	•	•
• Hospital stays (duration, reason)		•	•	•
• Consultation of specialists		•	•	•
Patient questionnaire:				
• Sociodemographics incl. best school leaving certificate and professional certificate, household composition, housing indicators, house care		•		
• Lifestyle		•		
• Generic health related quality of life (EuroQuoL, EQ-5D))		•	•	•
• Functional disability (Vulnerable Elderly Survey, VES-13)		•	•	•
• Attitude of patients to medicinal therapy (Beliefs about Medicines Questionnaire, BMQ)		•	•	•
• Severity of chronic pain in accordance with M. v. Korff, J. Ormel et al. 1992		•	•	•
• Satisfaction with shared decision making (Man-Sin-Hong scale)		•	•	•
• Future expectation, expected / desired lifetime duration		•	•	•
Telephone interview with patient				
• Sociodemographics		•		
• Current patient medication (incl. National drug code: PZN)		•	•	•
• Symptoms for adverse drug reactions		•	•	•
• Infirmity index (Sherbrooke Questionnaire)		•	•	•

Month	**Before trial begins**	**0**	**6 (+/- 1)**	**9 (+/- 1)**
Visits		**T0**	**T1**	**T2**
• Depression (Geriatric Depression Scale, GDS)		•	•	•
• Cognitive dysfunction (Verbal Fluency Test)		•	•	•
• Self reported adherence of patient (Morisky)		•	•	•
Measures for *intervention group only*				
• Intervention: Training for GP's and HCA's		•[#]		

[#]After baseline completion

9 POST-RECRUITMENT RETENTION STRATEGIES

Co-ordinating Centre responsibilities of the IGP:

- Provide study materials incl. self-addressed envelopes which will be supplied to the trial sites in sufficient quantities and postage will be paid by the recipient
- Help ensure complete data collection at baseline, at six months and at nine months
- Respond to any questions (e.g. from practices) about the trial via telephone and telefax (regular office hours Mon. to Fri. 9:00 a.m. to 5:00 p.m.), or mobile phone (Mon. till Fri. between 9:00 a.m. and 7:00 p.m., Sat. & Sun. between 10:00 a.m. and 6:00 p.m.), or email

10 SAFETY MONITORING AND ADVERSE EVENTS

No safety monitoring nor adverse events reporting will be conducted, since worse treatment than previous to the trial is not possible. The study team of the trial (Institute for General Practice, Johann Wolfgang Goethe-University, Frankfurt am Main, IGP) has no influence on the diagnostic-therapeutic decision-making of the GPs and their patients.

11 REGISTRATION, DATA COLLECTION AND MANAGEMENT

11.1 Registration of participants

Practice registration: takes place during the initiation visit by a trained study team member. The participating practices give written informed consents of a general practitioner (GP) and a healthcare assistant (HCA) to participate in the study and to implement the study protocol (centre registration form).

Patient registration: at the IGP the incoming telefaxes of registration forms and signed informed consents are controlled (patient ID is consistent with the patient ID of the random list, signature of the patient, fulfilment of in- and exclusion criteria) and patient registration is confirmed to the practice by telefax.

11.2 Data collection

11.2.1 Data collection of participating HCA and GP

First documentation takes place at the initiating visit at the trial site: social demography of HCA and GP and practice characteristics as well are documented in paper based forms (each one per HCA and GP and practice).

11.2.2 Data collection of participating patients

Examinations and documentation of the patient related data take place regularly during the aforementioned visits 1-3. Visits 1-3 take place in months 0, 6 and 9 (+/- one month) following the inclusion of the patient in the trial. An overview of the individual examinations is given in table 1 (see pp 23). The content of the individual examinations to be documented is described in detail in section 11.3 (see below). At each visit the following documents are collected:

- The patient registration document (T0) and control sheets (T1, T2) filled in by HCA and GP are sent to the IGP via telefax at the day of the patient's visit to the practice.
- The paper based case report form (CRF) completed by the HCA and GP. Every CRF includes information on filling in the form. Necessary correction to the CRF must take place in the following manner: invalid data should be crossed out whereby crossed-out details should be authorised with the date and the investigator's initials.
- The completed patient questionnaire (paper based as well): The patient questionnaires, including an envelope, will be issued by the HCA. The patients fill in the questionnaires in the practice and put them in the envelopes which they then seal themselves (confidentiality of information with respect to trial site). If necessary, the HCA provides help filling in the patient questionnaires and keeps an eye on the return of the completed documents.

The completed CRFs and the sealed envelope with the completed patient questionnaire will be put in the return envelopes (no stamp required) at the trial site and promptly returned to the IGP by mail.

Within five working days as after arrival of the patient registration document / control sheets, trial employees will contact the patient to conduct the telephone interview. Information from these interviews will be entered directly into the entry mask of an SQL data bank (Access©). If the interviewer cannot reach the patient, further attempts to do so will be made on the following days. After the fifth unsuccessful attempt, the responsible practice will be contacted by the trial assistant and asked for information on the whereabouts of the patient. If the attempts to contact the patient fail within one month, the telephone interview for this visit is considered as missing.

11.2.3 Data collection of non-participating patients

If a patient from the random list (see 5.3.2) does not agree to participate, or is not included for any other reason (e.g. the recruitment goal per practice is already fulfilled), then the following data will be documented on the patient registration form pseudonymously – age, gender, in- and exclusion criteria (without MMSE score), reason for non-inclusion. The documentation of further data and especially personal data such as name, date of birth or telephone

number is not permitted. The patient registration forms for those patients who are not included will also be faxed to the IGP and the originals will remain on the files of the GP and checked by the monitor after completion of the trial.

11.3 Description of data sets

11.3.1 Data set to determine practice profile

- Single-handed practice / group practice (incl. ambulatory healthcare centre, with the number of physicians and the question for additional general practitioners),
- Location: Big town (> 100.000 inhabitants) / middle size town (20.000 to 100.000) / small town (5.000 to 20.000) / rural area (< 5.000 inhabitants)
- Clinical specialisation of practice
- Number of registered patients in most recent quarter [in categories: 0 – 499, 500 – 999, 1000 – 1499, 1500 – 1999, 2000 and over]
- Quality management system used in practice
- (Brand name of practice EDV to provide any necessary support for the study by the IGP

11.3.2 Data set to determine profile and sociodemographics of the GP

- Practice-ID as provided by the IGP, GP-ID (consecutively for each participating GP)
- Age, gender of GP
- GPs professional practice experience (year doctor commenced private practice)
- Years of clinical experience in total
- GP: Specialist in primary care, specialist in internal medicine, GP / doctor with no specialist area
- Previous participation in a former clinical trial and name of trial

11.3.3 Data collection to determine profile and sociodemographics of the HCA

- Practice-ID as provided by the IGP, HCA-ID (consecutively for each participating HCA)
- Age, gender of HCA
- School leaving certificate, professional and additional qualifications
- Years of professional experience as health care assistant and at trial site
- Type of employment
- Previous participation in a former clinical trial and name of trial

11.3.4 Patient registration form

Registration form for every patient on random list with

- Practice-ID as provided by the IGP, GP-ID, patient-ID as used in practice computer, month and year of birth, age, gender
- Checklist for in- and exclusion criteria (items to be marked with a cross, exclusive MMSE score)
- Decision not to participate (if possible with reasons)
  vs. patient not approached (as recruitment target already reached)
  vs. readiness to participate (patient's written informed consent is on hand)
- If written informed consent on hand:

- Name, first name, patient's phone number
- MMSE Score

11.3.5 Case report forms (see prototype in appendix)

Sociodemographics and basic clinical data: insurance status (private, statutory or differing), name of insurance company, participation in one of the disease management programs (diabetes mellitus I/II, coronary artery disease, breast cancer, COPD, asthma), home care situation and assessment of quality of care, height (measured), weight (measured), current diagnoses, allergies / intolerances, consultations with specialists (specialisation of physician) and hospital stays during the last six months (date of admission to / release from hospital; inpatient, day hospital care, outpatient, inpatient rehabilitation; reason for treatment).

Laboratory: Laboratory values for serum electrolytes (sodium and potassium) and serum creatinine that are already available in the practice. The most recent values should be taken along with the date of the test, but should not be more than 12 months prior to patient inclusion in the trial.

Current medication: trade name, strength, application, dosage, indication, duration of therapy at time of documentation (more or less than three weeks) and estimated importance of the particular medicine within the concept of the therapy as a whole (4-point Likert scale: very important – important – of little importance – not important).

Current diagnoses: all active diseases of the patient at the time of documentation (acute and chronic diseases) and treatable conditions (e.g. hypertension without end organ failure, positive medical history for gastric ulcer)

Modified Cumulative Illness Rating Scale (CIRS): Assessment of organs / organ systems / areas (15 items in total) according to severity of impairment (5-point Likert scale: no impairment to extreme impairment),[55-57] with one supplementary item "chronic pain syndrome" and one supplementary response category entitled "not applicable" if the named organ (system) is not affected.

Expanded Charlson Comorbidity Index: List of underlying diseases in the Charlson Comorbidity Index[58] plus relevant diseases and situations that often result in contraindications to specific medication.

11.3.6 Patient questionnaires (see prototype in appendix)

Sociodemographics: marital status, number of persons living in the household (i.e. household composition), home care, socioeconomic status (best school leaving certificate, professional training), housing indicators (population size: big town [>100.000 inhabitants] / middle size town [20.000 to 100.000] / small town [5.000 to 20.000] / rural area [<5.000]; housing tenure [home ownership]; place attachment [home / neighbourhood]).

Generic health related **quality of life** (EuroQoL, EQ-5D),[39,40] maintenance of **functional status** (Vulnerable Elderly Survey, VES-13),[43] **Beliefs about Medicines** Questionnaire (BMQ),[27] **severity of chronic pain** (in accordance with M. v. Korff, J. Ormel et al.),[51] satisfaction with shared decision making (Man-Son-Hing scale),[29] future life expectancy (future expectation / expected lifetime duration / desired lifetime duration).[48,49]

11.3.7 Telephone interview with patients

At each visit a trained employee from IGP conducts interviews with patients using an interview guide (see appendix) and enters the answers directly into an Access-data base.

Medication incl. OTC drugs and supplements (trade name, National Drug Code, dose, prescribed by whom, duration of intake more or less than three weeks) currently being taken on a regularly basis; medication to be taken as needed, including OTC drugs (in case of what symptoms, single dose, total maximum dose); autonomous preparation and intake of medication vs. support from third parties, known allergies, symptoms for potentially adverse drug reactions.

Consultation of other healthcare providers: Other healthcare providers consulted during the last six months (name, location, profession/specialisation, number of consultations, reason(s) for consultation, and referral by GP vs. direct access).

Sherbrooke Questionnaire: Five items to identify positive predictors (lives alone, uses a walker, self-reported visual, hearing and memory impairment, sixth item already one of inclusion criteria: more than three long-term medicines daily).[59]

Use of medical aids and special therapeutic measures: Use of visual and/or hearing aids, use of home oxygen therapy, participation in dialysis therapy, ask about implant devices (pacemaker, defibrillator)

Patient interview on depression (Geriatric depression scale, GDS)[60,61]

Patient interview on adherence (Self reported adherence according to Morisky)[47]

Verbal fluency test: Patients are asked to tell as many animals as possible within one minute.[62] Answers are audiotaped and time is controlled by a stop watch. After the interview is finished, the interviewer transcripts the audiotape into the database and deletes the tape soon after.

11.3.8 Documentation of intervention

After completion of the trial the data from the completed intervention tools (MediMoL, AiD+) will be analysed (intervention group only).

11.4 Data management

The responsible trial employee will check all incoming post is complete and confirm receipt by marking it (date of receipt, date of check, initials - tracking). The due dates for sending the documentation is described in a guideline on data flow in the investigator's file. Missing information will be collected in preparation for the following query management (see below).

After confirmed reception of data it will be entered into an SQL trial database (Access©) by one of the trial employees. A data check will take place of this database according to predefined trial rules (range-, validity, and consistency checks according to defined SOPs developed during the course of the trial and documented in the TMF). Queries for the investigators that may crop up as a result of this data check will be formulated by the IGP (see below, Query management). Sending, collecting and processing patient data will always take place under the patient identification number (Pat.-ID) pseudonym.

Coding will be used for some of the data, partly when the data is entered. In retroactive processing steps, some free text information will be encoded into new variables. The encryption specifications will be deposited in the TMF.

11.5 Data Validation (Query management)

Data recognized as missing during the confirmation of receipt check will be collected for each practice using the patient IDs and then faxed to the trial sites as a written request for completion. These fax requests will be filled in and signed by the investigator and then faxed back to the IGP. The receipt of the returned faxes will then be confirmed and the process continued until all missing data have been collected. The checked data will then be forwarded and entered into the database, as described above.

Follow-up enquiries resulting from the data plausibility check will also be collected for each practice and formulated as a written fax request using the patient identification number. They will then be dealt with in the same way as described under (missing data).

If possible, query management will be undertaken during regular practice visits in order to limit the number of fax requests. However, timely query management has first priority.

All CRFs, patient questionnaires, queries and answers will be kept at the IGP in paper-form. Changes to the Access database will be documented in an audit trail. The necessary programming instructions will be developed along with the data management concept.

11.6 Quality control and quality assurance

The study team of the IGP guarantees that all processes in the trial will comply with the Good Clinical Practice (GCP) guidelines, the legal requirements and the SOPs of the IGP. General practitioners and healthcare assistants of the trial sites will be educated on the trial requirements during the investigators' training at the initiating practice visit.

Monitoring: The IGP will be responsible for monitoring the trial. A study employee will regularly visit the trail sites (at least two visits per practice) to ensure that

- the rights of the trial participants are protected,
- the study data are documented completely and in a correct manner and can be verified for defined variables in the source data (selection of appropriate variables will be defined in the data management and validation plan of the trial)
- the trial is conducted in accordance with the study protocol (and its amendments where required) and complies with GCP and legal requirements at the trial site.

Scientific Advisory Board: The board gives scientific advice in questions on planning, conducting and analysing the trial.

11.7 Archiving

The trial documents are to be archived for 15 years. The trial sites will be responsible for archiving their documents (contents of the investigator's file, especially the list of patients, patients' declaration of consent). The IGP will archive the central trial documents, the original CRF (including patient questionnaires, the final report and further reports where necessary).

11.8 End of Trial

11.8.1 Regular / premature end of trial

The **regular end** of the trial is reached when the documentation of the study visits is over for all patients participating in the trial.

The **premature end** of trial can be decided by the principal investigator after the consultation with the scientific advisory board, when recruitment of practices or patients does not meet the recruitment goals, when the number of practices or patients with a premature withdrawal from trial or a permanent violence against the study protocol is expected to avert a successful regular end of trial.

11.8.2 End of trial participation

11.8.2.1 End of trial participation for practices

The **regular end** of the trial participation for a practice is reached when a) the documentation of the study visits is over and b) the treatment in accordance for determined practice status is completed for all patients participating in the trial.

The **premature end** of the trial participation for a practice is reached when the GP withdraws his/her agreement to participate in the trial protocol, or when the principal investigator decides to withdraw a trial site (GP practice) from the trial. Withdrawal has to be done in a written reasoned form. The principal investigator can decide to withdraw a trial site from the trial if:

- It does not satisfy the protocol's technical requirements (e.g. organisational problems in implementing the protocol))
- The implementation of the trial is inadequate for the trial
- The quality of the data is inadequate

11.8.2.2 End of trial participation for patients

The **regular end** of patient's trial participation is reached when documentation of the last planned visit has been completed (T2).

The **premature end** of patient's trial participation is reached

- In cause of death for any reason before the end of trial. If possible, the date and the circumstances of the death (cause of death, location) should be documented.
- In cause of hospitalisation for any reason before the last planned visit has been completed (T2) and before the end of trial.
- In cause of GP decision: The GP can elect to remove a patient from the trial
    - If following the protocol would represent unacceptable stress for the patient because of his situation (that may have to do with the development of his disease),
    - If the patient moves to a nursing home and it is technically or organisationally no longer possible to conduct further telephone interviews
    - If the patient changes to another GP and leaves the trial site.

If the course of events is foreseeable or can be planned a follow-up survey should be brought forward.

- In cause of patient's decision: Patients have the right to discontinue the trial without giving reasons at any time and without losing the right to further treatment from the GP. If a patient does not arrive to an appointment, the GP must follow up the case until he has found out why the patient did not turn up. The GP must try to complete and document all the examinations designated in the protocol.

The IGP must be informed of the premature end by fax and will confirm it. In case of a withdrawal, the reasons/circumstances and the most recent status must be documented. If the patient does not withdraw his declaration of consent, his survival status or a hospital stay should be documented at the end of the regular observation period.

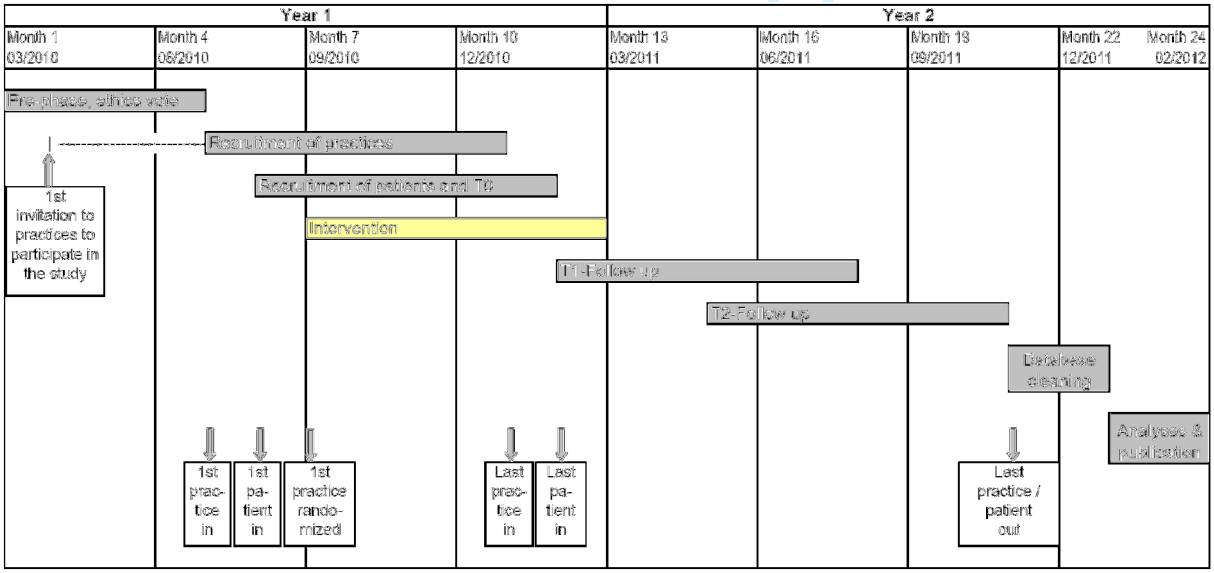
11.8.3 End of treatment

For patients of the control group no regular end of treatment has to be defined, since they are treated as usual.

For patients of the intervention group the **regular end** of treatment is reached when all components of the complex intervention are administered in accordance with the protocol.

For patients of the intervention group the **premature end** of treatment is reached when one or more components are lacking: Patients have the right to discontinue the treatment without giving reasons at any time and without losing the right to further treatment from the GP. If a patient does not arrive to an appointment, the GP must follow up the case until he has found out why the patient did not turn up. The GP must try to complete and document all the components of the complex intervention designated in the protocol. The documentation will continue in accordance with the protocol (intention-to-treat principle) accept the patient withdraws his/her written informed consent in the documentation of his/her data.

11.9 Schedule and expected duration of trial



- Pre-phase (development of all trial plans, materials and implemented instruments, ethics vote, study registration): 01/03/2010 to 30/06/2010
- First practice in – last practice out: 01/07/2010 to 30/10/2011

- First patient in – last patient out: 01/08/2010 to 30/10/2011
- Recruitment:
  a) Practices: 01/07/2010 to 31/12/2010
  b) Patients: 01/08/2010 to 31/01/2011
- Database Cleaning, analyses and publication: 01/11/2011 to 29/02/2012
- Total study duration: 01/03/2010 to 29/02/2012

12 STATISTICAL CONSIDERATIONS

A detailed description of the statistical methods of this study will be provided in a Statistical Analysis Plan (SAP). Data analysis will be done blinded to treatment arm allocation (i.e. the treatments will be identified as 1 and 2 until analysis is complete). The primary analysis will be based on the 6-month follow-up data (T1).

12.1 Populations for analysis

The Intention-to-treat (ITT) population will consist of all randomised practices and their patients. Following the ITT principle, practices and their patients will be analysed in the treatment arms to which they were originally randomized, regardless of whether they refused or discontinued treatment, or whether other protocol deviations are known.

The Per-protocol (PP) population will consist of those ITT practices and patients with no major protocol violations. The criteria for the exclusion of practices or patients from the PP population will be determined by the study team at the latest before database lock.

12.2 Statistical hypotheses, methods, and analyses

The primary objective of this study is to determine the effectiveness of a complex intervention compared to usual care in multimorbid elderly patients, and to show that the complex intervention improves the appropriateness of prescriptions, as compared to usual care. The primary efficacy endpoint is the change in MAI score from baseline (T0) to 6 months after baseline (T1), i.e. the difference MAI T1–T0. The study objective will be statistically formulated as a test of the null hypothesis H0: $\mu 1 = \mu 2$ (the mean difference MAI T1–T0 is equal in the two groups) against the alternative hypothesis H1: $\mu 1 \neq \mu 2$ (the mean MAI T1–T0 are different in the two groups). The null hypothesis will be tested at the two-sided significance level of $\alpha=0.05$.

Because of the cluster randomisation, the primary efficacy analysis will use a multilevel regression approach with patients at level one and practices at level two. The primary model will include treatment group as fixed factor and practice as random factor. The results will be presented as the mean between-group difference in MAI T1–T0 with the corresponding 95% confidence interval. The associated Cohen's effect size d will be calculated. In addition, the practice related intracluster correlation coefficient (ICC) will be estimated. To support the primary analysis, all potentially relevant baseline characteristics at practice level (e.g. practice status) and baseline characteristics at patient level (e.g. MAI score at T0) will be added as covariates to the model in sensitivity analyses. Further sensitivity analysis of the primary endpoint will include an unadjusted two-sample *t*-test on change in MAI from baseline to 6 months after baseline. Results from these sensitivity analyses will serve to explain and interpret the results of the primary analysis.

The primary analysis will be performed adhering to the intention-to-treat principle. An additional sensitivity analysis will be conducted on a per-protocol analysis set.

Baseline characteristics of participating practices and patients will be described by treatment arm. Categorical data will be presented as frequencies and percentages. For continuous data, N, mean, standard deviation, median, inter-quartile range (IQR), minimum, and maximum will be provided.

The statistical analyses of the secondary endpoints will use the same multilevel approach as the primary analysis. All statistical tests will be two-sided at the significance level of α=0.05. Because no adjustments for multiple endpoints are planned, findings will be interpreted with caution in view of the number of statistical tests undertaken. Only the result of the primary efficacy analysis will be interpreted in a confirmatory manner. Confirmatory subgroup analyses are not planned. No interim analysis with regard to efficacy will be done.

A complete case analysis will be performed. If any practices or patients are lost to follow-up, analyses will be done replacing the missing follow-up data with the last available or baseline data carried forward for that practice or patient.

12.3 Sample size

Sample size was calculated using the primary endpoint, the change in MAI score from baseline (T0) to 6 months after baseline (T1), i.e. MAI T1–T0. Because high MAI scores indicate inappropriate prescriptions, a negative difference MAI T1–T0 indicates an improvement in the appropriateness of prescriptions for the target population. The MAI T1–T0 difference is assumed to be normally distributed in each treatment arm population and the variances of the group specific differences T1–T0 are assumed to be equal. In the preliminary analysis of PRIMUM pilot with a total of 60 patients from 12 practices, a mean MAI of 4.2 was observed at baseline. Three months later (i.e. 6 weeks after the intervention), the MAI in the intervention group decreased by 0.9 units, while the MAI in the control group decreased by 0.5 units. Thus, the resulting between-group difference was 0.4 in favour of the complex intervention. In a previous study of a similar patient population, between-group differences of 3 and 4 for changes in MAI from baseline to 3 and 12 months after randomisation were reported.[32] However, the intervention in that study was even more intense than the intervention planned in PRIMUM. Thus, in the present study, a difference in the change values (MAI T1–T0) of at least 2 units between the treatment groups will be considered clinically relevant. In the PRIMUM pilot study, a pooled standard deviation of the MAI T1–T0 difference of 5.2 was observed. However, T1 was defined as 3 months from baseline, whereas in the present study, T1 is measured 6 months after baseline. Consequently, a greater standard deviation is expected for the MAI T1–T0 difference. Using the conservative assumption that the MAI scores at T0 and T1 are uncorrelated, we expect a standard deviation for MAI change of approximately 6 units. With this standard deviation, a between-group difference of 2 units corresponds to Cohen's effect size of d=0.3 and represents a small effect size.[63] Assuming an intracluster correlation coefficient (ICC) of 0.03 at practice level (which is also a conservative assumption because the ICC is assumed to be 0.01 in general practice setting[64]) and assuming an average cluster size of 7 patients, we estimated a design effect of DEFF = 1 + (7 – 1) x 0.03 = 1.18. Taking this design effect into consideration, a total of 62 practices and 434 patients (31 practices and 217 patients per treatment arm) will be required to detect a Cohen's d of 0.3 with a power of 1–β = 0.80 using a two-sample *t*-test at a two-sided significance level of α=0.05. The sample size calculation was performed using NCSS PASS 2008,

Inequality Tests for Two Means in a Cluster Randomised Trial. Assuming a drop-out rate of approximately 10%, the sample size was adjusted to a total of 70 practices and 490 patients (35 practices and 245 patients in each treatment group).

13 ETHICAL AND REGULATORY REQUIREMENTS

13.1 Ethical fundamentals

The project will be carried out in conformation with the Medical Association's code of conduct and good clinical practice (GPC) in line with the World Medical Association Declaration of Helsinki".[65] The trial will be checked and approved by the ethics commission of Frankfurt University Hospital. The original vote by the ethics commission will be kept in the Trial Master File at the Institute for General Practice. In addition, every participating practice will receive a copy to be kept in the investigator's file.

The voluntary participation of doctors and patients in the trial will be recorded in writing following an informed decision to do so. Patients in intervention practices who do not wish to participate will be treated without intervention and in accordance with usual care.

Data protection will be guaranteed for all person-related data: the data will be collected and stored separately from the other individual data in the trial, and deleted at the end of it. Participating patients will be separately informed about data protection in the trial and will give their consent by signing and dating a declaration to that effect. For data analyses, patient identifiers will be kept confidential and the data stored in a separate data base from the personalized one. The trial team are the only persons with access to trial data. Practice teams are also bound by the legal requirement to treat data confidentially.

The present trial will take ICH-GCP criteria into account, and all participants have undertaken an obligation to respect the Declaration of Helsinki and its amendments

The Ethics Commission is to be informed of all changes to the protocol and its renewed approval is to be sought if necessary.

Changes linked to the following points are regarded as requiring renewed approval:

- Necessary changes to the therapy regime, in particular:
  1. Intensification of intervention that is a burden to the patient or could be felt to be a burden by him,
  2. Reduction in intensity of intervention, in view of which a discussion on the likelihood of success must takes place,
  3. Inclusion of further elements in the intervention program about which the patient has not yet been informed,
  4. Changes in the therapy regime of the control arm,
  5. Revision in the risk estimate for participating patients;
  6. Additional examinations, data collection or analyses that necessitate a change in patient information and/or the consent form.

13.2 Subsequent changes to protocol

Changes to protocol may only occur with the prior agreement of all co-operation partners. All participating practices in the trial must be informed of such changes in written form. Changes must be dated and deposited in the Trial Master File.

If in the course of the trial it becomes clear that changes or additions must be made to the present trial protocol, then these must be laid down in the form of an amendment and signed by the principal investigator, the investigators and by those responsible for approving the trial protocol.

Changes to the timetable that may influence the safety of trial participants or the scientific analysis of the trial necessitate renewed approval by the responsible Ethics Commission. The Commission is to be informed of changes to the trial protocol that occur solely for logistical or administrative reasons.

13.3 Trial registration

The trial has been registered as a clinical, scientific based non-AMG-non-MPG-trial in the international trial register "The Current Controlled Trials (CCT)" (URL: http://controlled-trials.com) and - as far as possible - at the German Register of Clinical Trials (DRKS; http://www.germanctr.de) before it begins. The registration notice will be kept in the Trial Master File (TMF) in the IGP.

13.4 Finance and Insurance

No patient insurance is necessary for this trial, as it represents no health risk to patients.

13.5 Responsibility for preparing reports to the funding organization

Joint reports were agreed upon due to the networked nature of the project structure (PRIMUM trial and sub project E within a joint research project). The coordinator of the joint research project and head of the IGP, Prof. Ferdinand M. Gerlach, MPH, will be responsible for the coordination and composition of the reports in a standard format. To this end he will receive the full support of all participants in the project and the co-investigators will provide all required information in a timely fashion.

The reporting process includes

(1) Interim reports to the funding organisation about the trial management in April 2010, and 2011.

(2) A final report following the completion of the trial.

13.6 Publication agreements

The specifications laid down in the CONSORT Statement for cluster-randomised trials must be taken into account when the results of the trial are published.[66]

In principle, the publication should adhere to the suggestions made by the German Research Community (Deutsche Forschungs-Gemeinschaft DFG) to ensure good scientific practice, January 1998 which correspond to the uniform requirements for manuscripts submitted to biomedical journals, NEJM 336: 309 ff, 1977:

"Authorship credit should be based only on substantial contributions to (a) conception and design, or analyses and interpretation of data; and to (b) drafting the article or revising it critically for important intellectual content.; and on (c) final approval of the version to be published"

Conditions (a), (b), and (c) must all be met.

- Names and the sequence of authors' names will be determined collectively for every publication, and by means of asterisks, all particpating persons and their functions will be named at the end of each article.

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15 APPENDIX A

15.1 Abbreviations

ADR	Adverse Drug Reaction
AMG	Medication law
AS	Discrepancy score
BMQ	Beliefs about Medicines Questionnaire
CDSS	Computerized Decision Support System
CIRS	Cumulative Illness Rating Scale
CR	Center registration
CRF	Case Report Form
DEGAM	German Society of General Practice and Family Medicine
DS	Drug Score
DoS	Dose Score
GCP	Good Clinical Practice
GDS	Geriatric Depression Scale
GP	General Practitioner
HCA	Health Care Assistant
ICC	Intra-Cluster Correlation-coefficient
ICH	International Conference on Harmonisation
ID	Identifier
IGP	Institute for General Practice, Goethe university Frankfurt, Coordinating centre of the study
ITT	Intention To Treat
MAI	Medication Appropriateness Index
MSH	Man-Son-Hing scale
MediMoL	Medication Monitoring List
MMSE	Mini Mental Status Exam
MRCI	Medication Regimen Complexity Index
OTC	Over The Counter
PP	Per Protocol
PZN	National Drug Code
RS	Regimen Score

SOP	Standard Operating Procedure
SPSS	Statistical Package for Social Sciences (Software)
TMF	Trial Master File
VES-13	Vulnerable Elderly Survey, 13 items
VFT	Verbal Fluency Test
VRS	Verbal Rating Scale on pain

15.2 Instructions on the content of the investigators file

- Trial protocol (plan) incl. all data collection instruments (sample)
- Geriatrics Guideline from the Hesse Guideline Group (short versions parts 1 and 2)
- Copy of the Ethics Commission vote
- Center Registration (CR)
- Screening list
- Random list
- Original of the signed patient information and consent form to the trial
- Original of the signed data protection declaration
- Patient registration form
- Flow chart on the trial
- Guideline on data flow

Intervention group only:

- Appendix B of the study protocol
- Medication Monitoring List
- AiD+ user manual
- Training material for intervention

15.3 MAI manual

(follows)

16 APPENDIX B

16.1 Description of the intervention (for intervention group, only)

The intervention in the PRIMUM trial is a complex intervention and consists of the following elements:

1. Pre-consultation interview of the HCA with the patient based on a checklist (Medication Monitoring List, MediMoL)
2. Brown bag review: medication reconciliation by the HCA of what drugs are taken by the patient
3. Use of an internet-based, user-initiated computerised decision support system 'AiD+', which alerts in case of
   - discount contracts,
   - duplication with other drugs,
   - drug-drug interactions,
   - renal dose adjustments
   - incompatibilities of parenteral applied drugs

   and provides further information on divisibility of tablets, medication regimen complexity, and maximal dosage
4. Physician-patient-consultation on medication related problems

16.1.1 Intervention – Tools

- Web-based pharmaceutical information system: AiD+ (further information materials will be distributed during intervention training)
- Checklists to track medication-related problems and patients therapeutic aims: Medication-Monitoring-Lists (MediMoL, will be issued during intervention training)

16.1.2 AiD+ development for use in the trial

AiD+ has been developed on the basis of the existing AiD clinic by the Department of Clinical Pharmacology and Pharmacoepidemiology, Heidelberg, for use in the PRIMUM trial, whereby the functionality of AiD+ has been agreed upon with the Institute for General Practice, Frankfurt. With the exception of the features "medication regimen complexity", and "maximal dosage" AiD+ has been tested in the pilot study and has shown a suitable feasibility. The new features have been developed prior to the start of the trial in the practices. All further changes of the functionality of AiD+ will take place after agreement between IGP and AiD developers.

For each trial site, a study employee of the IGP will set up 15 patient files using the patient identification codes from the random list in the password-protected area of the system. If the trial site demands a second random list then the IGP will set up a further 15 patient files.

16.1.3 Schedule of the intervention

In the intervention arm, patients will be looked after by the GP and a trained HCA from the general practice. The practices in the intervention group will receive the simplified version of parts I and II of the latest geriatrics guideline from the Hessen guideline group as a "recommended standard".[1] All study patients from the intervention group will receive the following structured intervention:

	Procedural step	Content
1	HCA arranges appointment	The HCA arranges an appointment with the patient to visit the practice. The patient will be asked to bring all drugs to the appointment that he or she takes, whether occasionally or regularly (also including OTC drugs phytopharmaceuticals and nutrition supplements) including the original packaging wherever possible.
2	HCA enters patient's core data and "practice medication" into Medibox 1 (AiD+)	The HCA logs into the web-based AiD+ (Internet address and password for the protected area are kept in the investigator file. On the trial site's page she calls up the patient by entering the patient's ID and compares the patient's reference code with that of the practice EDP. She confirms that the written declaration of informed consent is dated, has been signed personally and is present in the investigator file. She enters the date of birth, size and weight and the most current laboratory values (serum-potassium, -sodium and -creatinine) in the core data page of AiD+. Then she enters the prescribed medication from the most current therapy plan into AiD+, (entered in practice software) (Medibox 1: "practice medication"). After entering the data she logs out of AiD+.
3	HCA interviews patient on basis of checklist (MediMoL)	The patient arrives at the practice at the arranged time with all the drugs currently being taken. The HCA systematically asks the patient on the basis of a checklist (Medication Monitoring List, MediMoL) about pain, common symptoms of ADRs, need for information on the drugs, reasons for not taking drugs (including technical reasons such as the need to split tablets), adherence aspects such as neglecting to take long-term medication, objections to specific medication and about preferred therapy goals. The MediMoL includes the possibility to answer in free text as well as in pre-provided response categories that take the form of a traffic light pattern, enabling quick comprehension, and more sophisticated reactions according to severity: ▪ Red response category ("Emergency"): in case of this answer, the interview with the patient will be interrupted and the HCA will contact the GP immediately who will then decide how to proceed. ▪ Orange response category ("potentially serious and with a high probability of a clinically relevant problem"): the interview with the patient will be continued as planned. The HCA will inform the GP of the findings on the same day (at the latest within the next 24

	Procedural step	Content
		hours). The GP will decide what to do next. · Yellow response category ('*potentially* a clinically relevant problem'): the interview is continued as planned. If the category yellow is the most serious answer the HCA puts the MediMoL into the general findings tray that is looked at by the GP. · Green response category ('no problem'): the GP is informed of the MediMoL by means of the general findings tray.
4	HCA enters "house medication" into Medibox 2 *brown bag review*	The HCA logs into the password protected area of AiD+ and opens the patient's file (compare patient ID and date of birth with the data in the investigator's file). The HCA enters all drugs (regular medication, medication to be taken as needed, prescriptions from co-treating doctors, OTC products including phytopharmaceuticals and nutrition supplements) using its trade name, the name of the active ingredient or National Drug Code. In addition she records the dosage. After entering the information she stores it under home medication (Medibox 2).
5	GP checks the medication and problems associated with the medication with the support of AiD+ and MediMoL	The GP logs into the password protected area of AiD+ and opens the patient's file. He checks AiD+, "home medication" and "practice medication" for agreement in terms of the active ingredient (on the ATC code level) and dose. Both home and practice medication appear in a shared AiD+ window (Medibox 3: "coordinated medication", sorted according to ATC group (groups of active ingredients), whereby the origin of the medication – whether home or practice medication – can be recognized by the coloured background. Thus if there is total agreement between home and practice medication (the prescribed medication is the same as the medication actually taken), Medibox 3 will contain drug pairs with identical active ingredients. The GP then deletes the drug pairs and checks the warnings (drug interactions, duplication with other drugs) and pointers (renal dose adjustment, tablet divisibility, exceeding maximal dose) for clinical relevance. He identifies patient problems using MediMoL. He prepares necessary therapy adjustments in „Medibox 3".
7	Consultation between GP and patient on medication	The GP discusses the identified problems and any necessary changes in the medication with the patient. He saves the prescription plan he has discussed with the patient in the practice computer and makes a note of other arrangements (further appointments, transfer to a specialist etc.) on the MediMoL. He ends the interview with the patient and gives the MediMoL back to the HCA.
8	HCA ends the intervention	The HCA prints out the updated prescription plan and gives it to the patient. She follows any other instructions that have been made on MediMoL by the GP (e.g. makes an appointment for further interviews, laboratory checks, transfers to a specialist).

Medication Monitoring List (MediMoL)

PRIMUM

Date of interview

Name of the patient ..... ID .....

Name of health care assistant .....

	Contact GP	Follow-up consultation within	Report to the GP	Normal findings

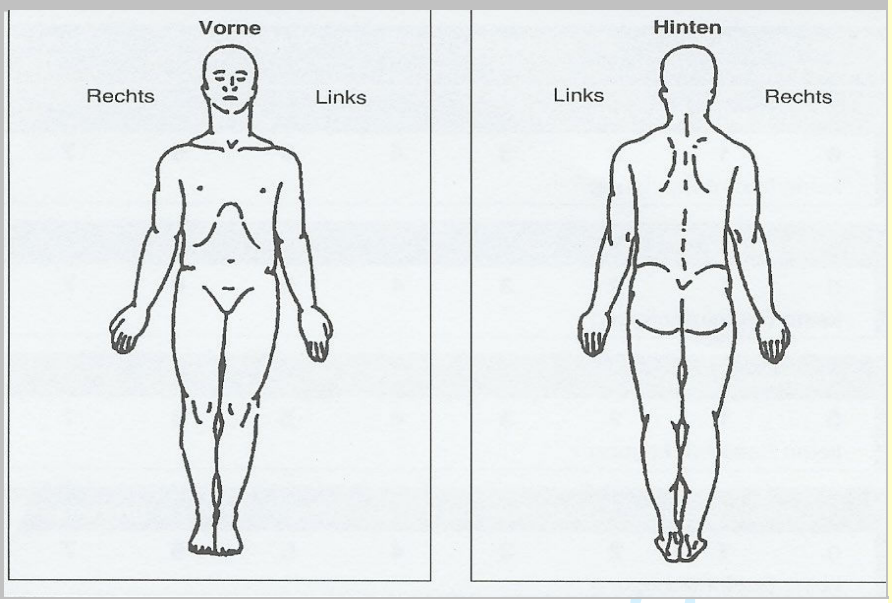
Pain: potential underuse?

1. Did you suffer from pain during the past 2 weeks?

Please take the time frame into consideration! If the patient reports pain, let him/her show the area that hurts. Circle all the aching regions on the map. If more than one area hurts, ask where the pain is most severe and mark the respective circle with an additional arrow.

Yes

Where?



Please present the verbal rating scale (VRS) to the patient and ask him/her about the intensity of the pain. If the patient reports pain in more than one place, ask him/her to describe the intensity at the location where it is most severe.

How intense was the pain during the past week?

- Worst imaginable pain
- Severe pain — 24h
- Moderate pain
- Mild pain
- No pain

Did the pain limit your ability to perform activities of daily living (e.g. shopping, gardening, etc.)?

- Yes
- No

No

Potential ADR

2. Did you suffer from the following complaints/symptoms during the past 2 wks?

Please take the time frame into consideration!

2.1 Nausea or vomiting? *Please underline as applicable.*

Yes
- Almost every day — 24h
- On a number of days
- Once

No
- Never

Did you suffer from the following complaints or symptoms during the past two weeks? (cont.)

Potential adverse drug reactions (ADR) or symptoms of underlying diseases

		Contact GP	Follow-up consultation within	Report to the GP	Normal findings
2.2 Dizziness?					
Yes	Almost every day		24h		
	On a number of days				
	Once				
No	Never				
2.3 Shortness of breath?					
Yes	Almost every day		24h		
	On a number of days				
	Once				
No	Never				
2.4 Abnormally rapid heart rate or irregular heartbeat? *Please underline as applicable.*					
Yes	Almost every day		24h		
	On a number of days				
	Once				
No	Never				
2.5 Swollen legs / edema?					
Yes					
No					
2.6 Do you think, your tendency to bleed has increased?					
Yes	Did you suffer from one of the following **more than once** during the past two weeks?				
	Bleeding gums?				
	Nosebleed?				
	Prolonged bleeding after a mild injury (e.g. when shaving or after a light cut)?				
	You have bruises that are more than 3 cm in diameter but you do not remember bumping yourself?				
	None of these problems.				
No					
2.7 Did you notice any black feces / melena during the past three months?					
Please take the time frame into consideration!					
Yes	Did the feces really look black and "tarry" (like tar) or was it just dark?				
	Yes, black and tarry. When did you last notice it?				
	Within the past three days				
	Within the past three weeks but not the past three days		24h		
	More than three weeks ago				
	No, only dark				
No					

Was the green box selected to answer questions 2.1 to 2.7? If so, go to question 3. If a different colored box was chosen to answer at least one question, go to question 2.8.

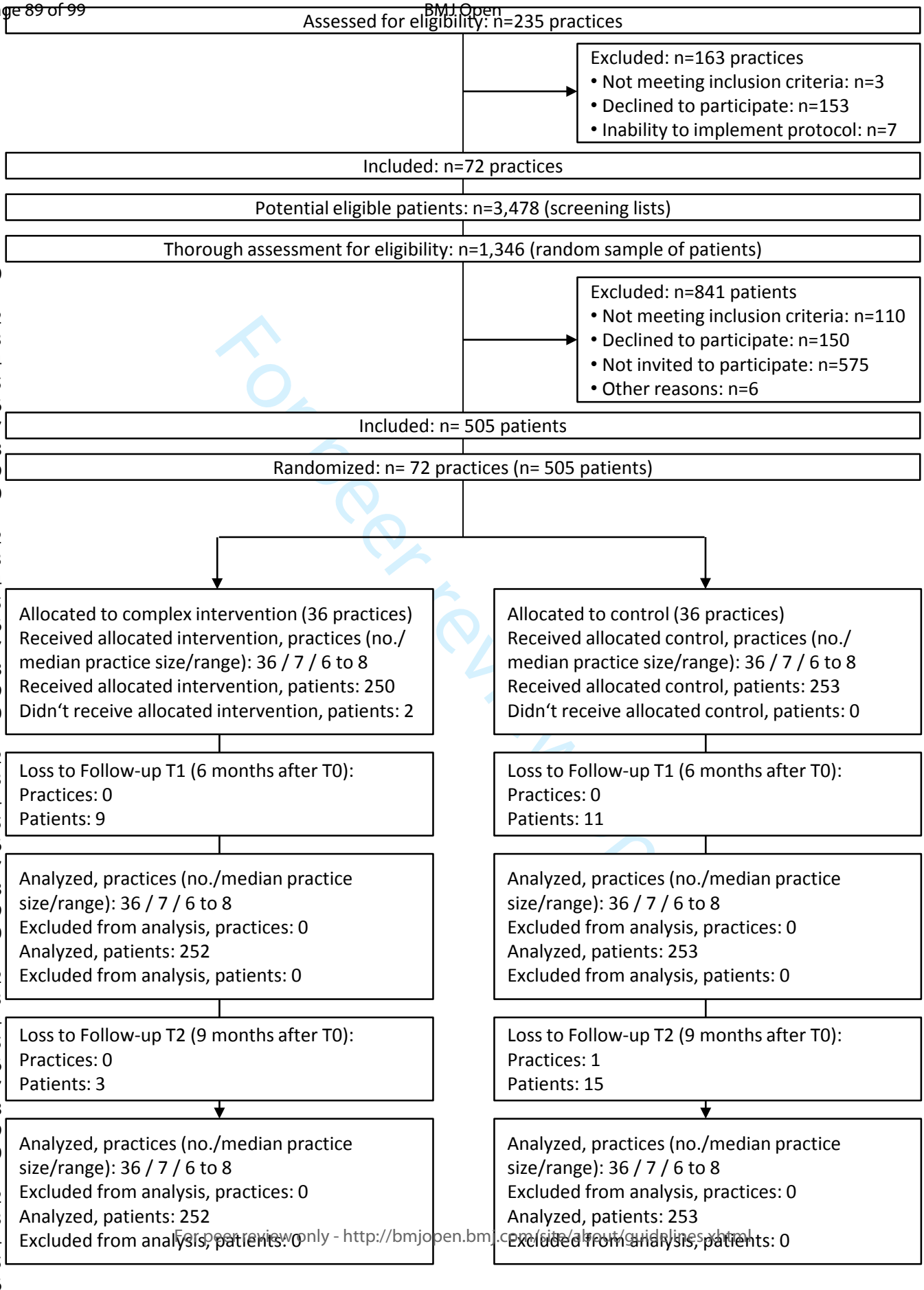
2.8 Do you think your symptoms/complaints are caused by your medication?					
Yes	What makes you think so?				
	_____				
	_____				
No					

		Contact GP	Follow-up consultation within	Report to the GP	Normal findings
Information	**3. Do you need more information on your medication?**				
	Yes What in particular would you like to know? _____			☐	
	No				☐
Problems to take medicines in	**4.1 Did you have any of the following problems handling your medication during the past two weeks?**				
	Getting medicine out of the box or blister pack?				
	Yes Which drugs? _____			☐	
	No				☐
	Splitting, crushing or dissolving tablets?				
	Yes Which drugs? _____			☐	
	No				☐
	Counting the drops of a solution or applying plasters?				
	Yes Which drugs? _____			☐	
	No				☐
	Inserting suppositories?				
	Yes Which drugs? _____			☐	
	No				☐
	Administering inhalers or nebulizers?				
	Yes Which drugs? _____			☐	
	No				☐
	4.2 Did you have any difficulties swallowing a medicine during the past two weeks?				
	Yes The medicine is too large			☐	
	The taste is bad			☐	
	I have always had difficulties swallowing tablets			☐	
	Other reasons: _____			☐	
	No				☐
Adherence	**5.1 Did you try a medicine which was recommended by relatives, friends, neighbors etc. during the past two weeks ?**				
	Yes Which drugs?			☐	
	No				☐
	5.2 During the past two weeks, did you only take certain medicines when you felt worse?				
	Yes Which drugs? _____			☐	
	No				☐
	5.3 During past two weeks, did you neglect to take your prescribed medicine now and then?				
	Yes Which drugs? _____				
	When do you neglect to take your medicine?				
	_____			☐	
	No				☐
	5.4 Would you like to take fewer medications?				
	Yes Would you like to discuss this with your physician?				
	Yes Anything in particular?			☐	
	No				☐
	No				☐

		Contact GP	Follow-up consultation within	Report to the GP	Normal findings
Adherence	**5.5 Do you take a medicine that you would prefer not to take?**				
	Yes — Which medicine?			☐	
	What don't you like about it?				
	I can't tolerate it.			☐	
	I don't believe it is effective.			☐	
	It is too expensive			☐	
	Because I have to take so many other medications.			☐	
	Other reasons: _____			☐	
	No				☐
Patientent's preferences & treatment goals	**6.1 What are your medications supposed to achieve in your current situation?**				
	Please answer by ticking the blue boxess. ***Several answers possible*** *.*				
	☐ Prolonged survival?			☐	
	☐ Fewer hospitalizations?			☐	
	☐ Less pain?			☐	
	☐ Improved functional status (e.g., able to go shopping)			☐	
	☐ More enjoyment of life?			☐	
	☐ Others: _____			☐	
	6.2 What is most important to you?				
	Please tick one of the yellow boxes above (6.1). *Please note:* ***one answer only!***				
Communication within the practice team	**7. Making an appointment for a consultation with the physician (depending on find**				
	If you ticked any orange boxes, please inform the patient that after checking with the GP, you may well call him up and ask him to come to the practice. If you ticked only yellow and / or green boxes: please follow the procedure you have agreed upon in your practice for dealing with study patients.				
	Date of appointment with the physician: ..... **End of interview**				
	8. Health care assistant's assessment				
	Was there anything striking about the patient, e.g., exceptional circumstances or conflicts?				
	9. Information provided to the health care assistant by the physician after the physician-patient consultation on medication-related problems				
	Order lab tests: _____				
	☐ Electrolytes, creatinine				
	☐ Blood count				
	☐ Others				
	☐ Referral				
	☐ No changes to treatment				
	Treatment changes:				
	☐ Changes in medication				
	☐ Others				
	☐ Next consultation (follow up)				
	☐ Others				

Acknowledged:

Date Physician ..... Date Health care assistant .....



Characteristics of non-responding practices

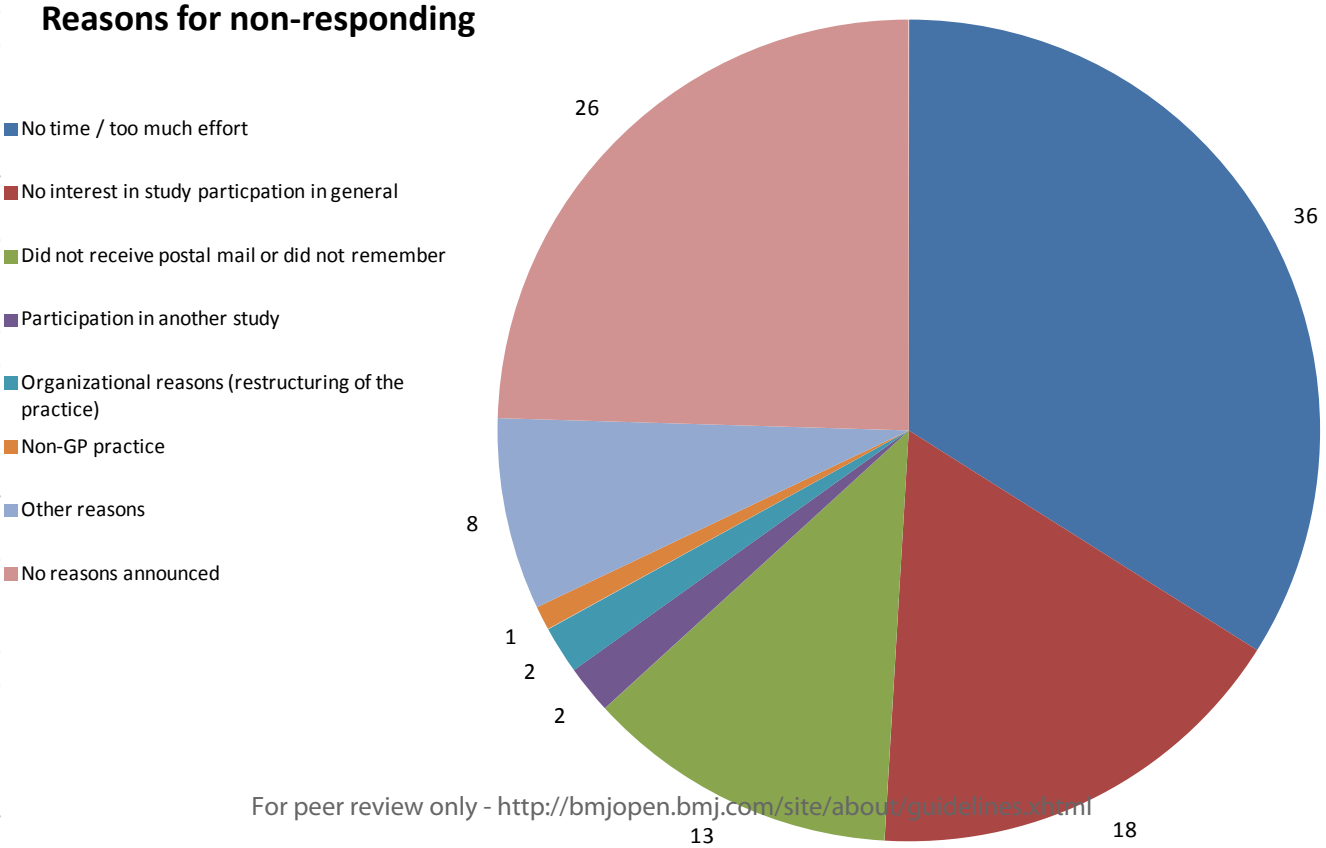
In total, 132 practices were called up to three times, of them 6 did not answer the phone.

107/126 were active general practices, 7 were not, and 12 practices did not provide information about it at the phone.

55/107 (51%) of the general practices had internet access, 50/107 had not, 2 did not provide details.

	Participating practices (total)	Non-responding practices
Practices	**N=72**	**N=132**
Location: no. (%)	N=72	N=132
City (>100,000 inhabitants)	22 (31%)	46 (35%)
Middle size town (20,000 to 100,000)	16 (22%)	37 (28%)
Small town (5,000 to 20,000)	25 (35%)	47 (36%)
Rural area (<5,000 inhabitants)	9 (13%)	2 (2%)
Practice type: no. (%)	**N=72**	**N=126**
Single handed practices	41 (57%)	75 (60%)
Group practice	27 (38%)	27 (21%)
Practice community	4 (6%)	6 (5%)
Not announced	-	18 (14%)

Reasons for non-responding



Effectiveness of a complex intervention on PRIoritising MUltimedication in Multimorbidity (PRIMUM) in primary care: results of a pragmatic cluster-randomised controlled trial.

Christiane Muth, Lorenz Uhlmann, Walter E. Haefeli, Justine Rochon, Marjan van den Akker, Rafael Perera, Corina Güthlin, Martin Beyer, Frank Oswald, Jose M. Valderas, André Knottnerus, Ferdinand M. Gerlach, Sebastian Harder

Web-appendix 4: Symptoms for potential adverse drug reactions (ADR) - descriptive analysis

Symptom† *(number, percentage)*	T0		T1		T2	
	Control group (n=253)	Intervention group (n=252)	Control group (n=237)	Intervention group (n=238)	Control group (n=225)	Intervention group (n=231)
Bleeding diathesis#	44 (17)	33 (13)	28 (12)	43 (18)	34 (15)	39 (17)
Ankle edema	78 (31)	84 (33)	79 (33)	87 (37)	67 (30)	90 (39)
Dizziness#	54 (21)	54 (21)	61 (26)	52 (22)	59 (26)	46 (20)
Dyspnea#	86 (34)	70 (28)	62 (26)	68 (29)	55 (24)	53 (23)
Difficulties urinating	51 (20)	64 (25)	56 (24)	54 (23)	43 (19)	47 (20)
Abdominal pain#	36 (14)	37 (15)	29 (12)	24 (10)	38 (17)	30 (13)
Tachycardia or palpitation#	36 (14)	36 (14)	28 (12)	26 (11)	21 (9)	21 (9)
Nausea or vomiting#	16 (6)	11 (4)	22 (9)	10 (4)	8 (4)	15 (6)

†for details see Figure 1, item "h", #symptoms appeared on at least several or almost every day

Manuscript: "Effectiveness of a complex intervention on PRIoritising MUltimedication in Multimorbidity (PRIMUM) in primary care: results of a pragmatic cluster-randomised controlled trial."

Table 1: CONSORT 2010 checklist of information to include when reporting a cluster randomised trial

Section/Topic	Item No	Standard Checklist item	Extension for cluster designs	Page No *
Title and abstract				
	1a	Identification as a randomised trial in the title	Identification as a cluster randomised trial in the title	✓
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)[i,ii]	See table 2	✓
Introduction				
Background and objectives	2a	Scientific background and explanation of rationale	Rationale for using a cluster design	7 Introduction section for scientific background
	2b	Specific objectives or hypotheses	Whether objectives pertain to the the cluster level, the individual participant level or both	7
Methods				
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	Definition of cluster and description of how the design features apply to the clusters	7
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons		**none**
Participants	4a	Eligibility criteria for participants	Eligibility criteria for clusters	7, 8
	4b	Settings and locations where the data were collected		7
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Whether interventions pertain to the cluster level, the individual participant level or both	8-9 plus PaTplot (figure 1, icons "2" to "5" and "j" to "k"), provision of an instrument (web-appendix 2)
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	Whether outcome measures pertain to the cluster level, the individual participant level or both	9-10 plus PaTplot (figure 1, icons "f" to "h")
	6b	Any changes to trial outcomes after the trial commenced, with reasons		**none**
Sample size	7a	How sample size was determined	Method of calculation, number of clusters(s) (and whether equal or unequal cluster sizes are assumed), cluster size, a	10-11

			coefficient of intracluster correlation (ICC or *k*), and an indication of its uncertainty	
	7b	When applicable, explanation of any interim analyses and stopping guidelines		n.a.
Randomisation:				
Sequence generation	8a	Method used to generate the random allocation sequence		8 plus PaTplot (figure 1: icon "i")
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Details of stratification or matching if used	8 plus PaTplot (figure 1: icon "i")
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Specification that allocation was based on clusters rather than individuals and whether allocation concealment (if any) was at the cluster level, the individual participant level or both	8
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Replace by 10a, 10b and 10c	
	10a		Who generated the random allocation sequence, who enrolled clusters, and who assigned clusters to interventions	8 plus PaTplot (figure 1: icon "i")
	10b		Mechanism by which individual participants were included in clusters for the purposes of the trial (such as complete enumeration, random sampling)	PaTplot (figure 1: icons "c" to "e")
	10c		From whom consent was sought (representatives of the cluster, or individual cluster members, or both), and whether consent was sought before or after randomisation	PaTplot (figure 1: icons "a", "b", "e")
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how		8
	11b	If relevant, description of the similarity of interventions		8-9 (both groups received practice guidelines for older adults)

Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	How clustering was taken into account	11
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses		11
Results				
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	For each group, the numbers of clusters that were randomly assigned, received intended treatment, and were analysed for the primary outcome	Web-appendix 3 (Flow chart)
	13b	For each group, losses and exclusions after randomisation, together with reasons	For each group, losses and exclusions for both clusters and individual cluster members	11-12 plus web-appendix 3
Recruitment	14a	Dates defining the periods of recruitment and follow-up		PaTplot (figure 1)
	14b	Why the trial ended or was stopped		N.a., trial was completed.
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Baseline characteristics for the individual and cluster levels as applicable for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	For each group, number of clusters included in each analysis	Table 1; web-appendix 3 (flow chart), table 1 and 2; web-appendix 4,
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Results at the individual or cluster level as applicable and a coefficient of intracluster correlation (ICC or k) for each primary outcome	Web-appendix 4, table 1 and 2; web appendix 3, flow chart
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended		n.a.
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory		Figure 2 (2a and 2b)
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms[iii])		n.a.
Discussion				
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses		14-15
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	Generalisability to clusters and/or individual participants (as relevant)	22
Interpretation	22	Interpretation consistent with results, balancing		23

		benefits and harms, and considering other relevant evidence	
Other information			
Registration	23	Registration number and name of trial registry	4
Protocol	24	Where the full trial protocol can be accessed, if available	Web-appendix 1
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	17

** Note: page numbers refer to the numbers within the original WORD file*

Table 2: Extension of CONSORT for abstracts[i,ii] to reports of cluster randomised trials

Item	Standard Checklist item	Extension for cluster trials
Title	Identification of study as randomised	**Identification of study as cluster randomised** ✓
Trial design	Description of the trial design (e.g. parallel, cluster, non-inferiority)	✓
Methods		
Participants	Eligibility criteria for participants and the settings where the data were collected	**Eligibility criteria for clusters** We did not apply inclusion criteria of major relevance for practices and provided this information with main text.
Interventions	Interventions intended for each group	✓
Objective	Specific objective or hypothesis	**Whether objective or hypothesis pertains to the cluster level, the individual participant level or both** ✓
Outcome	Clearly defined primary outcome for this report	**Whether the primary outcome pertains to the cluster level, the individual participant level or both** ✓
Randomization	How participants were allocated to interventions	**How clusters were allocated to interventions** ✓
Blinding (masking)	Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment	✓
Results		
Numbers randomized	Number of participants randomized to each group	**Number of clusters randomized to each group** ✓
Recruitment	Trial status[1]	N.a.
Numbers analysed	Number of participants analysed in each group	**Number of clusters analysed in each group** ✓
Outcome	For the primary outcome, a result for each group and the estimated effect size and its precision	**Results at the cluster or individual participant level as applicable for each primary outcome**

[1] Relevant to Conference Abstracts

		✓
Harms	Important adverse events or side effects	n.a.
Conclusions	General interpretation of the results	✓
Trial registration	Registration number and name of trial register	✓
Funding	**Source of funding**	Due to the word limit, we provided the source of funding with the plain text

The TIDieR (Template for Intervention Description and Replication) Checklist*:

Information to include when describing an intervention and the location of the information

Item number	Item	Where located **	
		Primary paper (page or appendix number)	Other † (details)
	BRIEF NAME		
1.	Provide the name or a phrase that describes the intervention.	The title: "complex intervention in PRIoritising MUltimedication in Multimorbidity (PRIMUM) in primary care"	_____
	WHY		
2.	Describe any rationale, theory, or goal of the elements essential to the intervention.	Abstract: objectives Main text: introduction (p. 6-7)	Pilot study [iv]
	WHAT		
3.	Materials: Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (e.g. online appendix, URL).	Abstract: interventions Main text: p. 8, last paragraph Figure 1 (icons "j" and "3" to "5") web-appendices 1 (study protocol) and 2 (checklist MediMoL)	_____
4.	Procedures: Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities.	Abstract: interventions Main text: p. 8-9 Figure 1 (icons "j" and "3" to "5") web-appendices 1 (study protocol) and 2 (checklist MediMoL)	_____
	WHO PROVIDED		
5.	For each category of intervention provider (e.g. psychologist, nursing assistant), describe their expertise, background and any specific training given.	Abstract: interventions Main text: methods section; for expertise and background of health care assistants (introduction: p. 6, last paragraph); Figure 1	_____

		(icon "j" for intervention training)	
	HOW		
6.	Describe the modes of delivery (e.g. face-to-face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group.	Figure 1 (icons "j" and "3" to "5")	_____
	WHERE		
7.	Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features.	Figure 1 (icons "j" and "3" to "5")	_____
	WHEN and HOW MUCH		
8.	Describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity or dose.	Methods section p. 8, last paragraph	_____
	TAILORING		
9.	If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how.	N/A	_____
	MODIFICATIONS		
10.‡	If the intervention was modified during the course of the study, describe the changes (what, why, when, and how).	N/A - the intervention was not modified during the study.	_____
	HOW WELL		
11.	Planned: If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them.	N/A	_____
12.‡	Actual: If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned.	N/A	_____

** **Authors** - use N/A if an item is not applicable for the intervention being described. **Reviewers** – use '?' if information about the element is not reported/not sufficiently reported.

† If the information is not provided in the primary paper, give details of where this information is available. This may include locations such as a published protocol or other published papers (provide citation details) or a website (provide the URL).

ǂ If completing the TIDieR checklist for a protocol, these items are not relevant to the protocol and cannot be described until the study is complete.

* We strongly recommend using this checklist in conjunction with the TIDieR guide (see *BMJ* 2014;348:g1687) which contains an explanation and elaboration for each item.

* The focus of TIDieR is on reporting details of the intervention elements (and where relevant, comparison elements) of a study. Other elements and methodological features of studies are covered by other reporting statements and checklists and have not been duplicated as part of the TIDieR checklist. When a **randomised trial** is being reported, the TIDieR checklist should be used in conjunction with the CONSORT statement (see www.consort-statement.org) as an extension of **Item 5 of the CONSORT 2010 Statement.** When a **clinical trial protocol** is being reported, the TIDieR checklist should be used in conjunction with the SPIRIT statement as an extension of **Item 11 of the SPIRIT 2013 Statement** (see www.spirit-statement.org). For alternate study designs, TIDieR can be used in conjunction with the appropriate checklist for that study design (see www.equator-network.org).

REFERENCES

[i] Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG, et al. CONSORT for reporting randomised trials in journal and conference abstracts. *Lancet* 2008, 371:281-283

[ii] Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG at al (2008) CONSORT for reporting randomized controlled trials in journal and conference abstracts: explanation and elaboration. *PLoS Med* 5(1): e20

[iii] Ioannidis JP, Evans SJ, Gotzsche PC, O'Neill RT, Altman DG, Schulz K, Moher D. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Ann Intern Med* 2004; 141(10):781-788.

[iv] Muth C, Harder S, Uhlmann L, Rochon J, Fullerton B, Guthlin C, et al. Pilot study to test the feasibility of a trial design and complex intervention on PRIoritising MUltimedication in Multimorbidity in general practices (PRIMUMpilot). BMJ Open 2016;6(7):e011613.

BMJ Open

Effectiveness of a complex intervention on PRIoritising MUltimedication in Multimorbidity (PRIMUM) in primary care: results of a pragmatic cluster-randomised controlled trial.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-017740.R2
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Date Submitted by the Author:	30-Nov-2017
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Primary Subject Heading:	Patient-centred medicine
Secondary Subject Heading:	General practice / Family practice, Health services research, Medical management, Research methods, Geriatric medicine
Keywords:	Multimorbidity, Multiple Chronic Conditions, polypharmacy, medication reconciliation, drug therapy, computer-assisted, medication appropriateness index

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Key words:

Multimorbidity; Multiple Chronic Conditions[MeSH]; comorbidity [MeSH]; polypharmacy [MeSH]; complex intervention; medication reconciliation [MeSH]; drug therapy, computer-assisted [MeSH]; medication appropriateness index; primary care [MeSH]; general practice [MeSH]

WORD COUNT: (aim but not strictly limited: ≤4,000 – currently: 4,589)

Abstract: (300 words)

Objectives: Investigate the effectiveness of a complex intervention aimed at improving the appropriateness of medication in older patients with multimorbidity in general practice.

Design: Pragmatic, cluster-randomised controlled trial with general practice as unit of randomisation.

Setting: 72 general practices in Hesse, Germany.

Participants: 505 randomly sampled, cognitively intact patients (≥60 years, ≥3 chronic conditions under pharmacological treatment, ≥5 long-term drug prescriptions with systemic effects); 465 patients and 71 practices completed the study.

Interventions: Intervention group (IG): The health care assistant conducted a checklist-based interview with patients on medication-related problems and reconciled their medications. Assisted by a computerised decision-support system, the general practitioner optimized medication, discussed it with patients and adjusted it accordingly. The control group (CG) continued with usual care.

Outcome measures: The primary outcome was a modified medication appropriateness index (MAI, excluding item 10 on cost effectiveness), assessed in blinded medication reviews and calculated as the difference between baseline and after 6 months; secondary outcomes after six- and nine-months follow-up: quality of life, functioning, medication adherence etc.

Results: At baseline, a high proportion of patients had appropriate to mildly inappropriate prescriptions (MAI 0-5 points: n=350 patients). Randomisation revealed balanced groups (IG: 36 practices/252 patients; CG: 36/253). Intervention had no significant effect on primary outcome: mean MAI sum scores decreased by 0.3 points in IG and 0.8 points in CG, resulting in a non-significant adjusted mean difference of 0.7 (95% CI -0.2 to 1.6) points in favour of CG. Secondary outcomes showed non-significant changes (quality of life slightly improved in IG but continued to decline in CG) or remained stable (functioning, medication adherence).

Conclusions: The intervention had no significant effects. Many patients already received appropriate prescriptions and enjoyed good quality of life and functional status. We can therefore conclude that in our study, there was not enough scope for improvement.

Trial registration: Controlled Trials: ISRCTN99526053 - August 31, 2010 - http://www.controlled-trials.com/ISRCTN99526053 and ClinicalTrials.gov: NCT01171339 - July 27, 2010 - http://clinicaltrials.gov/ct2/show/NCT01171339?term=PRIMUM&rank=1

"Strengths and limitations of this study"

- The PRIMUM intervention was developed and piloted in accordance with the latest MRC guidance on complex interventions.
- The effectiveness of the PRIMUM intervention was evaluated in a rigorously conducted cluster-randomised trial that involved random sampling of patients, disclosure of treatment allocation after baseline completion, and adherence to the protocol.
- To evaluate the generic patient-centred strategy of applying PRIMUM, we used the commonly used medication appropriateness index (MAI), as this implicit measure allows individualized assessments.
- We blinded both the assessment of the primary outcome MAI and the statistical analyses.
- Key limitations were that the baseline values of MAI and the secondary outcomes did not provide enough scope for improvement, and that medication underuse in polypharmacy was not sufficiently reflected in our outcome measures.

Introduction:

The prevalence of multimorbidity, i.e. the co-occurrence of multiple chronic or acute diseases and medical conditions in one person,[1] increases with age, and most primary care consultations currently involve patients with multiple conditions.[2-4] Multiple disorders in patients are likely to result in multiple drug prescriptions. This increases the risk of drug-drug and drug-disease interactions, inappropriate dosages or drug selection, and non-adherence of patients. They may, however, also result in undertreatment.[5-10] Inappropriate prescriptions may result in hospitalisations, falls and related injuries, decreased quality of life, cognitive and physical dysfunction, loss of autonomy, and increased mortality, particularly in the elderly.[6-8, 11-14] Negative health outcomes caused by inappropriate polypharmacy are responsible for high outlays for hospital treatment, home care and nursing homes.[15-17] Much morbidity and many costs may be preventable – for instance 20% to 50% of medication-related hospitalisations on internal wards have been estimated to be avoidable.[13, 16, 18-20] Recently, Dreischulte and co-researchers observed a reduction in hospital admission rates for gastrointestinal ulcers or bleeding in their trial evaluating a complex intervention addressing nine specific high-risk prescribing patterns such as nonsteroidal anti-inflammatory drugs (NSAIDs) in renal failure, or in combination with oral anticoagulants.[21] Further trials also evaluated interventions addressing safety indicators and achieved a reduction in high-risk prescribing through adherence to explicit criteria that are relevant to public health.[22, 23] However, 'the range of reported effect sizes was modest, and it is unclear whether such interventions can result in clinically significant improvements in patient outcomes'.[24]

Furthermore, considering there are more than 10,000 known diseases, the number of possible interactions between diseases and treatments in patients with multimorbidity is vast, and patients may not be able to cope with the treatment burden.[25] Generic patient-centred strategies to assess potential interactions and to prioritise and individualise management in accordance with patients' preferences and shared treatment goals have been recommended for patients with multimorbidity and polypharmacy.[26-32] In these patients, evidence of interventions with proven effectiveness on clinical outcomes remains scarce. However, recent Cochrane reviews have identified strategies that appear to be beneficial in terms of reducing inappropriate prescribing.[33, 34] Based on promising strategies to combat inappropriate polypharmacy and in accordance with guiding principles to manage patients with multimorbidity, we developed and piloted a complex intervention.[35] As the prevalence of multimorbidity and polypharmacy in older people is high, they made up the target population. To reduce the workload on the General Practitioner (GP), the intervention also involved a health care assistant (HCA) from the practice.[35] In Germany, HCAs receive less training than nurses and are comparable to certified medical assistants in the USA. In usual care, HCAs work as

receptionists, assist GPs (e.g. in diagnostic procedures or wound management) and conduct, for instance, dietary counselling. On many occasions, HCAs have successfully participated in chronic care interventions where they have, for example, surveyed patients by following protocols with fixed interview questions for conditions such as osteoarthritis, major depression, and chronic heart failure, under the supervision of GPs.[36-40]

In accordance with Medical Research Council (MRC) guidance on developing and evaluating complex interventions, we tested the feasibility of the complex intervention in a pilot study.[35] On the basis of overall feasibility findings, we improved the intervention and trial design. To compare the effectiveness of the complex PRIMUM intervention with usual care in older patients with multimorbidity and polypharmacy in general practice, we used the medication appropriateness index (MAI) as primary outcome. This implicit (non-criteria-based) measure allows an individualized assessment of medication appropriateness.[41-43] We investigated whether the appropriateness of drug prescriptions changed after 6 months follow-up measured as a difference in the MAI-Score 6 months from baseline minus baseline (MAI T1–T0).

Methods:

Study design

The study was a pragmatic, cluster-randomised controlled trial with the general practice as the unit of randomisation. To further reduce contamination of the control group and unlike the pilot study, detailed information on the intervention treatment was only provided to the intervention group.[35] Primary and secondary outcomes were measured at patient level (**Figure** 1[44-69] and web-appendix 1: study protocol).

[About here: Figure 1. PaT plot [70] of the PRIMUM trial.]

Setting and participants

General practices in the German state of Hesse were eligible if they provided primary care under the German statutory health insurance system, and if at least one of the HCA staff members was able to access the internet in the practice. Practices specializing in unconventional treatments or in special indications (e.g. HIV) were excluded. To recruit practices, we sent letters to about 1,600 practice addresses provided by the Association of Statutory Health Insurance Physicians of Hesse –

addressees were not exclusively active general practitioners. We checked inclusion and exclusion criteria for those who were interested by phone and agreed upon a time for investigator training (**Figure 1**: icon "1"). In both groups, GPs and HCAs received a lump-sum of €300 in recompense for the work involved in documenting results. In the intervention group, GPs and HCAs received an additional €150 for the extra work that the intervention entailed.

GPs that did not respond to the original letter received a reminder phone call. We phoned a random 10% sample of those who did not respond to either the letter or the reminder up to three times in order to collect data on inclusion and exclusion criteria, practice characteristics, and reasons for non-participation.

Patients: A random sample of seven patients per practice were included (**Figure 1**, patient recruitment, icons "c" to "e"). Patients were required to be≥ 60 years old, have ≥ 3 chronic conditions under pharmacological treatment, ≥ 5 long-term prescriptions of drugs with systemic effects (the medication regimen may have included drugs with local effects but these did not fulfil the inclusion criterion), have made ≥ 1 practice visit during the past quarter, and be able to fill in questionnaires and participate in telephone interviews. To include a greater number of patients at risk of (manageable) interactions than in the pilot study,[35] patients had to have diseases affecting at least two different organ systems operationalized as two different chapters of ICD-10. The chapters "H" (diseases of the eyes and ears) and "E00" to "E04" (diseases of the thyroid gland without hyperthyroidism) were not counted because their potential for systemic interactions was considered to be low. We excluded patients with dementia and cognitive impairment (Mini-Mental Status Examination, MMSE < 26),[47] because we designed our intervention for cognitively intact patients and did not target caregivers. Further exclusion criteria were a life expectancy ≤ 12 months, alcohol and drug abuse (based on the GP's assessment), or participation in another clinical trial 30 days prior to inclusion.

Randomisation, allocation concealment, and blinding

The first patient from each practice served as the basis for randomisation (**Figure 1**, icon "i"). Patients registered thereafter were treated according to practice status (control or intervention), which was assigned in an allocation ratio of 1:1 using a block randomisation of variable block length. At the study centre, an external researcher generated the allocation sequence using the random number generator of Microsoft EXCEL. Treatment allocation was disclosed to the practice after baseline completion. Owing to the nature of the intervention, it was not possible to blind GPs, HCAs, patients, and the study team. Treatment allocation was blinded to the clinical pharmacologist conducting

medication reviews for the primary outcome (MAI - medication appropriateness index) and to the statistician.

Intervention and control groups

Intervention group

The PaTplot [70] (**Figure 1**, icons "j" and "3" to "5") shows the four elements of the complex intervention. It consists of (1) a brown bag review and (2) a checklist-based pre-consultation interview with the patient that is conducted by the HCA (**web-appendix 2**), (3) a CDSS-assisted medication review carried out by the GP and (4) a GP-patient consultation to optimise and prioritise medication. GPs had the option to use the CDSS to help prepare the medication review with the patient, and during the consultation itself. Trained HCAs and GPs (**Figure 1**, item "2") implemented the intervention on a single occasion, which took the GP and the HCA a per-patient average of 35 and 45 minutes respectively.[35] The practice team for the intervention group received the GP guidelines for ambulatory geriatric care prepared by the Hesse Guideline Group (**Figure 1**, item "k"). Recommendations in the guideline focus on primary and secondary prevention (e.g. physical exercise, fall assessment and prevention).[46]

Control group

The control group continued to receive usual care but the practice team also received the GP guidelines for ambulatory geriatric care (**Figure 1**, item "k")[46] to harmonize usual care in both groups.

Outcomes

The *primary outcome* was the difference in MAI sum score [41, 71] at 6 months minus the corresponding baseline score (MAI T1–T0). The MAI is commonly used in RCTs[42, 43] and consists of ten items: indication, effectiveness, correctness of dosage, correctness of direction, practicality of direction, drug–drug interactions, drug-disease interactions, unnecessary drug duplications, correctness of treatment duration, and costs. The MAI item on cost was omitted because variable discount contracts between pharmaceutical companies and statutory health insurers preclude cost comparisons in Germany. The medication reviews were conducted by the same clinical pharmacologist (SH) that performed the pilot study. He rated nine items per prescription from '1'

(appropriate) to '3' (inappropriate) where '2' represents a middle rating of uncertain appropriateness in a blinded chart review. In line with the piloted procedures,[35] he coded the MAI according to the GP's prescriptions, renal function, electrolytes, multimorbidity (diagnoses, Cumulative Illness Rating Scale—CIRS)[44, 45] (Figure 1, icon f) and symptoms of adverse drug reactions (Figure 1, icon h). Phytopharmaceuticals, homeopathic and other complementary and alternative medicine products were excluded from the rating. MAI sum scores for the entire medication regimen were calculated on the basis of these ratings. Based on the intra-rater reliability of the MAI ratings in the pilot study (B-statistics: the intra-rater reliability for the nine MAI items ranged from 0.90 to 0.99 and was slightly better than inter-rater reliability),[35] we did not perform a duplicate MAI rating. MAI ratings were transformed by subtracting 1 from the original rating, resulting in values ranging from '0' (best rating) to '2' (worst rating), and summed to give an MAI score per prescription (theoretically ranging from 0 to 18) and across the entire medication regimen of the patient. Lower MAI sum scores denoted better prescribing appropriateness. A negative difference in MAI sum scores (MAI T1-T0) therefore reflected an improvement in prescribing quality.

Secondary outcomes (6 vs. 9 months): we measured the change in the MAI score after 9 months (MAI T2–T0). On the assumption, improved medication appropriateness would result in improved health-related quality of life and functional status, we measured the differences in the EQ-5D index score,[48, 49] changes in perceived future life expectancy (a quality of life-related concept indicating wellbeing and positive life evaluation measured in years of expected and desired lifetime duration),[52, 53] functional status (differences in vulnerable elderly survey, VES-13),[50] all-cause hospitalisation and severity of chronic pain (von Korff-Index)[51] after six and nine months (T1-T0 and T2-T0).

To explain intervention effects, we also measured changes in satisfaction with shared decision making (Man Son Hing scale, MSH)[54, 55] and medication adherence after six and nine months (T1-T0 and T2-T0). We investigated a) self-reported adherence in accordance with Morisky (low scores indicating good adherence);[62] b) "observed adherence" measured in terms of discrepancies between medicines actually taken (reported during patient interviews) and medicines prescribed (reported by GP), as expressed in the three scores developed by Barat et al.[72] The scores were based on ratios calculated as follows:

(1) The drug score (DS) representing the ratio of the number of drugs reported by the patients to the number of drugs reported by the GP,

(2) The dose score (DoS=d1(a1)+d2(a2)+d3(a3)+…/n), where d_i is the drug used by the patients (value 0 or 1), n is the number of drugs in the GP's report, and a_i is the dose-

deviation ratio calculated by dividing the patient's reported daily dose by the daily dose prescribed by the GP, and

(3) The regimen score (RS=d1(b1)+d2(b2)+d3(b3)+…/n), where b_i is the regimen-deviation ratio and calculated by dividing the patient's reported daily intake frequency (once daily, twice daily, etc.) by the corresponding frequency prescribed by the GP.[72]

Scores outside an interval of 0.8–1.2 were considered to be divergent.

Further adherence-related measures assessed the complexity of the medication (total number of prescriptions, number of single doses/day, and Medication Regimen Complexity Index, MRCI),[73] patients' beliefs and attitudes toward medication (Beliefs about Medicine Questionnaire, BMQ), [56, 57] cognitive function (verbal fluency test, VFT)[59] and depressive symptoms (Geriatric Depression Scale, GDS) [60, 61] – GDS and VFT will be reported elsewhere.

Sample size

Based on the results obtained in previous studies,[35, 74] a difference in the change values (MAI T1–T0) of at least 2 units between the treatment groups was considered clinically relevant. Based on the pilot study, a standard deviation of 6 units was expected, resulting in a Cohen's effect size d of 0.3 and representing a small effect size.[75] Assuming an intra-cluster correlation coefficient (ICC) of 0.03 at practice level [76] and an average cluster size of 7 patients, a total of 62 practices and 434 patients (31 practices and 217 patients per treatment arm) were required to detect such an effect with 80% power using a two-sample t-test at a two-sided significance level of α=0.05. The sample size calculation was performed using NCSS PASS 2008 (Inequality Tests for Two Means in a Cluster Randomised Trial). On the basis of an assumed drop-out rate of approximately 10%, the sample size was adjusted to a total of 70 practices and 490 patients (35 practices and 245 patients in each treatment group).

Statistical analysis

We performed descriptive analyses of the primary endpoint, the secondary endpoints, and all patient and practice characteristics (separately for patients in both groups) and calculated mean and standard deviation for continuous variables, and relative and absolute frequencies for categorical data.

In the primary analysis and using a two-sided significance level of α=0.05, we tested the null hypothesis H0: $\mu1 = \mu2$ (the mean difference MAI T1–T0 is the same in both groups) against the

alternative hypothesis H1: $\mu 1 \neq \mu 2$ (the mean MAI T1–T0 differs). Because of cluster randomisation, we used a multilevel regression approach with patients at level one and practices at level two. The primary model included treatment group and MAI baseline as fixed factors and practice as a random factor. In a mixed model, estimates are adjusted for the correlation of observations on the same level, whereby a specific structure has to be chosen. We applied the compound symmetry correlation structure on the assumption that a correlation exists between patients from the same practice and that a specific numerical value can be attached to this correlation. We assumed the value was 0 for the correlation with patients from other practices. The results are presented as the adjusted mean between-group difference in MAI T1–T0 with the corresponding 95% confidence interval. In addition, the practice-related ICC was estimated. The primary analysis was performed in accordance with the intention-to-treat principle,[77] and additional sensitivity analyses were conducted on a per-protocol analysis set. In the multilevel approach, we made use of the missing at random assumption that the baseline or the treatment variable can explain missing data in the response. No additional imputation of missing data was conducted. In a sensitivity analysis, we replaced missing values for the primary endpoint using the baseline observation carried forward (BOCF) approach. The statistical analyses of the secondary endpoints used the same multilevel approach as the primary analysis. A linear, binary or Poisson mixed model was fitted in accordance with the scaling of the considered endpoint. The obtained p-values in the secondary analyses are only interpreted exploratively. All evaluations were carried out using software package R (version 2.15.0 and higher),[78] in combination with the R-packages xtable,[79] nlme,[80] lme4,[81] multilevel,[82] and psychometric[83].

Results:

Participant flow and non-responders

Of the 1,662 practice addresses we sent letters to (1,332 of them also received a phone call reminder), 1,325 did not reply at all, 102 answered but were not interested in further information, and 235 general practices asked for further details and were assessed for eligibility. Of those, 153 practices finally declined to participate, three did not meet inclusion criteria, and seven were not able to create screening lists using their practice computer. Of the 72 included practices, 3,478 IDs for potentially eligible patients were provided, from which a random sample of 1,346 IDs was drawn at the study centre and sent to the practices. In total, 505 patients were consecutively included from the random sample and 465 completed the study (intervention group 238/252, control group 227/253) (flow chart: **web-appendix 3**).

Of the 1,325 practices that did not reply, we called 132 randomly selected practices. Six practices did not answer the phone, 51 were willing to answer all questions, and 75 provided partial information. Sixty-one interviewed practices (48%) were not eligible (seven were not active GPs; 51 had no internet access, and three declined to say). Practice characteristics and reasons for not responding are provided in **web-appendix 3**.

Baseline characteristics of participants

Most practices were single-handed (57%), medium-sized (64%), and located in small to mid-sized towns (57%). Slightly more male GPs (57%) participated; they were either specialists in general practice (83%) or in internal medicine. On average, they were 51 years of age, had more than 23 years of clinical experience, and had worked in private practice for about 15 years. With one exception, HCAs were female. They averaged about 40 years of age, had about 17 years of clinical experience, and had worked in the practice at various employment levels (49% less than full time) for an average of 10 years. About three-quarters were qualified HCAs. Patients were slightly more often female (52%), had a median age of 72 years, and averaged eight prescriptions in nine single doses per day. Almost all patients were covered by statutory health insurance (96%), and looked after themselves (94%). 58% participated in one of the national disease management programs (DMP). Overall, baseline characteristics were well balanced in both groups (**Table 1**).

[About here: Table 1: Baseline characteristics of practices and patients]

Outcomes

Our study found the intervention to have no significant effect. The mean MAI sum scores had decreased minimally in both groups six months after baseline – by 0.3 points in the intervention group and 0.8 points in the control group – revealing a non-significant adjusted mean difference of 0.7 (95% CI -0.2 to 1.6) points in favour of the control group (ITT, per protocol analysis and BOCF approach did not differ). To control for the effects of oversampled patients registered in a DMP, we compared DMP participants with non-participants, which revealed no effects on MAI. Furthermore, socio-demographic factors did not have an influence (**Table 2**).

[About here: Table 2: Intention to treat analysis of primary and secondary outcomes and sensitivity analyses]

To explore our results, we conducted additional, non-prespecified analyses. As the sample size was not sufficiently large to perform subgroup analyses, we calculated multilevel models, which revealed strong effects of the baseline values of MAI sum scores on the primary outcome MAI T1-T0 ($p < 0.001$) (**Figure 2a**)**.** The figure also shows the low proportion of patients with high inappropriateness at baseline, and the size and direction of the MAI changes in both groups after six months. To explain the relationship between the number of prescriptions and MAI values, we conducted exploratory regression analysis, which approximately revealed a square function (**Figure 2b**).

[About here:

Figure 2 – Distribution and changes in the medication appropriateness index (MAI) using baseline values and number of prescriptions

Figure 2a (upper image): Changes in MAI scores in intervention and control groups six months after baseline compared to baseline values (absolute numbers of study participants and boxes and whiskers per subgroup are provided)

Figure 2b (lower image): MAI scores at baseline in terms of the number of prescriptions (higher diameters of drops represent higher numbers of study participants)]

Secondary outcomes showed small, non-significant changes. In the intervention group, patients' self-reported quality of life improved minimally (about 2.3% in EQ-5D, 0.5 years in both expected and desired lifetime) after six and nine months, whereas it continued to decline in the control group (**Figure 3**). Additionally, in the intervention group the mean number of hospital stays decreased and the mean number of days spent in hospital had dropped by half after six months, but in both groups the event rate was too small to show significant differences (intention-to-treat analyses of the primary and secondary outcomes: **Table 2**, descriptive analysis of symptoms for potential adverse drug reactions (ADR): **Web-appendix 4**).

[About here: Figure 3: Secondary outcomes related to patients' self-reported quality of life measures]

Discussion:

Key findings of the study

This study found the complex PRIMUM intervention to have no significant effects in older patients with multimorbidity and polypharmacy in general practice. At baseline, many patients already received appropriate prescriptions and enjoyed good quality of life and functional status. We can therefore conclude that in our study, there was not enough scope for improvement.

Strengths and limitations of study

The systematic development and stepwise evaluation of the PRIMUM intervention in accordance with MRC guidance on complex interventions[84] was a strength as demonstrated by refinements in the design of the main trial, based on the results of pilot testing.[35] Recruitment to target, random sampling of patients, minimal attrition (we lost one cluster to follow-up because the GP moved to another town), and adherence to the protocol are additional strengths when compared with previous studies.[85, 86] However, our study also had several limitations.

Firstly, there is no agreed definition of polypharmacy and patient inclusion at the numerical threshold of ≥5 prescriptions was somewhat arbitrary,[87, 88] but using a higher threshold would have meant losing patients whose medication was highly inappropriate (Figure 2b). Moreover, the association between the number of prescriptions and health outcomes is not linear: Payne and co-authors found only the most extreme levels of polypharmacy to be associated with increased admission rates in patients with multimorbidity,[89] while Gnjidic and her co-researchers identified the best discriminating threshold to be between 4.5 and 6.5 medicines for associations with frailty, disability, mortality, and falls.[90]

Secondly, our study population may limit the generalisability of the results. Our study was population-based and involved no pre-selection, and the response rate of practices was low. We cannot rule out that relatively ambitious GPs volunteered more frequently. As far as the choice of patients is concerned, we took a random sample within each practice and our selection criteria aimed at including a broad range of diseases involving as many organ systems as possible. We

applied the cognition test during recruitment and after consent. As our ultimate aim was to promote regular practice consultations, we excluded patients with dementia. The study required that patients who were unable to fill in questionnaires or to answer telephone calls should not attend (e.g., some nursing home residents and migrants). These groups may therefore have been under-represented. To enable random sampling, we applied a systematic case finding using prescription costs as a proxy but oversampled DMP participants. However, German DMPs do not address multimorbidity or polypharmacy and we did not find any DMP impact on outcomes in our study.

Thirdly, our outcome measures were slightly insensitive. In the intervention group, the increase in the average number of prescriptions indicates that GPs had more often begun to prescribe patients a new medicine. If undertreatment had been a key problem in our study, having the MAI as the main outcome variable would have led us to underestimate its impact, because it does not reliably detect underuse.[42] It is noteworthy that the number of medicines used in intervention and control groups had diverged after 6 and 9 months, with the adjusted mean number of drugs being 1.0 higher in the intervention group (Table 2). Figure 2b shows that the more drugs a physician prescribes, the greater the chance that the MAI score will increase. The intervention may have induced increased prescribing of medicines (e.g. in case of otherwise undetected underuse), which may explain the trend towards smaller reductions of the MAI scores in the intervention group.

Fourthly, our efforts to reduce contamination of controls by using a cluster-randomised design and withholding intervention details may have been substantially offset by a potentially important Hawthorne effect, as has been noted in other studies.[85, 91] GPs and HCAs collected extensive data on medication, diseases and laboratory parameters (see icon 'f' in Figure 1) at each study visit. It can be assumed that data collection will have had the same effect as the structured medication reviews: we also observed improvements in MAI mean values in the control group at the first follow-up (Figure 2a), and a slight decrease in the average numbers of prescriptions. The net effect was that the decrease in MAI scores in the control group was slightly larger than in the intervention group where it had been partly offset by an increase in the number of prescriptions (and higher MAI scores) resulting from identified underuse. However, the differences were very small.

Comparison with other studies

Most primary care studies have investigated pharmacist-led interventions, and have shown inconclusive results in various outcomes.[33, 92-96] However, pharmacist-led interventions may be difficult to implement in health care contexts in which pharmacists have no access to clinical information (e.g. patients' diagnoses, laboratory tests), patients often visit many different

pharmacies, and inter-professional relationships between GPs and pharmacists are not well established, as in Germany.[85, 86] In this context in particular, information technology systems have been identified by European GPs as supporting safer prescribing.[97-99] Further factors that have been addressed include support from other health care professionals such as nurses, systematic medication reviews, and greater involvement of the patient.[97-99] However, the efficacy of these measures is inconclusive: Olsson and co-investigators found that a physician-led medication review had no effect on indicators of high-risk prescribing in older patients with polypharmacy.[100] In contrast, a large-scale cluster-randomised controlled trial achieved reductions in unintentional drug duplications, drug-drug interactions, and new prescriptions of potentially inappropriate medications, but failed to show an impact on the discontinuation of inappropriate medicines.[101]

No evidence yet exists that polypharmacy interventions lead to decrease in mortality and hospitalisations,[94] functional decline and falls,[102, 103] and health-related quality of life[85, 86, 100, 104-107]. A recent meta-analysis revealed a modest reduction in the number of drugs (on average -0.2 in the intervention group vs.+0.2 in controls) but the results of the included studies differed widely [94] and, considering the frequency and potential impact of medication underuse,[6-8] a reduction in net prescription numbers is an ambiguous study endpoint.

Possible explanations and implications of the study

Our study showed the intervention to have no significant effect. We cannot rule out that there was not enough scope for improvement in our study (Figure 2a: the MAI of the patients included in the left two box plots in both groups could not improve). Additionally, there was a relevant Hawthorne effect (Figure 2a: the patients included in the four box plots of the control group on the right hand side also improved). The patients depicted in the four box plots of the intervention group on the right hand side (Figure 2a) improved less than corresponding patients in the control group, which probably reflects the small numbers of patients and the lack of an intervention effect. In addition, given the MAI's inability to detect changes in inappropriate underuse, it may have not been sensitive enough for the purpose of our study. As any newly prescribed drug worsens the MAI score, unless it is completely appropriate, this may at least partially explain the difference. Ongoing process evaluation concerning medication changes may provide further explanations of the outcomes and information on the implications of the study.

Further research is needed to identify patients that stand to benefit significantly from an intervention that aims to support the care of complex patients with multimorbidity and high treatment

burden.[108, 109] Future studies may also benefit from considering a refined choice of outcome measures that adequately takes underuse into account.

Conclusion

We did not find the intervention to have significant effects. Many patients already received appropriate prescriptions and enjoyed good quality of life and functional status. We can therefore conclude that in our study, there was not enough scope for improvement. Further research should seek to identify groups of patients that are most likely to benefit from such resource-intensive interventions. Outcome measures should be patient-relevant and detect changes in underuse.

(Statements)

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Ethics approval: The ethics commission of the medical faculty of the Johann Wolfgang Goethe University, Frankfurt / Main approved the study (resolution number E 46/10, file number 123/10, date: 20/05/2010) and all of the participants gave their written informed consent before taking part.

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Transparency declaration: Christiane Muth affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies between information contained in the trial registration and the actual study have been explained.

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- Muth C, Uhlmann L, Haefeli WE, Rochon J, van den Akker M, Beyer M, Perera R, Knottnerus A, Gerlach FM, Harder S (2014) PRIorisierung von MUltimedikation bei Multimorbidität (PRIMUM)* Cluster-RCT in Hausarztpraxen zeigte keine Effekte auf die Angemessenheit der Verschreibung. 48. Kongress der DEGAM, 18.-20.09.2014, Hamburg; Abstractband V3c | 3, S. 88.
- Muth C, Rochon J, Namyst A, Fullerton B, Harder S, van den Akker M, Perera-Salazar R, Gerlach FM, Beyer M. Anwendung der MRC Guidance in der allgemeinmedizinischen Forschung: Ergebnisse aus der PRIMUM-Studie (PRIorisierung von MUltimedikation bei Multimorbidität. Vortrag auf 13. Jahrestagung des Deutschen Netzwerks Evidenzbasierte Medizin, Hamburg, 15.–17.03.2012, Abstractband IV/1a

Table 1: Baseline characteristics of practices and patients

	Control group	Intervention group
Practices	**n=36**	**n=36**
Practice characteristics		
Location (number, percentage):		
City (>100,000 inhabitants)	16 (44)	6 (17)
Mid-sized town (20,000 to 100,000)	6 (17)	10 (28)
Small town (5,000 to 20,000)	10 (28)	15 (41)
Rural area (<5,000 inhabitants)	4 (11)	5 (14)
Single-handed practices (number, percentage)	21 (58)	20 (56)
Panel size‡ (number, percentage):		
Fewer than 1,000	11 (31)	12 (33)
1,000-1,499	14 (39)	11 (31)
1,500 or more	11 (31)	13 (36)
General practitioners		
Age (mean, SD)	50.2 ± 7.6	51.9 ± 7.0
Male sex (number, percentage)	21 (58)	20 (56)
Board certificate GP (number, percentage)	30 (83)	30 (83)
Years of clinical experience (mean, SD)	22.6 ± 8.6	23.3 ± 7.9
Years at practice site (mean, SD)	14.3 ± 9.1	15.7 ± 8.4
Health care assistants		
Age (mean, SD)	40.1 ± 8.8	37.8 ± 12.6
Female sex (number, percentage)	36 (100)	35 (97)
Fully qualified HCA (number, percentage)	25 (69)	27 (75)
Years of professional experience (mean, SD)	18.4 ± 9.3	15.9 ± 10.6
Years at practice site (mean, SD)	10.4 ± 8.2	9.6 ± 8.5
Full-time employment (number, percentage)	17 (47)	20 (56)
Cluster size (median number of patients, range)	7 (6 to 8)	7 (6 to 8)
Patients	**n=253**	**n=252**
Sociodemographics		
Age (mean, SD)	71.7 ± 7.4	72.5 ± 6.5
Female sex (number, percentage)	131 (52)	133 (53)
Covered by statutory health insurance (number, percentage)	243 (96)	243 (96)
Participation in a DMP (number, percentage)	139 (55)	153 (61)
Consultation with specialists in previous six months (number, percentage)	222 (88)	227 (90)
Living with spouse: yes (number, percentage)	166 (67)	152 (61)
Fending for themselves (number, percentage)	236 (94)	237 (94)
Home care situation rated as 'good' or 'very good' in GP assessment (number, percentage)	233 (92)	239 (95)
CASMIN educational classification (number, percentage):		
High	25 (10)	14 (6)
Middle	80 (32)	66 (27)
Low	144 (58)	169 (68)
Morbidity and medication		
Charlson comorbidity score (mean, SD)	3.2 ± 2.4	3.0 ± 2.0

		Control group	Intervention group
	CIRS sum score (mean, SD)	7.3 ± 4.3	8.1 ± 4.8
	CIRS number of affected organ systems (mean, SD)	4.4 ± 2.3	4.6 ± 2.4
	Potential ADR symptoms† (number, percentage):		
	Bleeding diathesis#	44 (17)	33 (13)
	Ankle edema	78 (31)	84 (33)
	Dizziness#	54 (21)	54 (21)
	Dyspnea#	86 (34)	70 (28)
	Difficulties urinating	51 (20)	64 (25)
	Abdominal pain#	36 (14)	37 (15)
	Tachycardia or palpitation#	36 (14)	36 (14)
	Nausea or vomiting#	16 (6)	11 (4)
Others			
	BMI (mean, SD)	30.3 ± 7.5	30.1 ± 5.6
	Geriatric Depression Scale (mean, SD)	2.4 ± 2.3	2.3 ± 2.2
	Verbal Fluency Test (mean, SD)	19.1 ± 5.6	18.6 ± 5.8

‡The number of patient registrations in a practice over a 3-month period, †for details see Figure 1, item "h", #symptoms appeared on at least several or almost every day;
Abbreviations: ADR – adverse drug reaction, BMI – body mass index, CASMIN - Comparative Analysis of Social Mobility in Industrial Nations, CIRS - Cumulative Illness Rating Scale, GP – general practitioner, HCA – health care assistant, SD – Standard Deviation

Table 2: Intention to treat analysis of primary and secondary outcomes and sensitivity analyses

	Control group		Intervention group				
	n_c	Mean (SD)	n_i	Mean (SD)	Adjusted difference (95% CI)	ICC/ICC_{adj}	P
Medication appropriateness index (MAI)							
MAI, Baseline (T0)	253	4.6 (5.8)	252	4.8 (5.4)	-	-	-
No. of prescriptions rated with MAI, Baseline#	253	7.8 (2.3)	252	8.0 (2.6)			
Primary outcome							
MAI, 6 months (T1)	243	3.8 (4.3)	241	4.6 (5.5)	MD: 0.7 (-0.2 to 1.6)*	0.016/0.017	0.137
No. of prescriptions rated with MAI, 6 months#	243	7.6 (2.2)	241	8.1 (2.8)	RR: 1.0 (1.0 to 1.1)	0.067/-	0.354
Secondary outcome							
MAI, 9 months (T2)	228	3.9 (4.9)	238	4.8 (5.2)	MD 0.6 (-0.5 to 1.7)*	0.000/0.000	0.272
No. of prescriptions rated with MAI, 9 months#	228	7.7 (2.3)	238	8.1 (3.0)	RR: 1.0 (1.0 to 1.1)	0.075/-	0.497
Sensitivity analysis							
DMP non-participants:							
MAI, baseline	114	4.1 (5.2)	99	3.8 (3.8)	-	-	-
MAI, 6 months	110	3.5 (4.2)	92	4.2 (4.7)	MD: 0.7 (-0.4 to 1.9)*	0.000/0.000	0.200
MAI, 9 months	103	4.5 (5.7)	91	4.5 (5.1)	MD: 0.1 (-1.5 to 1.6)*	0.000/0.000	0.939
DMP participants:							
MAI, baseline	139	5.1 (6.2)	153	5.4 (6.1)	-	-	-
MAI, 6 months	133	4.0 (4.5)	149	4.8 (5.9)	MD: 0.7 (-0.6 to 1.9)*	0.006/0.010	0.295
MAI, 9 months	125	3.5 (4.0)	147	4.9 (5.3)	MD: 1.1 (0.0 to 2.2)*	0.000/0.000	0.049
Secondary outcomes on quality of life-related measures							
EQ-5D index (percentage)							
Baseline	240	74.9 (23.0)	241	73.9 (24.4)	-	-	-
6 months	225	73.2 (24.8)	229	73.9 (23.8)	MD: 1.4 (-2.5 to 5.3)	0.080/0.082	0.471
9 months	214	72.8 (25.1)	222	74.8 (23.4)	MD: 2.3 (-1.6 to 6.2)	0.049/0.048	0.247

	Control group		Intervention group				
	n_c	Mean (SD)	n_i	Mean (SD)	Adjusted difference (95% CI)	ICC/ICC_{adj}	P
Expected life duration (years)							
Baseline	200	11.6 (6.9)	209	10.3 (6.9)	-	-	-
6 months	200	12.0 (7.1)	202	11.0 (7.3)	MD: 0.0 (-1.1 to 1.1)	0.000/0.000	0.987
9 months	184	12.3 (7.0)	195	11.7 (7.9)	MD: 0.5 (-1.3 to 2.4)	0.185/0.192	0.588
Desired life duration (years)							
Baseline	207	16.5 (9.1)	218	15.2 (8.9)	-	-	-
6 months	196	16.6 (9.1)	200	15.2 (8.7)	MD: -0.4 (-1.6 to 0.7)*	0.000/0.000	0.423
9 months	180	16.8 (9.2)	195	16.4 (9.8)	MD: 0.5 (-0.9 to 1.8)	0.078/0.081	0.479
Secondary outcomes on functional status, pain and hospitalisation							
Functional status (VES-13)							
Baseline	228	3.0 (2.9)	223	2.6 (2.7)	-	-	-
6 months	217	3.0 (2.9)	222	2.6 (2.8)	MD: 0.1 (-0.3 to 0.5)	0.000/0.000	0.681
9 months	199	2.7 (2.8)	204	2.8 (2.8)	MD: 0.4 (0.0 to 0.8)	0.051/0.043	0.047
Pain (von Korff index)							
Baseline	197	1.7 (1.3)	204	1.7 (1.2)	-	-	-
6 months	184	1.7 (1.4)	198	1.8 (1.2)	MD: 0.2 (-0.1 to 0.4)*	0.000/0.000	0.135
9 months	168	1.6 (1.2)	194	1.7 (1.2)	MD: 0.0 (-0.2 to 0.3)	0.004/0.006	0.782
Number of hospital stays							
Baseline	40	1.4 (0.7)	42	1.7 (1.0)		-	-
6 months	45	1.4 (0.7)	34	1.4 (0.5)	RR: 1.2 (0.6 to 2.3)	0.000 / -	0.646
9 months	25	1.2 (0.4)	28	1.3 (0.6)	RR: 1.0 (0.3 to 3.1)	0.000 / -	0.949
Number of days spent in hospital							
Baseline	40	14.9 (12.9)	42	19.0 (12.2)	-	-	-
6 months	45	13.1 (11.5)	34	9.8 (8.9)	RR: 1.1 (0.5 to 2.3)	0.894 / -	0.850
9 months	25	9.7 (8.2)	28	28 (11.6)	RR: 0.4 (0.1 to 2.8)	0.859 / -	0.336
Secondary outcomes of adherence and related measures							
Self-reported adherence							

	Control group		Intervention group				
	n_c	Mean (SD)	n_i	Mean (SD)	Adjusted difference (95% CI)	ICC/ICC_{adj}	P
Baseline	252	3.7 (0.8)	250	3.7 (0.6)	-	-	-
6 months	238	3.8 (0.5)	237	3.6 (0.8)	MD: -0.1 (-0.2 to 0.0)	0.005/0.002	0.044
9 months	225	3.7 (0.6)	231	3.7 (0.7)	MD: 0.0 (-0.2 to 0.1)	0.005/0.007	0.629
Observed adherence: Drug score (no. and percentage of deviating patients)							
Baseline	251	101 (40.2%)	250	87 (34.8%)	-	-	-
6 months	237	101 (42.6%)	237	78 (32.9%)	OR: 0.7 (0.5 to 1.0)	0.000/0.000	0.051
9 months	224	88 (39.3%)	231	85 (36.8%)	OR: 0.9 (0.6 to 1.4)	0.010/0.009	0.736
Observed adherence: Dose score (no. and percentage of deviating patients)							
Baseline	251	125 (49.8%)	248	134 (54%)	-	-	-
6 months	235	128 (54.5%)	236	136 (57.6%)	OR: 1.1 (0.7 to 1.6)*	0.000/0.000	0.756
9 months	222	121 (54.5%)	229	145 (63.3%)	OR: 1.4 (0.9 to 2.0)*	0.013/0.005	0.119
Observed adherence: Regimen score (no. and percentage of deviating patients)							
Baseline	251	124 (49.4%)	249	131 (52.6%)	-	-	-
6 months	235	117 (49.8%)	236	134 (56.8%)	OR: 1.3 (0.8 to 2.0)*	0.057/0.051	0.297
9 months	222	114 (51.4%)	229	137 (59.8%)	OR: 1.4 (0.9 to 2.1)*	0.050/0.042	0.148
Number of prescriptions							
Baseline	253	8.0 (2.4)	252	8.1 (2.8)	-	-	-
6 months	242	7.8 (2.3)	241	8.4 (3.0)	RR: 1.0 (1.0 to 1.1)*	0.097 / -	0.183
9 months	227	7.8 (2.2)	238	8.4 (3.2)	RR: 1.0 (1.0 to 1.1)*	0.100 / -	0.310
Number of single doses:							
Baseline	253	9.2 (3.5)	252	9.4 (4.1)	-	-	-
6 months	242	8.9 (3.3)	241	9.4 (4.1)	RR: 1.0 (1.0 to 1.1)*	0.183/-	0.573

	Control group		Intervention group				
	n_c	Mean (SD)	n_i	Mean (SD)	Adjusted difference (95% CI)	ICC/ICC_{adj}	P
9 months	227	9.0 (3.6)	238	9.4 (4.4)	RR: 1.0 (0.9 to 1.1)*	0.212/-	0.761
MRCI							
Baseline	253	26.9 (12.3)	252	28.4 (14.3)	-	-	-
6 months	242	26.3 (12.2)	241	28.6 (14.3)	MD: 0.7 (-0.7 to 2.1)*	0.030/0.032	0.308
9 months	227	26.3 (11.9)	238	29.1 (15.6)	MD: 1.0 (-0.6 to 2.5)*	0.042/0.042	0.212
Man Song Hing scale							
Baseline	241	8.4 (3.4)	246	8.6 (3.4)	-	-	-
6 months	233	8.6 (3.2)	233	8.4 (3.4)	MD: -0.1 (-0.7 to 0.5)	0.047/0.050	0.789
9 months	219	8.8 (3.5)	231	8.7 (3.7)	MD: -0.2 (-1.0 to 0.5)	0.041/0.041	0.519
BMQ, specific necessities							
Baseline	233	22.1 (3.3)	240	22.1 (3.1)	-	-	-
6 months	219	22.0 (2.9)	230	21.8 (3.5)	MD: -0.2 (-0.8 to 0.4)	0.043/0.046	0.557
9 months	207	21.6 (3.6)	226	21.9 (3.4)	MD: 0.3 (-0.4 to 1.0)	0.000/0.000	0.349
BMQ, specific concerns							
Baseline	229	13.4 (5.2)	238	13.4 (5.2)	-	-	-
6 months	223	13.1 (4.8)	227	12.8 (4.8)	MD: -0.2 (-1.0 to 0.7)	0.021/0.023	0.714
9 months	211	12.6 (5.0)	226	12.5 (5.1)	MD: 0.1 (-0.8 to 1.0)	0.044/0.047	0.838
BMQ, general overuse							
Baseline	237	10.5 (3.5)	241	10.5 (3.7)	-	-	-
6 months	229	10.4 (3.6)	226	10.4 (3.4)	MD: -0.2 (-0.8 to 0.5)	0.048/0.050	0.637
9 months	213	10.5 (3.6)	225	10.6 (3.6)	MD: 0.0 (-0.7 to 0.6)	0.054/0.057	0.917
BMQ, general harms							
Baseline	239	8.0 (3.0)	245	7.9 (3.0)	-	-	-
6 months	229	7.9 (2.8)	234	7.9 (3.2)	MD: 0.1 (-0.4 to 0.6)	0.000/0.002	0.631
9 months	214	8.2 (3.1)	232	8.0 (3.2)	MD: -0.2 (-0.8 to 0.4)	0.045/0.047	0.602

n_c / n_i – number of patients in control group / intervention group; SD - standard deviation; MD – mean differences, OR – Odds Ratio, and RR – Relative Risk are provided with 95% confidence intervals (CI), and adjusted for clustering effects and baseline. ICCs are provided as crude values using a mixed model without any adjustment (either group or baseline). The adjusted values use a mixed model that includes the group variable. P-values are adjusted for cluster effects and

baseline. #Phytopharmaceuticals, homeopathic and other complementary and alternative medicine products were excluded from rating. *control group tended to perform better.

Abbreviations: BMQ – Beliefs about Medicine Questionnaire, CIRS - Cumulative Illness Rating Scale, DMP – Disease Management Program, EQ-5D – EuroQuol five dimensions, MAI – Medication Appropriateness Index, MRCI – Medication regimen Complexity Index, VES-13 – Vulnerable Elderly Survey-13 items

List of Tables and Figures:

Table 1: Baseline characteristics of practices and patients

Legend: ‡The number of patient registrations in a practice over a 3-month period, †for details see Figure 1, item "h", #symptoms appeared on at least several or almost every day;
Abbreviations: ADR – adverse drug reaction, BMI – body mass index, CASMIN - Comparative Analysis of Social Mobility in Industrial Nations, CIRS - Cumulative Illness Rating Scale, GP – general practitioner, HCA – health care assistant, SD – Standard Deviation

Table 2: Intention to treat analysis of primary and secondary outcomes and sensitivity analyses

Legend: n_c / n_i – number of patients in control group / intervention group; SD - standard deviation; MD – mean differences, OR – Odds Ratio, and RR – Relative Risk are provided with 95% confidence intervals (CI), and adjusted for clustering effects and baseline. ICCs are provided as crude values using a mixed model without any adjustment (either group or baseline). The adjusted values use a mixed model that includes the group variable. P-values are adjusted for cluster effects and baseline. #Phytopharmaceuticals, homeopathic and other complementary and alternative medicine products were excluded from rating. *control group tended to perform better.

Abbreviations: BMQ – Beliefs about Medicine Questionnaire, CIRS - Cumulative Illness Rating Scale, DMP – Disease Management Program, EQ-5D – EuroQuol five dimensions, MAI – Medication Appropriateness Index, MRCI – Medication regimen Complexity Index, VES-13 – Vulnerable Elderly Survey-13 items

Figure 1: PaT plot [70] of the PRIMUM trial.

Abbreviations: GP - general practitioner; HCA - health care assistant; †structured symptoms of side effects: dizziness, dyspnea, tachycardia / palpitations, nausea / vomiting, abdominal pain, bleeding diathesis, difficulties urinating, ankle oedema - frequency expressed as occurrence on one day / several days / almost every day during the past two weeks.

Figure 2: Distribution and changes in the medication appropriateness index (MAI) using baseline values and number of prescriptions

Figure 2a (upper image): Changes in MAI scores in intervention and control groups six months after baseline compared to baseline values (absolute numbers of study participants and boxes and whiskers per subgroup are provided)

Figure 2b (lower image): MAI scores at baseline in terms of the number of prescriptions (higher diameters of drops represent higher numbers of study participants)

Figure 3: Secondary outcomes related to patients' self-reported quality of life measures

Supplemental files:

- Web-appendix 1: study protocol
- Web-appendix 2: Medication Monitoring List (MediMoL) – checklist used by health care assistants
- Web-appendix 3: CONSORT flowchart and practice characteristics of non-responders
- Web-appendix 4: Symptoms for potential adverse drug reactions (ADR) - descriptive analysis
- CONSORT and TIDieR checklists

List of abbreviations

ADR	Adverse Drug Reaction
BMI	Body Mass Index
BMQ	Beliefs about Medicines Questionnaire
CASMIN	Comparative Analysis of Social Mobility in Industrial Nations
CDSS	Computerized Decision Support System
CIRS	Cumulative Illness Rating Scale
CRF	Case Report Form
DS	Drug Score
DoS	Dose Score
GDS	Geriatric Depression Scale
GP	General Practitioner
ICC	Intra-Cluster Correlation-coefficient
ID	Identifier
ITT	Intention To Treat
HCA	Health care assistant
MAI	Medication Appropriateness Index
MediMoL	Medication Monitoring List
MMSE	Mini Mental Status Exam
MRCI	Medication Regimen Complexity Index
RS	Regimen Score
SD	Standard Deviation

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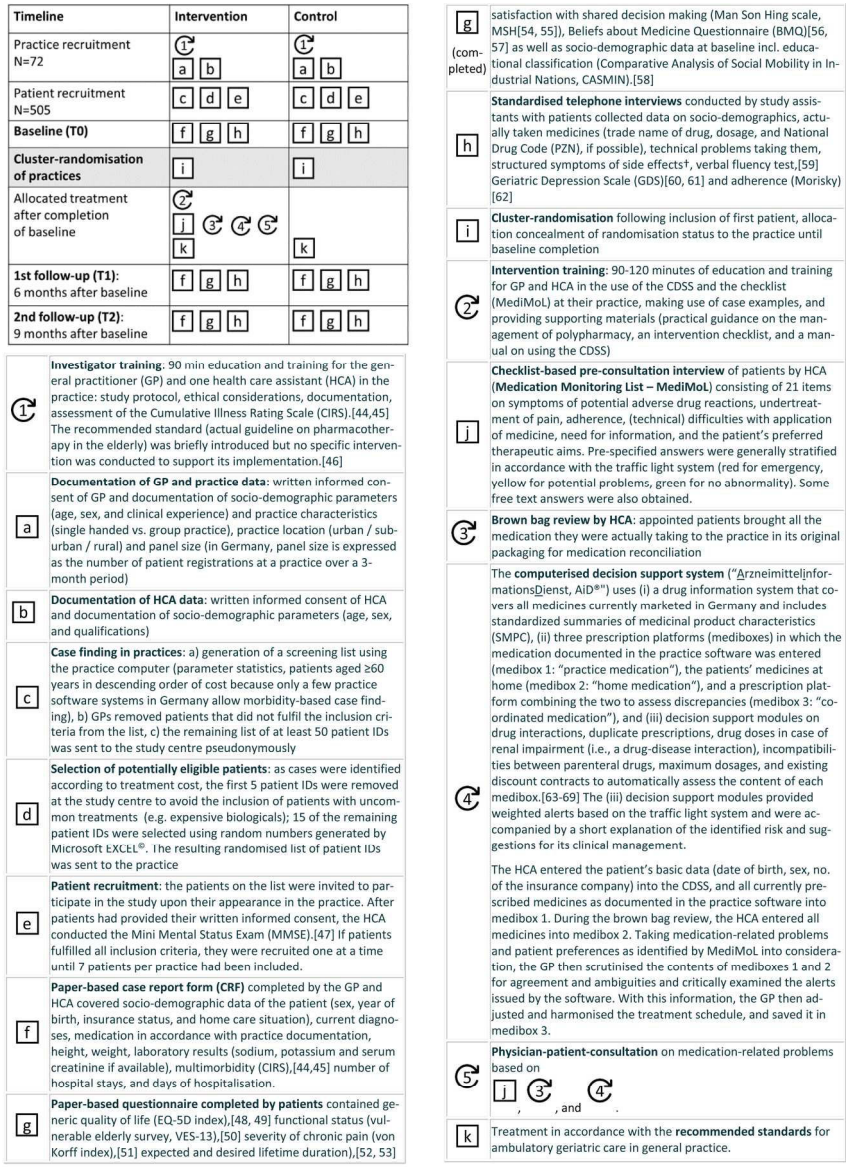

Figure 1: PaT plot [70] of the PRIMUM trial.

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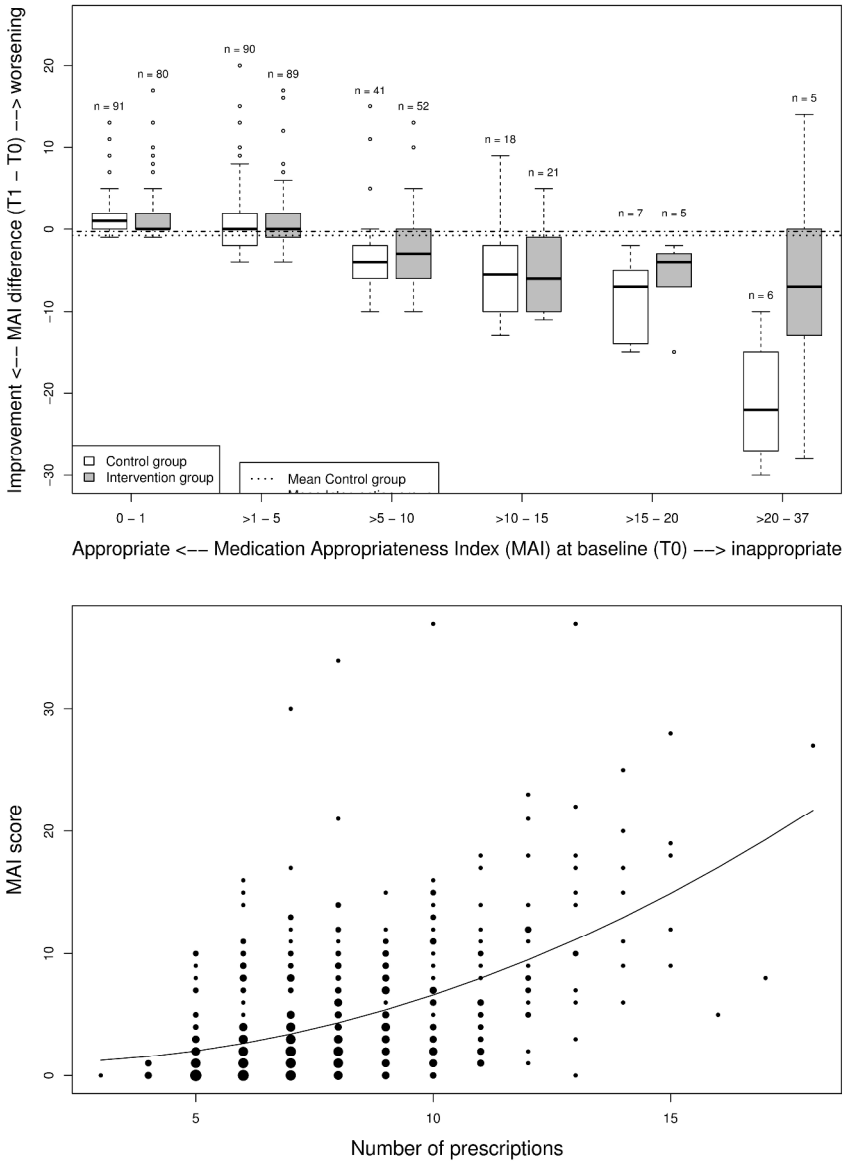

Figure 2: Distribution and changes in the medication appropriateness index (MAI) using baseline values and number of prescriptions

Figure 2a (upper image): Changes in MAI scores in intervention and control groups six months after baseline compared to baseline values (absolute numbers of study participants and boxes and whiskers per subgroup are provided)

Figure 2b (lower image): MAI scores at baseline in terms of the number of prescriptions (higher diameters of drops represent higher numbers of study participants)

381x519mm (300 x 300 DPI)

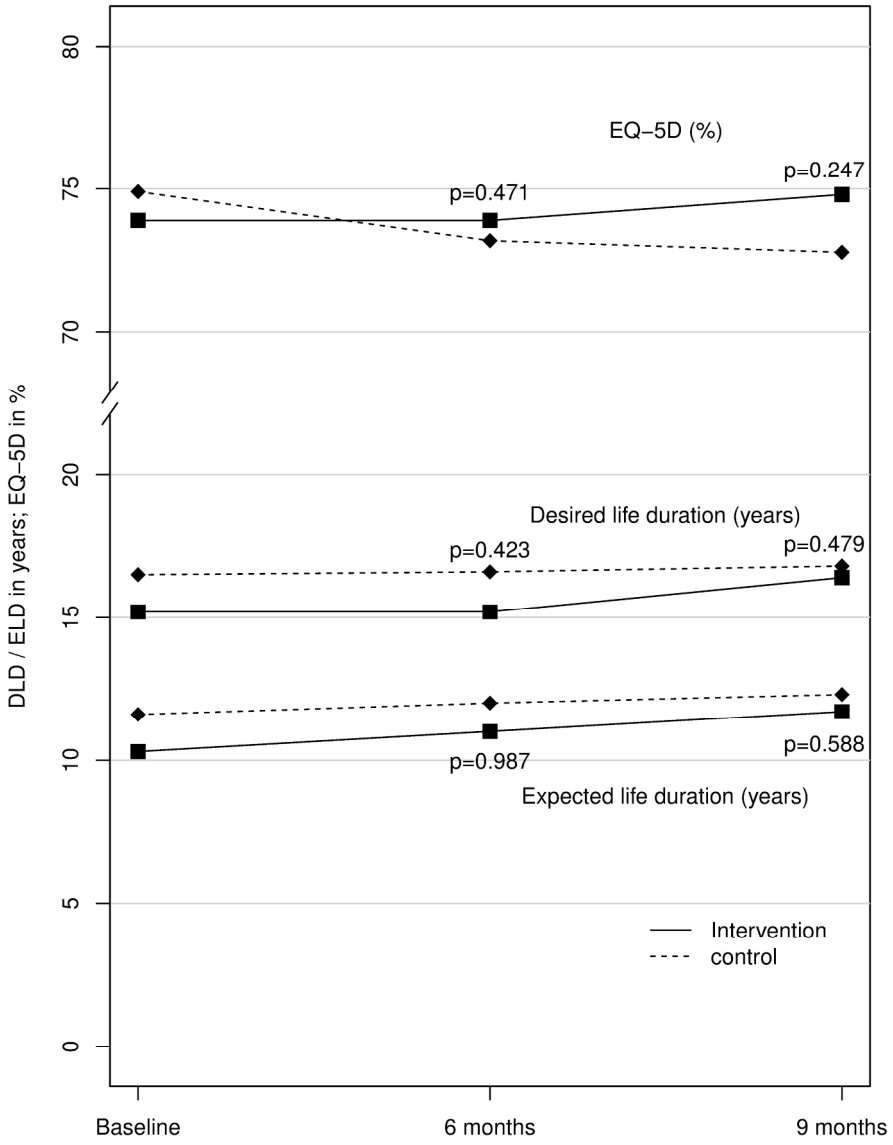

Figure 3: Secondary outcomes related to patients' self-reported quality of life measures

228x293mm (300 x 300 DPI)

Title:

Prioritising and optimising multiple medications in elderly multi-morbid patients in general practice. - A pragmatic cluster-randomised controlled trial.

[PRIMUM]

PRIoritising ***MU***ltimedication in ***M***ultimorbid patients

Sponsor: **Johann Wolfgang Goethe University Hospital, Frankfurt am Main**

Theodor-Stern-Kai 7
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The International Standard Randomised Controlled Trial Number (ISRCTN): (follows)

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Sponsor	German Federal Ministry for Education and Research (BMBF) Grant Number: 01GK0702 – Notification of 31.03.2009 and 08.02.2010

1.2 Signature Page

Prioritising and optimising multiple medications in elderly multi-morbid patients in general practice

PRIMUM - PRIoritising MUltimedication in Multimorbid patients [ISRCTN (follows)]

The study protocol (version 1.1, date: 20/07/2010) is approved by the following:

Principal Investigator:

Dr. med. Christiane Muth, MPH

Date	Signature

Co-Investigators:

Prof. Dr. F. Gerlach, MPH:

Date	Signature

Prof. Dr. med. Walter E. Haefeli:

Date	Signature

Prof. Dr. med. Sebastian Harder:

Date	Signature

Study Statistician:

Dipl.-Psych. Justine Rochon, M.Sc. Medical Biometry:

Date	Signature

On behalf of the Scientific Advisory Board:

Date	Signature

1.3 Signature Page for Participating General Practitioners

Prioritising and optimising multiple medications in elderly multi-morbid patients in general practice

PRIMUM - PRIoritising MUltimedication in Multimorbid patients [ISRCTN (follows)]

The study protocol (version 1.1, date: 20/07/2010) is approved by the following:

(to be signed by the investigator of each trial site before commencing the trial)

I herewith confirm that I have read and understood the present protocol and accept it in all its constituent parts. I agree to ensure that all the patients from my trial site who are included in the trial will be treated, observed and documented in accordance with all stipulations of the protocol and in accordance with the principles outlined in the Declaration of Helsinki.

Investigator:

Name, first name: _____

Practice stamp:

_____ _____

Date Signature

1.4 Synopsis of the Protocol

Principal investigator	Dr. Christiane Muth, MD, MPH; Institute for General Practice, Johann Wolfgang Goethe University, Frankfurt / Main
Sponsor	Johann Wolfgang Goethe University, Frankfurt / Main
Title of trial	Prioritising and optimising multiple medications in elderly multimorbid patients in general practice. - A pragmatic cluster-randomised controlled trial.
Abbreviated name of trial	PRIMUM: PRIoritization and optimization of MUltimedication in Multimorbid patients
Indication	Multimedication in elderly, multimorbid patients: Age ≥ 60, ≥ 3 chronic diseases, ≥ 5 long-term prescriptions
Objective	To investigate whether the complex intervention will improve the appropriateness of prescriptions in elderly multi-morbid patients
Intervention	Intervention: Healthcare assistant (HCA) and computer assisted optimization of multi-medication (complex intervention) in accordance with recommended standard[#] Control: Usual care in accordance with recommended standard[#] [#]Recommended standard: clinical practice guideline "Geriatrie" of the guideline group of Hesse (part 1 and 2)[1] Follow-up per patient: 9 months Study duration per patient: 9 months
Rationale	Key problems of multimedication in multimorbidity: 1. Multimorbidity, multimedication and increasing age raise the risk of inappropriate prescriptions and adverse drug reactions, and under-treatment. 2. Multimedication and high complexity of medication reduce adherence among patients. 3. Physician-patient consultations on medication related problems are dominated by doctors in content, focus mostly on effectiveness, and neglect side effects and strategies to manage them. 4. Patients do not generally inform doctors of adverse drug reactions and autonomous decisions to adjust medication dose. Key elements of intervention: Basic assessment of (1) medicines that were actually taken and (2) problems relating to medicines (technical handling, potential adverse drug reactions) and patient's therapeutic aims by HCA provides structured information in the Medication-Monitoring-List (MediMoL) for the general practitioner (GP) and enables patients to discuss their problems with the GP. (3) GP uses a computerized decision support system (pharmaceutical information system, AiD+) to optimize medication (reducing number of inappropriate prescriptions, e.g. pharmaceutical interactions, renal dose adjustments, duplicate prescriptions) and (4) prioritizes medication in the physician-patient consultation taking into consideration patient's preferences. Desired effects: → Prescriptions become more appropriate → Prescriptions become less complex → Prescriptions take the patient's perspective into account (avoidance of adverse drug reactions and under-treatment, patients' preferences are taken into account and priorised) → Patients are more likely to adhere to the doctor's therapy

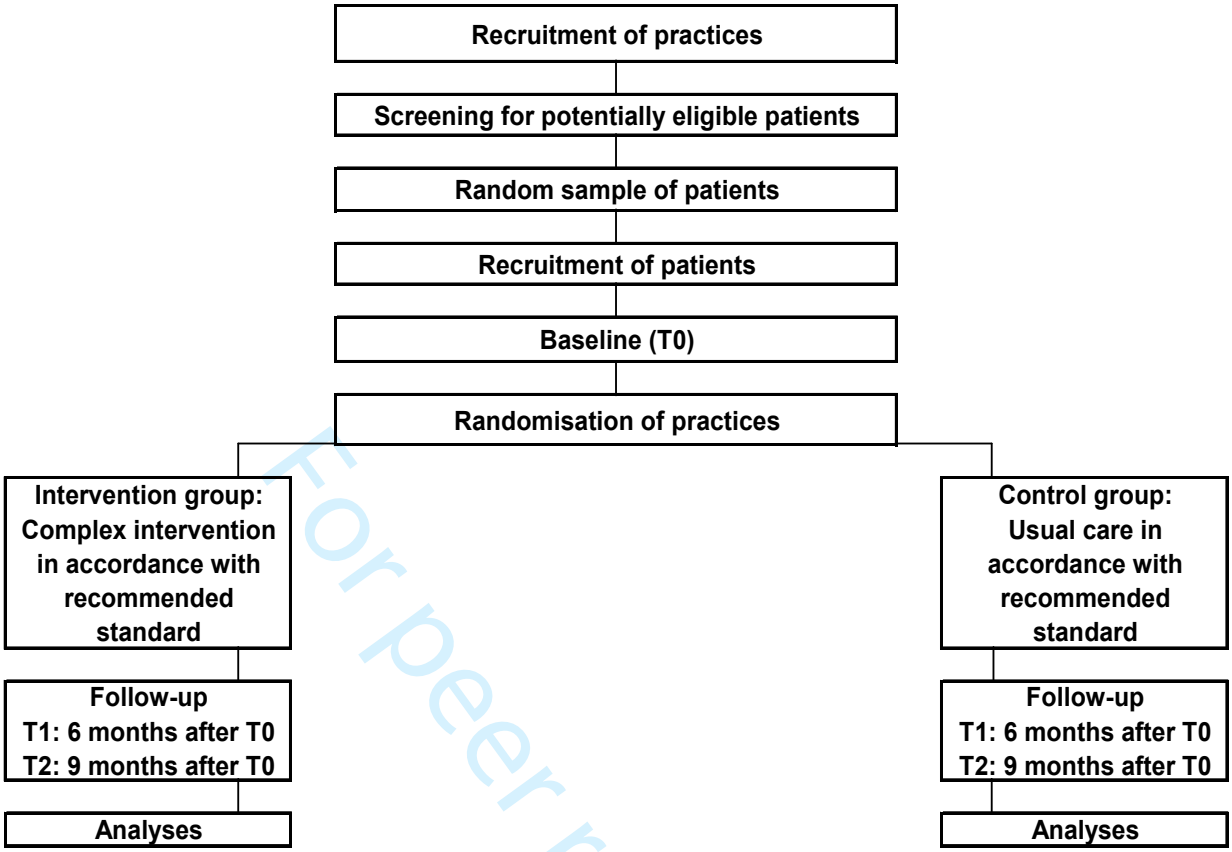
In- and exclusion criteria for trial sites (practices)	Inclusion criteria - General practice cares for patients covered by statutory health insurance and is active in primary care - Specialist doctor for general practice or internal medicine, or doctor with no specialist field. - Practice has internet access - Investigator's agreement to fulfil the contractual obligations arising from the trial - Investigator's agreement to the training of a HCA from the practice for the intervention, as required by the trial Exclusion criteria - Practice focuses on unconventional medical treatments - Practice focuses on special indications (e.g. HIV)
In- and exclusion criteria for patients	Inclusion criteria: - Age ≥ 60 and - ≥ 3 chronic diseases affecting ≥ 2 organ systems, requiring pharmaceutical treatment and - ≥ 5 long-term prescriptions with systemic effects and - Health care provided by GP (at least one contact in most recent quarter) and - Patient is legally competent to sign any documents and - Ability to understand and participate in trial of own free will, to fill out questionnaires and participate in telephone interviews as well as - Written informed consent to participate in trial Exclusion criteria: - Diseases cause life expectancy of < 12 months - Abuse of alcohol or illegal drugs and visible clinical signs or symptoms thereof - Cognitive disability that prevents trial participation (MMSE < 26) - emotional stress that prevents participation in trial - Participation in a clinical investigation within the last 30 days
Outcomes	Primary outcome: difference in Medication Appropriateness Index (MAI)-Score 6 months from baseline minus baseline (MAI T1–T0) Secondary outcomes: MAI T2-T0 and the difference in the following scores 6 and 9 months from baseline minus baseline (T1-T0 and T2-T0): EQ-5D, VES-13, all cause hospitalisation, medication adherence (observed: AS, DS, DoS, RS, self-reported: Morisky-Score), MRCI, BMQ, pain assessment (grade of severity of chronic pain in accordance with M. von Korff, J. Ormel et al. 1992), satisfaction with shared decision making (MSH), patient's future expectation, expected / desired lifetime duration, cognitive dysfunction (VFT), depression (GDS)
Study design	Pragmatic, cluster-randomised controlled trial with the general practice as the unit of randomisation to reduce treatment group contamination. Allocation concealment will be disclosed after baseline but before the intervention on practice level begins. Treatment allocation will be blinded to the pharmacologist (MAI rating) and the statistician. Primary and secondary outcomes will be measured at patient level.
Statistics	The primary analysis will be performed adhering to the intention-to-treat principle and will be based on the change in MAI from baseline (T0) to 6 months after baseline (T1), i.e. MAI T1–T0. Multilevel regression approach will be used to take into account the clustering of patients within practices. Treatment group will be considered fixed factor and variation between practices will be fitted as a random effect. The effect of intervention will be tested at the two-sided significance level of α=0.05. The results will be presented as the mean

	between-group difference in MAI T1–T0 with the corresponding 95% confidence interval. The practice related intracluster correlation coefficient (ICC) will be provided. Results from sensitivity analyses will serve to explain and interpret the results of the primary analysis. The statistical analyses of the secondary endpoints will use the same multilevel approach as the primary analysis. Only the result of the primary efficacy analysis will be interpreted in a confirmatory manner.
Number of trial sites and patients	Number of included general practices: 70 Number of general practices considered in analyses: 62 Number of potentially eligible patients (screening lists): 3.500 Number of included patients: 490 Number of patients considered in analyses: 434
Visits	Visit T0 (baseline), visit T1 (1st follow up 6 months after baseline), visit T2 (2nd follow up 9 months after baseline)
Potentially confounding factors	▪ Age, gender, marital status, lifestyle, socioeconomic status, household composition, housing indicators, house care ▪ Insurance status, participation in disease management programs ▪ Additional prescribers in treatment process ▪ Co-morbidity: Cumulative Illness Rating Scale (CIRS), Charlson-Comorbidity-Index, depression (GDS)
Schedule:	- Pre-phase (development of all trial plans, materials and implemented instruments, ethics vote, study registration): 01/03/2010 to 30/06/2010 - First practice in – last practice out: 01/07/2010 to 30/10/2011 - First patient in – last patient out: 01/08/2010 to 30/10/2011 - Recruitment: a) Practices: 01/07/2010 to 31/12/2010 b) Patients: 01/08/2010 to 31/01/2011 - Database Cleaning, analyses and publication: 01/11/2011 to 29/02/2012 - Total study duration: 01/03/2010 to 29/02/2012

1.5 Key words

Elderly, multimorbidity, polypharmacy, multimedication, medication appropriateness, cluster-randomised controlled trial, pragmatic trial

1.6 Flow chart



2 INTRODUCTION

2.1 Current situation and problem

Chronic conditions accounted for 47% of the global burden of disease in 2002 and are projected to account for about 60% by the year 2020.[2] Along with demographic changes and the change from infectious diseases that are increasingly often cured to chronic diseases the prevalence of multimorbidity increases. Studies carried out in primary care settings found an increase with all age groups from 10% in the 0–19-year-old age group up to 78% in subjects aged 80 and over in the Netherlands, and from 69% in 18–44 year olds up to 98% in those aged over 65 in Canada.[3,4] In 2002 in the U.S., Medicare beneficiaries with five or more chronic conditions accounted for 76% of Medicare expenditures.[5] Therefore, the problems associated with multiple chronic diseases are recognized as a leading healthcare problem.

Multiple disorders in patients are likely to result in multiple drug prescribing but may also result in under-treatment, in particular in the elderly: too little prescriptions or too low dosages have been reported in patients with multimorbidity/polypharmacy, asking for additional prescription(s).[6-10] The potential risks and harmful consequences of polypharmacy, such as drug-drug and drug-disease interactions which potentially cause adverse drug events (ADE), as well as the decreased adherence of patients to complex regimens of multiple medications, are research objectives in pharmacology and geriatrics.[11-13] Several studies investigated inappropriate prescribing and potentially preventable ADE.[14-16] In consequence, guidance on rational prescribing in multimorbid patients recommend a prudent, drug-sparing, and patient centred, not disease-oriented approach: clear therapeutic objectives, prioritisation according to the severity of diseases, efficacy and safety of available therapies, therapeutic individualisation and monitoring, patient implication and attention to their desires and expectations, and avoiding under-treatment.[1,11-13,17,18] Nevertheless, the implementation of these recommendations is still insufficient, as ongoing studies on the prevalence of inappropriate prescribing demonstrate. In our cross-sectional study in 18 general practices and 169 elderly multimorbid adults, patients received a median of 8 drug prescriptions (range 5-16).[19] We found non-considerations of drug-disease interactions in 15%, the necessity of renal dose adjustments in 23%, drug-drug interactions in 25% and an inappropriate choice and dosage of medicines with regard to age in 21% of the patients.[20] Major issues are the often lacking therapeutic goals and their prioritisation as well as inadequate communication with patients.[21,22]

2.2 Background

The risk of inappropriate prescriptions (interactions, non-consideration of renal dose adjustments and contraindications, inappropriate choice of medicines with regard to age and sex and associated discrepancies in terms of pharmacokinetics and -dynamics) rises with increasing age, multimorbidity and multimedication.[6,8,10,23] Inappropriate prescriptions are determining factors for adverse drug events, especially in the aged.[7] At the same time, the risk of under-prescribing rises in patients on multimedication regimes, and this should be avoided if the therapy is to be optimised.[9]

Multimedication and highly complex medication regimes are associated with poor therapy adherence among patients, whereby Horne et al. differentiate between unintended (e.g. technical problems with the intake of medicine, forgetting to take medicine – cognition) and

intended non-adherence (e.g. a lack of information about the aim of the prescribed medicine, attitude towards illness and medication, such as a general rejection of pharmacotherapy). Depression is also linked to non-adherence to medical prescriptions.[24]

Discussions between physician and patient concerning medication are generally initiated by the doctor who tends to control the content to a large degree, focusing on therapeutic benefits and frequently avoiding a discussion of risks, adverse drug reactions and necessary precautionary measures, and rarely checks how much of the content of the consultation has been understood by the patient. Patients often fail to inform their doctor when they have changed the doses of a medicine autonomously, or if they have ceased taking a prescribed medicine.[21,22]

Evidence from previous studies shows benefits from certain strategies in order to avoid inappropriate prescriptions: [22,25,26]

- Regular checks of which drugs have been taken
- The use of computerised decision support systems (CDSS), which automatically generate alerts in case of potentially inappropriate prescriptions and present suitable strategies to prevent them.
- Communication between doctor and patient is more likely to cover problems concerning medication when patients feel at ease to discuss these in pre-consultation interviews with medical assistants (non-physicians). This effect could also be demonstrated for interventions carried out for elderly patients. As a result patients showed higher medication and appointment adherence.

2.3 Rationale

Considering that

1. Multimorbidity, multimedication and increasing age increase the risk of inappropriate prescriptions, adverse drug events, and under-treatment,
2. Multimedication and high medication complexity reduce patient adherence,
3. Consultations between doctor and patient on medication-related problems generally focus on the benefit of a therapy and are dominated by the doctor, and
4. Patients do not usually inform their doctor about changes they make in their medication intake

an intervention was developed that includes the following components:

(1) A medication reconciliation by a general practice based healthcare assistant (HCA),

(2) The systematic assessment of medication-related problems (technical handling, symptoms of potential adverse drug reactions, adherence, patient preferences) by means of a checklist (MediMoL) in a pre-consultation interview conducted by a HCA.

(3) The use of a computerised decision support system (internet based medication information system, AiD+)

(4) Physician-patient consultation on medication-related problems.

The basic assessment in (1) and (2) provide the GP with structured information. This can then be checked by means of the AiD+ to alert the doctor of potentially inappropriate prescriptions, the need for renal dose adjustments and of unintended duplicate prescriptions.

The pre-consultation interview with the HCA should enable patients to discuss their problems with the GP and to tell him about their expectations, wishes, fears, concerns etc.

The GP and patient then discuss necessary changes in the therapy and decide on a new medication. We expect that after taking into consideration the AiD+ alerts and the patients' problems taking the medicine, as well as their dislikes and preferences, the adapted medication will be more suitable, leading to a reduction in potentially inappropriate prescriptions, under-treatment and medication complexity. Furthermore, we expect that a prioritisation of the medication will take place as a result of directly asking and taking into account the patient's perspective.

In consequence, it can be expected that patients are more likely to adhere to the doctor's instructions. Patient health can be improved through the avoidance of under-treatment in pain therapy and possibly through a reduction in adverse drug reactions and associated events. As a result, patient's functional situation, generic quality of life and the desired lifetime duration should be improved.

3 STUDY OBJECTIVES

(1) Primary objective of this trial is to investigate whether the complex intervention will improve the appropriateness of prescriptions in elderly multi-morbid patients six months after baseline as compared to usual care.

(2) Secondary objectives of this study are:

- to ascertain whether the complex intervention will improve the appropriateness of prescriptions in elderly multi-morbid patients nine months after baseline as compared to usual care.
- to assess whether the complex intervention will improve the generic health related quality of life, the functional disability, the desired lifetime duration, the all-cause hospitalisation, and the medication adherence of elderly multimorbid patients six and nine months after baseline.

(3) The following secondary objectives will be investigated to explain the mechanism of the intervention effects at six and nine months after baseline:

a. Patients' beliefs about their medication, since negative attitudes toward medication are associated with non-adherence[27]

b. Medication complexity, as a high complexity is correlated with reduced adherence[24]

c. Severity of chronic pain to ascertain whether this intervention leads to an optimised pain therapy. Results will support the interpretation of intervention effects on health related quality of life and functional disability.

d. Satisfaction with shared decision making to investigate whether the complex intervention leads to a higher patient's satisfaction with involvement[28,29]

e. Depressive symptoms, since depression is associated with reduced adherence[24]

f. Cognitive dysfunction to investigate whether the intervention effects are modified by patient's individual cognitive performance

4 STUDY DESIGN

PRIMUM is scheduled as a pragmatic, cluster-randomised controlled trial with the general practice as the unit of randomisation. A clustered design (practices as clusters) was chosen to reduce treatment group contamination, since HCA and GP trained in the intervention will plausible not be able to provide usual care.

Allocation concealment will be disclosed after completion of the baseline documentation for all study patients within a practice but before the intervention begins. Intervention will take place on practice level.

Due to the type of intervention, neither GPs and their patients nor the PRIMUM study team will be blinded to the treatment allocation. However, allocation will neither be revealed to the pharmacologist who is responsible for the MAI rating nor to the study statistician who is responsible for the statistical analyses.

To reduce the contamination of the control group only general information of the treatment in the intervention group is provided in the regular study protocol (a complex intervention including a checklist based pre-consultation interview by the HCA and the use of an internet based CDSS). Detailed information about the intervention treatment is provided only to the intervention group as an appendix to the study protocol in the intervention training.

All primary and secondary outcomes will be measured at patient level at baseline (T0), and at follow-up: 6 months after baseline (T1) and 9 months after baseline (T2).

5 SETTING AND TRIAL POPULATION

5.1 Setting

The trial will be conducted in general practices of the state of Hesse, Germany.

5.2 In- and exclusion criteria

5.2.1 Criteria for trial sites (General practices)

Inclusion criteria:

- Practice provides health services to persons with German statutory health insurance
- GP practice
- Physician specialises in general practice, internal medicine or has no specialist area
- Practice has internet access which can be used by healthcare assistant
- Investigating physician agrees to the contractual obligations of the trial
- Investigating physician agrees to train a healthcare assistant from the practice as part of the trial for intervention.

Exclusion criteria:

To avoid selection bias for rare diseases and unconventional treatments the following practices are excluded:

- Practice specialises in unconventional medical treatments
- Practice specialises in special indications (e.g. HIV)

5.2.2 Criteria for healthcare assistants (HCA)

Inclusion criteria:

- Written agreement to complete the necessary qualification measures and to perform the tasks associated with the trial.

5.2.3 Patient criteria

Inclusion criteria:

- At least 60 years of age
- Multimorbidity, defined as the existence of at least three chronic diseases, which:
    - Affect at least two different organ systems
    - Require pharmaceutical treatment
    - Represent a disease entity, i.e. arthritis affecting different joints (arthritis of the knee, arthritis of the hip, etc.) is counted as one disease "polyarthritis", irrespective of the location
    - Are not coded in the International Classification of Diseases, version 10 (ICD-10, 2010) in the chapter "H" (diseases of the eye and adnexa, or of the ear and mastoid process) or in the chapters "E00" to "E04" (diseases of the thyroid gland: congenital iodine-deficiency syndrome, iodine-deficiency-related thyroid disorders and allied conditions, subclinical iodine-deficiency hypothyroidism, other hypothyroidism and other non-toxic goitre), since the latter require substitution of iodine and/or thyroxine, only.
- Multimedication, defined as follows: Regularly takes at least five medicines (long-term medication) with systemic effects.
- Care is provided by a GP working at a trial site (at least one contact in most recent quarter).
- Patient is legally competent to sign any documents,
- Patient is capable to give a free and written informed consent to participate in the trial, to fill in questionnaires and to participate in telephone interviews.

Exclusion criteria:

- Diseases that result in an estimated patient's life expectancy under 12 months
- Alcohol or illegal drug abuse with recognisable clinical signs or symptoms
- Cognitive impairment (MMSE < 26), that would prevent participation in the trial
- Emotional stress that would prevent participation in the trial
- Participation in a clinical trial within the last 30 days.

5.3 Recruitment

5.3.1 Recruitment of practices

General practices in the state of Hesse and up to 200 kilometres away from Frankfurt are invited to participate in the study. For this purpose about 1.600 practice addresses provided by the Association of Statutory Health Insurance Physicians of Hesse will be contacted by mail – among them not only active general practitioners. Of those who are interested, the in- and exclusion criteria are checked by phone and a date for an initiating visit is agreed. Of those who decline to participate the reasons for refusal and the in- and exclusion criteria are questioned by phone as far as possible. Of those who do not respond a 10% random sample

is contacted by phone and asked for participation, fulfilment of in- and exclusion criteria and their reasons for denial as well.

5.3.2 Recruitment of patients

HCA or GP creates a list of patient-IDs per practice from the practice computer (systematic query on patients born before 1950, who had a practice contact in the most recent quarter, whose treatment costs accounted for more than € 100 per quarter, sorted by costs). The top five patient-IDs on the list are cancelled to avoid a selection bias for rare diseases with extraordinary treatment costs. From the remaining list all patient IDs are cancelled who do not fulfil the in- and exclusion criteria until a screening list of 50 potentially eligible patient-IDs results. The screening list of pseudonymous patient-IDs is sent to the study centre (Institute for General Practice, Frankfurt, IGP) by telefax. The IGP selects a random sample of the 15 patient IDs (via random numbers by Microsoft Excel©) and sends them (the random list) back to the practice. The 15 patients of the random list are invited to participate in the study consecutively, until 7 patients are included in the study. For each of the 15 patients of the random list, basic characteristics (age, gender, fulfilment of in- and exclusion criteria, exclusive the MMSE score) are documented pseudonymously in a registration form. Only after the written informed consent of the patient the MMSE is conducted by the HCA, its sum score and the personal data (name and telephone number) are also documented. For those patient-IDs which are not related to patients taking part in the study the reasons are documented (reasons for refusal vs. the achievement of the recruitment goal). All written informed consents and registration forms are sent to the IGP via telefax.
This recruitment strategy was found to be feasible in the pilot study.

5.4 Information for participants

5.4.1 Investigator information and training

At the initiating visit at the trial site, both GP and one HCA per practice, are trained in documentation. HCA will participate in order to be in a position to support data documentation and to carry out the Mini-Mental Status Test (MMSE). GP will be informed about the study protocol, ethical considerations and the recommended standard, and will be trained in the use of the Cumulative Illness Rating Scale (CIRS).

Content:

1. Introduction to the PRIMUM trial
2. Introduction to the execution of the trial
3. Introduction to “recommended standards“ (Geriatrics guideline, parts I and II by the Hesse guideline group[1])
4. Explanation of patient clarification, information and declaration of consent
5. Training in execution of MMSE and CIRS-appraisals
6. Introduction to trial documentation including CRFs
7. Content and execution of patient survey
8. Data monitoring, query management and reminder mechanism

9. Presentation of exact trial procedure including timeline
10. Investigators' participation agreement

5.4.2 Patient information and declaration of consent

When the patients in the random list appear in the practice, the GP in person will conduct a patient briefing with them with the help of the patient information sheet prepared for the trial. Patients are to be informed of the aims and the content of the trial, the times, the methods and the content of data collection, the random selection either for the intervention or the control group, of the intervention itself, and on data protection. The patient will be expressly advised of the fact that participation is voluntary and on the possibility to withdraw ones consent. Consent to participate in the trial, as well as the declaration on data protection should be signed and dated by the patient himself. The originals will be sent to the IGP via telefax and archived in the investigator's file. In addition to the time, date and duration of the briefing, the trial number and trial abbreviation should also be entered into the patient's medical records. The patient will receive the patient information sheet and dated and signed copies of his declaration of consent and declaration on data protection.

6 RANDOMISATION AND ALLOCATION CONCEALMENT

Practices will be randomly allocated to the complex intervention or control arm in the ratio of 1:1. Block randomisation with randomly varying block sizes will be used to provide treatment groups of approximately equal size. Randomisation lists will be provided by the Institute of Medical Biometry and Informatics at the University of Heidelberg, using computer generated numbers. Practice allocation to treatment groups will be performed by central randomisation by a study-independent researcher at the IGP after registration of the first patient per practice. Once a practice has been randomised, all the patients recruited for the practice will be deemed intervention or control depending on which arm of the study each practice was allocated. After completion of the baseline documentation of all study patients per practice, the study-independent researcher at the IGP will inform the study team at the IGP about the practice status as either intervention or control. The study team will send a fax with the randomisation result to the practice.

7 TREATMENT PLAN FOR INTERVENTION AND CONTROL GROUPS

7.1 Description of trial treatment in the intervention arm

For detailed intervention see appendix B (handed out merely to the intervention group at the time of the intervention training to avoid contamination of the control group).

As a "recommended standard", the practices in the intervention group will receive the short form of the current geriatrics guideline, parts I and II, published by the Hessen guideline group.[1]

7.2 Description of treatment in the control arm

For the duration of the trial, the patients in the control group will continue to receive the usual treatment from their GP.

As a "recommended standard", the practices in the control group will receive the short form of the current geriatrics guideline, parts I and II, published by the Hessen guideline group.[1]

8 OUTCOME ASSESSMENT

8.1 Outcome measures

8.1.1 Primary Outcome

The primary outcome is the change in the appropriateness of prescriptions after 6 months follow-up measured as a difference in the Medication Appropriateness Index (MAI)-Score 6 months from baseline minus baseline (MAI T1–T0).

The criterion appropriateness of the medication will be calculated and evaluated on the basis of the *Medication Appropriateness Index* (MAI).[30,31]

- The MAI by Hanlon et al. consists of 10 items: (1) Is there an indication for the drug?, (2) Is the medication effective for the condition?, (3) Is the dosage correct?, (4) Are the directions correct?, (5) Are the directions practical?, (6) Are there clinically significant drug-drug interactions?, (7) Are there clinically significant drug-disease/condition interactions?, (8) Is there unnecessary duplication with other drug(s)?, (9) Is the duration of the therapy acceptable?, (10) Is this drug the least expensive alternative compared to others of equal utility? The rating will take place on a three point scale whereby "1" represents the best rating (expressed as correct, practicable etc. depending on the question), "3" the worst rating (incorrect, impracticable etc. depending on the question) and "2" a middle rating. As an alternative, it is also possible to respond with "not applicable" or "unknown".
- The MAI will be used in the following modifications that are comparable to modifications by others:[30,32-34]
    - Item (10) will not be rated, since this is not possible under the current conditions of discount contracts between pharmaceutical industries and different statuatory health insurance companies in Germany. They are based on § 78 Abs. 3 Arzneimittelgesetz (A) and § 130a Absatz 8 SGB V (B). Both paragraphs describe the possibility to offer discounts on official prices of pharmaceuticals by pharmaceutical industry. In conclusion "best prices" vary between health insurance companies and over time.
    - Ratings are specifically defined for each item, e.g. items (5) and (6) are limited to the most commonly observed combinations of drug-drug and drug-disease interactions, and current symptoms (taken from the telephone interview) will be considered for assignment. Operationalisation is summarised in a referenced manual (Appendix A).
- The MAI showed good intra-rater reliability for well-experienced pharmacologists.[30,33,35-37] In Prof. Harder's trial group, an MAI Rating will be carried out independently

of the project and blinded for the patient's group allocation (intervention vs. control). In a random sample of about 20% of the cases an independent second MAI rating will be carried out.

Changes of the medication regime (1) are recommended stepwise[38] and (2) are assumed to be in primary care not always realised by the patient immediately (pers. comm. practice advisory board). Reasons for the delay of changes in the medication taken by the patients probably rely on the prescribing behaviour for the chronically ill (large package sizes) and on financial constraints of the patients (extra out-of-pocket payments per package). Based on (1) and (2) an estimated delay of three months to implement prescriptions into taking is reasonable. To ascertain the effectiveness of the intervention the MAI should be appraised at least three months after intervention, therefore.

8.1.2 Secondary Outcomes

(1) Change in the appropriateness of prescriptions after 9 months follow-up measured as the difference in the Medication Appropriateness Index (MAI)-Score 9 months from baseline minus baseline (MAI T2–T0): To study late intervention effects a second interval will be measured for the medication appropriateness at T2 (9 months after baseline). Furthermore, treatment effects on each MAI item will be determined.

The following parameters will be determined in order to identify treatment effects on patient related outcomes:

(2) Change in generic health related quality of life measured as the difference in the EQ-5D-Score[39,40] 6 months from baseline minus baseline (T1–T0) and 9 months from baseline minus baseline (T2–T0): To ascertain whether the intervention improves the generic health related quality of life the EuroQuoL (EQ-5D) will be used.[39,40] The EQ-5D was feasible in the pilot study and detects even relatively small changes.[41,42]

(3) Change in functional disability measured as the difference in the VES-13-Score[43] 6 months from baseline minus baseline (T1–T0) and 9 months from baseline minus baseline (T2–T0): To ascertain whether the intervention improves functional disability, the activities of daily living will be assessed. In the pilot study the WHO DAS-II was found not to be feasible. In the main study the Vulnerable Elderly Survey, 13 items (VES-13) will be used.[43] The VES-13 predicts death and functional decline in vulnerable elderly patients,[43-45] encompasses physical and instrumental activities of daily living and is feasible to use (pers. comm. Dr. U. Thiem, geriatrician, VES-13 use in the German PRISCUS-project; pers. comm. M. v. d. Akker: VES-13 use in the Maastricht multimorbidity project).

(4) Change in all cause hospitalisation: To ascertain whether the intervention improves all cause hospitalisation of patients, hospital days are counted irrespectively of reasons for admission.

(5) Change in medication adherence: To determine whether the intervention improves the medication adherence the following outcomes will be measured:

- Change in observed adherence measured as the difference between intake (*patient's interview*) and prescribed medication (CRF reported by physician's) 6 months from baseline minus baseline (T1–T0) and 9 months from baseline minus baseline (T1–T0)

- Discrepancy score, DS (Sum of all differences in drug, time of intake, frequency and dose) / Sum of all prescriptions, AS<0.8 or >0.2=1
- Drug Score (DS, Sum of all drugs taken/sum of all prescriptions), DS<0.8 or DS>1.2=1[46]
- Dose Score, (DoS, Sum of all daily doses taken/sum of all prescriptions), DoS<0.8 or DS>1.2=1[46]
- Regimen Score (RS, actual frequency of intake per day / prescribed frequency per day), RS<0.8 or DS>1.=1[46]

- Change in self-reported adherence measured as the difference in the Morisky-Score[47] 6 months from baseline minus baseline (T1–T0) and 9 months from baseline minus baseline (T2–T0)

5) Change in perceived future life expectancy reflects concepts of will to life or years of desired life [YDL] measured as the difference of the three items future expectation / expected lifetime duration / desired lifetime duration in the interval 6 months from baseline minus baseline (T1–T0) and 9 months from baseline minus baseline (T2–T0): Desired and expected life time duration are considered to be sensitive for personal experiences and scientific influences,[48] as well as indicating well being and positive life evaluation.[49] Moreover it is argued that YDL itself reflects mortality on the long run. Thus, if our intervention effects change in YDL, one might argue that participants consider the intervention as relevant in relation to their own life expectancy and life quality.

8.1.3 Secondary outcomes to explain the intervention mechanisms

1) Change in complexity of medication measured as the difference 6 months from baseline minus baseline (T1–T0) and 9 months from baseline minus baseline (T2–T0) in terms of

- Total number of prescriptions
- Number of single doses / day
- Medication Regimen Complexity Index (MRCI),[50]

since a high complexity is associated with a reduced adherence.[24]

2) Change in health and illness beliefs and attitudes measured as the difference in the Beliefs about Medicines Questionaire (BMQ) score[27] 6 months from baseline minus baseline (T1–T0) and 9 months from baseline minus baseline (T2–T0), since denial of illness and / or medication in general might explain non-adherence.[24]

3) Change in severity of chronic pain measured as the difference in *Characteristic Pain Intensity score,* the *Disability Score,* in *Disability Points* and the resulting *Grades of chronic pain severity* in accordance with M. von Korff, J. Ormel[51] et al. in the interval 6 months from baseline minus baseline (T1–T0) and 9 months from baseline minus baseline (T2–T0):

Prevalence of chronic or persistent pain in elderly ranges between 25 and 50%. Nevertheless, under-assessment and under-treatment of pain is frequent in the elderly.[52] Under-treatment is often associated with polypharmacy,[9] and is not adequately captured by MAI

appraisal. Therefore, pain is hypothesised as a surrogate for under-treatment[a] and will be assessed to reveal possible negative intervention effects (i.e. a reduction of polypharmacy at a cost of an impaired pain management). The different scores to grade the severity developed by von Korff, Ormel et al. have been modified for, integrated in the German pain inventory (Deutscher Schmerzfragebogen – questions 11 a-c, and 12 a-d) and validated in a German population.[51,53,54]

4) Change in satisfaction with shared decision making measured as the difference in the *Man Son Hing* scale (MSH)[28,29] interval 6 months from baseline minus baseline (T1–T0) and 9 months from baseline minus baseline (T2–T0): For an appropriate prescription in elderly multimorbid patients a patient centred rather than a disease centred approach is recommended. MSH scale measures the satisfaction with the shared decision making process. It was found feasible, showed high reliability and sensitivity of change and acceptable validity in the German "arriba"-study conducted in primary care practices.[28]

8.2 Timing of outcome assessment

Study visits: at baseline (T0), 6 months (T1) and 9 months (T2) after baseline. Each time the HCA makes a practice appointment with the patient, and measures body height and weight. Patients fill out a questionnaire in the practice and reply it to the HCA in a closed envelope before leaving. HCA and GP fill out a paper based case report form (CRF). At the end of each visit the HCA sends a control sheet by telefax to the IGP to inform that the visit has taken place. The completed CRF and patient questionnaire are sent by mail to the IGP. Immediately after the receipt of the control sheet trained members of the study team conduct the telephone interview with the patient.

Table 1: Study visits

Month	**Before trial begins**	**0**	**6 (+/- 1)**	**9 (+/- 1)**
Visits		**T0**	**T1**	**T2**
Trial measures for *control and intervention group*				
Documentation training, GP and HCA	•			
Profile of practices participating in trial	•			
Sociodemographics of GP				
Sociodemographics of HCA	•			
Identification of potentially eligible patients – screening lists	•			
Random lists	•			
Patient registration sheet (In- and exclusion criteria, reasons for non-participation of patients; for included patients with written informed	•			

[a] Additional searches should reveal literature, where a direct association between polypharmacy and under-treatment of pain is shown (references are welcome). Otherwise we will get the prevalence of severe pain in our population at baseline.

Month	**Before trial begins**	**0**	**6 (+/- 1)**	**9 (+/- 1)**
Visits		**T0**	**T1**	**T2**
consent also: name, first name, telephone number, MMSE score)				
CRF, practice documentation				
• Detailed sociodemographics, patient incl. Disease Management Program (DMP) status		•		
• Patient's current diagnoses		•	•	•
• Patient's current medication		•	•	•
• Height and weight of patient		•	•	•
• Laboratory test results of patient, if available (serum electrolytes K, Na, serum creatinine)		•	•	•
• Degree of patient's multimorbidity (CIRS)		•	•	•
• Existing co- and multimorbidity of patient (Charlson Comorbidity Index)		•	•	•
• Hospital stays (duration, reason)		•	•	•
• Consultation of specialists		•	•	•
Patient questionnaire:				
• Sociodemographics incl. best school leaving certificate and professional certificate, household composition, housing indicators, house care		•		
• Lifestyle		•		
• Generic health related quality of life (EuroQuoL, EQ-5D))		•	•	•
• Functional disability (Vulnerable Elderly Survey, VES-13)		•	•	•
• Attitude of patients to medicinal therapy (Beliefs about Medicines Questionnaire, BMQ)		•	•	•
• Severity of chronic pain in accordance with M. v. Korff, J. Ormel et al. 1992		•	•	•
• Satisfaction with shared decision making (Man-Sin-Hong scale)		•	•	•
• Future expectation, expected / desired lifetime duration		•	•	•
Telephone interview with patient				
• Sociodemographics		•		
• Current patient medication (incl. National drug code: PZN)		•	•	•
• Symptoms for adverse drug reactions		•	•	•
• Infirmity index (Sherbrooke Questionnaire)		•	•	•

Month	**Before trial begins**	**0**	**6 (+/- 1)**	**9 (+/- 1)**
Visits		**T0**	**T1**	**T2**
• Depression (Geriatric Depression Scale, GDS)		•	•	•
• Cognitive dysfunction (Verbal Fluency Test)		•	•	•
• Self reported adherence of patient (Morisky)		•	•	•
Measures for *intervention group only*				
• Intervention: Training for GP's and HCA's		•[#]		

[#]After baseline completion

9 POST-RECRUITMENT RETENTION STRATEGIES

Co-ordinating Centre responsibilities of the IGP:

- Provide study materials incl. self-addressed envelopes which will be supplied to the trial sites in sufficient quantities and postage will be paid by the recipient
- Help ensure complete data collection at baseline, at six months and at nine months
- Respond to any questions (e.g. from practices) about the trial via telephone and telefax (regular office hours Mon. to Fri. 9:00 a.m. to 5:00 p.m.), or mobile phone (Mon. till Fri. between 9:00 a.m. and 7:00 p.m., Sat. & Sun. between 10:00 a.m. and 6:00 p.m.), or email

10 SAFETY MONITORING AND ADVERSE EVENTS

No safety monitoring nor adverse events reporting will be conducted, since worse treatment than previous to the trial is not possible. The study team of the trial (Institute for General Practice, Johann Wolfgang Goethe-University, Frankfurt am Main, IGP) has no influence on the diagnostic-therapeutic decision-making of the GPs and their patients.

11 REGISTRATION, DATA COLLECTION AND MANAGEMENT

11.1 Registration of participants

Practice registration: takes place during the initiation visit by a trained study team member. The participating practices give written informed consents of a general practitioner (GP) and a healthcare assistant (HCA) to participate in the study and to implement the study protocol (centre registration form).

Patient registration: at the IGP the incoming telefaxes of registration forms and signed informed consents are controlled (patient ID is consistent with the patient ID of the random list, signature of the patient, fulfilment of in- and exclusion criteria) and patient registration is confirmed to the practice by telefax.

11.2 Data collection

11.2.1 Data collection of participating HCA and GP

First documentation takes place at the initiating visit at the trial site: social demography of HCA and GP and practice characteristics as well are documented in paper based forms (each one per HCA and GP and practice).

11.2.2 Data collection of participating patients

Examinations and documentation of the patient related data take place regularly during the aforementioned visits 1-3. Visits 1-3 take place in months 0, 6 and 9 (+/- one month) following the inclusion of the patient in the trial. An overview of the individual examinations is given in table 1 (see pp 23). The content of the individual examinations to be documented is described in detail in section 11.3 (see below). At each visit the following documents are collected:

- The patient registration document (T0) and control sheets (T1, T2) filled in by HCA and GP are sent to the IGP via telefax at the day of the patient's visit to the practice.
- The paper based case report form (CRF) completed by the HCA and GP. Every CRF includes information on filling in the form. Necessary correction to the CRF must take place in the following manner: invalid data should be crossed out whereby crossed-out details should be authorised with the date and the investigator's initials.
- The completed patient questionnaire (paper based as well): The patient questionnaires, including an envelope, will be issued by the HCA. The patients fill in the questionnaires in the practice and put them in the envelopes which they then seal themselves (confidentiality of information with respect to trial site). If necessary, the HCA provides help filling in the patient questionnaires and keeps an eye on the return of the completed documents.

The completed CRFs and the sealed envelope with the completed patient questionnaire will be put in the return envelopes (no stamp required) at the trial site and promptly returned to the IGP by mail.

Within five working days as after arrival of the patient registration document / control sheets, trial employees will contact the patient to conduct the telephone interview. Information from these interviews will be entered directly into the entry mask of an SQL data bank (Access©). If the interviewer cannot reach the patient, further attempts to do so will be made on the following days. After the fifth unsuccessful attempt, the responsible practice will be contacted by the trial assistant and asked for information on the whereabouts of the patient. If the attempts to contact the patient fail within one month, the telephone interview for this visit is considered as missing.

11.2.3 Data collection of non-participating patients

If a patient from the random list (see 5.3.2) does not agree to participate, or is not included for any other reason (e.g. the recruitment goal per practice is already fulfilled), then the following data will be documented on the patient registration form pseudonymously – age, gender, in- and exclusion criteria (without MMSE score), reason for non-inclusion. The documentation of further data and especially personal data such as name, date of birth or telephone

number is not permitted. The patient registration forms for those patients who are not included will also be faxed to the IGP and the originals will remain on the files of the GP and checked by the monitor after completion of the trial.

11.3 Description of data sets

11.3.1 Data set to determine practice profile

- Single-handed practice / group practice (incl. ambulatory healthcare centre, with the number of physicians and the question for additional general practitioners),
- Location: Big town (> 100.000 inhabitants) / middle size town (20.000 to 100.000) / small town (5.000 to 20.000) / rural area (< 5.000 inhabitants)
- Clinical specialisation of practice
- Number of registered patients in most recent quarter [in categories: 0 – 499, 500 – 999, 1000 – 1499, 1500 – 1999, 2000 and over]
- Quality management system used in practice
- (Brand name of practice EDV to provide any necessary support for the study by the IGP

11.3.2 Data set to determine profile and sociodemographics of the GP

- Practice-ID as provided by the IGP, GP-ID (consecutively for each participating GP)
- Age, gender of GP
- GPs professional practice experience (year doctor commenced private practice)
- Years of clinical experience in total
- GP: Specialist in primary care, specialist in internal medicine, GP / doctor with no specialist area
- Previous participation in a former clinical trial and name of trial

11.3.3 Data collection to determine profile and sociodemographics of the HCA

- Practice-ID as provided by the IGP, HCA-ID (consecutively for each participating HCA)
- Age, gender of HCA
- School leaving certificate, professional and additional qualifications
- Years of professional experience as health care assistant and at trial site
- Type of employment
- Previous participation in a former clinical trial and name of trial

11.3.4 Patient registration form

Registration form for every patient on random list with

- Practice-ID as provided by the IGP, GP-ID, patient-ID as used in practice computer, month and year of birth, age, gender
- Checklist for in- and exclusion criteria (items to be marked with a cross, exclusive MMSE score)
- Decision not to participate (if possible with reasons)
  vs. patient not approached (as recruitment target already reached)
  vs. readiness to participate (patient's written informed consent is on hand)
- If written informed consent on hand:

- Name, first name, patient's phone number
- MMSE Score

11.3.5 Case report forms (see prototype in appendix)

Sociodemographics and basic clinical data: insurance status (private, statutory or differing), name of insurance company, participation in one of the disease management programs (diabetes mellitus I/II, coronary artery disease, breast cancer, COPD, asthma), home care situation and assessment of quality of care, height (measured), weight (measured), current diagnoses, allergies / intolerances, consultations with specialists (specialisation of physician) and hospital stays during the last six months (date of admission to / release from hospital; inpatient, day hospital care, outpatient, inpatient rehabilitation; reason for treatment).

Laboratory: Laboratory values for serum electrolytes (sodium and potassium) and serum creatinine that are already available in the practice. The most recent values should be taken along with the date of the test, but should not be more than 12 months prior to patient inclusion in the trial.

Current medication: trade name, strength, application, dosage, indication, duration of therapy at time of documentation (more or less than three weeks) and estimated importance of the particular medicine within the concept of the therapy as a whole (4-point Likert scale: very important – important – of little importance – not important).

Current diagnoses: all active diseases of the patient at the time of documentation (acute and chronic diseases) and treatable conditions (e.g. hypertension without end organ failure, positive medical history for gastric ulcer)

Modified Cumulative Illness Rating Scale (CIRS): Assessment of organs / organ systems / areas (15 items in total) according to severity of impairment (5-point Likert scale: no impairment to extreme impairment),[55-57] with one supplementary item "chronic pain syndrome" and one supplementary response category entitled "not applicable" if the named organ (system) is not affected.

Expanded Charlson Comorbidity Index: List of underlying diseases in the Charlson Comorbidity Index[58] plus relevant diseases and situations that often result in contraindications to specific medication.

11.3.6 Patient questionnaires (see prototype in appendix)

Sociodemographics: marital status, number of persons living in the household (i.e. household composition), home care, socioeconomic status (best school leaving certificate, professional training), housing indicators (population size: big town [>100.000 inhabitants] / middle size town [20.000 to 100.000] / small town [5.000 to 20.000] / rural area [<5.000]; housing tenure [home ownership]; place attachment [home / neighbourhood]).

Generic health related **quality of life** (EuroQoL, EQ-5D),[39,40] maintenance of **functional status** (Vulnerable Elderly Survey, VES-13),[43] **Beliefs about Medicines** Questionnaire (BMQ),[27] **severity of chronic pain** (in accordance with M. v. Korff, J. Ormel et al.),[51] satisfaction with shared decision making (Man-Son-Hing scale),[29] future life expectancy (future expectation / expected lifetime duration / desired lifetime duration).[48,49]

11.3.7 Telephone interview with patients

At each visit a trained employee from IGP conducts interviews with patients using an interview guide (see appendix) and enters the answers directly into an Access-data base.

Medication incl. OTC drugs and supplements (trade name, National Drug Code, dose, prescribed by whom, duration of intake more or less than three weeks) currently being taken on a regularly basis; medication to be taken as needed, including OTC drugs (in case of what symptoms, single dose, total maximum dose); autonomous preparation and intake of medication vs. support from third parties, known allergies, symptoms for potentially adverse drug reactions.

Consultation of other healthcare providers: Other healthcare providers consulted during the last six months (name, location, profession/specialisation, number of consultations, reason(s) for consultation, and referral by GP vs. direct access).

Sherbrooke Questionnaire: Five items to identify positive predictors (lives alone, uses a walker, self-reported visual, hearing and memory impairment, sixth item already one of inclusion criteria: more than three long-term medicines daily).[59]

Use of medical aids and special therapeutic measures: Use of visual and/or hearing aids, use of home oxygen therapy, participation in dialysis therapy, ask about implant devices (pacemaker, defibrillator)

Patient interview on depression (Geriatric depression scale, GDS)[60,61]

Patient interview on adherence (Self reported adherence according to Morisky)[47]

Verbal fluency test: Patients are asked to tell as many animals as possible within one minute.[62] Answers are audiotaped and time is controlled by a stop watch. After the interview is finished, the interviewer transcripts the audiotape into the database and deletes the tape soon after.

11.3.8 Documentation of intervention

After completion of the trial the data from the completed intervention tools (MediMoL, AiD+) will be analysed (intervention group only).

11.4 Data management

The responsible trial employee will check all incoming post is complete and confirm receipt by marking it (date of receipt, date of check, initials - tracking). The due dates for sending the documentation is described in a guideline on data flow in the investigator's file. Missing information will be collected in preparation for the following query management (see below).

After confirmed reception of data it will be entered into an SQL trial database (Access©) by one of the trial employees. A data check will take place of this database according to predefined trial rules (range-, validity, and consistency checks according to defined SOPs developed during the course of the trial and documented in the TMF). Queries for the investigators that may crop up as a result of this data check will be formulated by the IGP (see below, Query management). Sending, collecting and processing patient data will always take place under the patient identification number (Pat.-ID) pseudonym.

Coding will be used for some of the data, partly when the data is entered. In retroactive processing steps, some free text information will be encoded into new variables. The encryption specifications will be deposited in the TMF.

11.5 Data Validation (Query management)

Data recognized as missing during the confirmation of receipt check will be collected for each practice using the patient IDs and then faxed to the trial sites as a written request for completion. These fax requests will be filled in and signed by the investigator and then faxed back to the IGP. The receipt of the returned faxes will then be confirmed and the process continued until all missing data have been collected. The checked data will then be forwarded and entered into the database, as described above.

Follow-up enquiries resulting from the data plausibility check will also be collected for each practice and formulated as a written fax request using the patient identification number. They will then be dealt with in the same way as described under (missing data).

If possible, query management will be undertaken during regular practice visits in order to limit the number of fax requests. However, timely query management has first priority.

All CRFs, patient questionnaires, queries and answers will be kept at the IGP in paper-form. Changes to the Access database will be documented in an audit trail. The necessary programming instructions will be developed along with the data management concept.

11.6 Quality control and quality assurance

The study team of the IGP guarantees that all processes in the trial will comply with the Good Clinical Practice (GCP) guidelines, the legal requirements and the SOPs of the IGP. General practitioners and healthcare assistants of the trial sites will be educated on the trial requirements during the investigators' training at the initiating practice visit.

Monitoring: The IGP will be responsible for monitoring the trial. A study employee will regularly visit the trail sites (at least two visits per practice) to ensure that

- the rights of the trial participants are protected,
- the study data are documented completely and in a correct manner and can be verified for defined variables in the source data (selection of appropriate variables will be defined in the data management and validation plan of the trial)
- the trial is conducted in accordance with the study protocol (and its amendments where required) and complies with GCP and legal requirements at the trial site.

Scientific Advisory Board: The board gives scientific advice in questions on planning, conducting and analysing the trial.

11.7 Archiving

The trial documents are to be archived for 15 years. The trial sites will be responsible for archiving their documents (contents of the investigator's file, especially the list of patients, patients' declaration of consent). The IGP will archive the central trial documents, the original CRF (including patient questionnaires, the final report and further reports where necessary).

11.8 End of Trial

11.8.1 Regular / premature end of trial

The **regular end** of the trial is reached when the documentation of the study visits is over for all patients participating in the trial.

The **premature end** of trial can be decided by the principal investigator after the consultation with the scientific advisory board, when recruitment of practices or patients does not meet the recruitment goals, when the number of practices or patients with a premature withdrawal from trial or a permanent violence against the study protocol is expected to avert a successful regular end of trial.

11.8.2 End of trial participation

11.8.2.1 End of trial participation for practices

The **regular end** of the trial participation for a practice is reached when a) the documentation of the study visits is over and b) the treatment in accordance for determined practice status is completed for all patients participating in the trial.

The **premature end** of the trial participation for a practice is reached when the GP withdraws his/her agreement to participate in the trial protocol, or when the principal investigator decides to withdraw a trial site (GP practice) from the trial. Withdrawal has to be done in a written reasoned form. The principal investigator can decide to withdraw a trial site from the trial if:

- It does not satisfy the protocol's technical requirements (e.g. organisational problems in implementing the protocol))
- The implementation of the trial is inadequate for the trial
- The quality of the data is inadequate

11.8.2.2 End of trial participation for patients

The **regular end** of patient's trial participation is reached when documentation of the last planned visit has been completed (T2).

The **premature end** of patient's trial participation is reached

- In cause of death for any reason before the end of trial. If possible, the date and the circumstances of the death (cause of death, location) should be documented.
- In cause of hospitalisation for any reason before the last planned visit has been completed (T2) and before the end of trial.
- In cause of GP decision: The GP can elect to remove a patient from the trial
    - If following the protocol would represent unacceptable stress for the patient because of his situation (that may have to do with the development of his disease),
    - If the patient moves to a nursing home and it is technically or organisationally no longer possible to conduct further telephone interviews
    - If the patient changes to another GP and leaves the trial site.

If the course of events is foreseeable or can be planned a follow-up survey should be brought forward.

- In cause of patient's decision: Patients have the right to discontinue the trial without giving reasons at any time and without losing the right to further treatment from the GP. If a patient does not arrive to an appointment, the GP must follow up the case until he has found out why the patient did not turn up. The GP must try to complete and document all the examinations designated in the protocol.

The IGP must be informed of the premature end by fax and will confirm it. In case of a withdrawal, the reasons/circumstances and the most recent status must be documented. If the patient does not withdraw his declaration of consent, his survival status or a hospital stay should be documented at the end of the regular observation period.

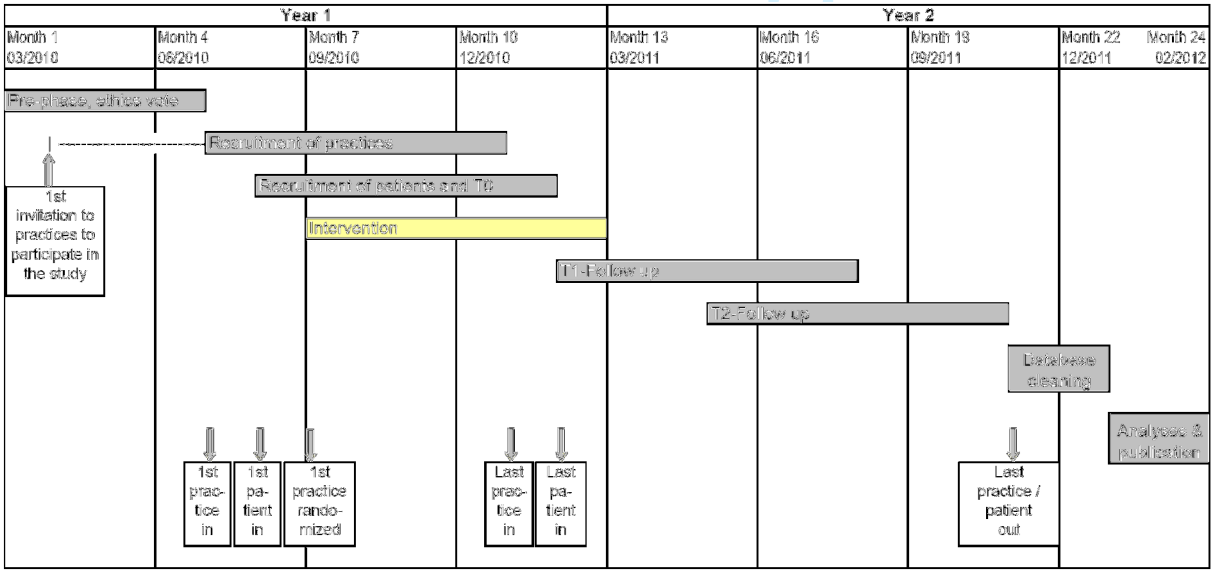
11.8.3 End of treatment

For patients of the control group no regular end of treatment has to be defined, since they are treated as usual.

For patients of the intervention group the **regular end** of treatment is reached when all components of the complex intervention are administered in accordance with the protocol.

For patients of the intervention group the **premature end** of treatment is reached when one or more components are lacking: Patients have the right to discontinue the treatment without giving reasons at any time and without losing the right to further treatment from the GP. If a patient does not arrive to an appointment, the GP must follow up the case until he has found out why the patient did not turn up. The GP must try to complete and document all the components of the complex intervention designated in the protocol. The documentation will continue in accordance with the protocol (intention-to-treat principle) accept the patient withdraws his/her written informed consent in the documentation of his/her data.

11.9 Schedule and expected duration of trial



- Pre-phase (development of all trial plans, materials and implemented instruments, ethics vote, study registration): 01/03/2010 to 30/06/2010
- First practice in – last practice out: 01/07/2010 to 30/10/2011

- First patient in – last patient out: 01/08/2010 to 30/10/2011
- Recruitment:
  a) Practices: 01/07/2010 to 31/12/2010
  b) Patients: 01/08/2010 to 31/01/2011
- Database Cleaning, analyses and publication: 01/11/2011 to 29/02/2012
- Total study duration: 01/03/2010 to 29/02/2012

12 STATISTICAL CONSIDERATIONS

A detailed description of the statistical methods of this study will be provided in a Statistical Analysis Plan (SAP). Data analysis will be done blinded to treatment arm allocation (i.e. the treatments will be identified as 1 and 2 until analysis is complete). The primary analysis will be based on the 6-month follow-up data (T1).

12.1 Populations for analysis

The Intention-to-treat (ITT) population will consist of all randomised practices and their patients. Following the ITT principle, practices and their patients will be analysed in the treatment arms to which they were originally randomized, regardless of whether they refused or discontinued treatment, or whether other protocol deviations are known.

The Per-protocol (PP) population will consist of those ITT practices and patients with no major protocol violations. The criteria for the exclusion of practices or patients from the PP population will be determined by the study team at the latest before database lock.

12.2 Statistical hypotheses, methods, and analyses

The primary objective of this study is to determine the effectiveness of a complex intervention compared to usual care in multimorbid elderly patients, and to show that the complex intervention improves the appropriateness of prescriptions, as compared to usual care. The primary efficacy endpoint is the change in MAI score from baseline (T0) to 6 months after baseline (T1), i.e. the difference MAI T1–T0. The study objective will be statistically formulated as a test of the null hypothesis H0: $\mu 1 = \mu 2$ (the mean difference MAI T1–T0 is equal in the two groups) against the alternative hypothesis H1: $\mu 1 \neq \mu 2$ (the mean MAI T1–T0 are different in the two groups). The null hypothesis will be tested at the two-sided significance level of $\alpha=0.05$.

Because of the cluster randomisation, the primary efficacy analysis will use a multilevel regression approach with patients at level one and practices at level two. The primary model will include treatment group as fixed factor and practice as random factor. The results will be presented as the mean between-group difference in MAI T1–T0 with the corresponding 95% confidence interval. The associated Cohen's effect size d will be calculated. In addition, the practice related intracluster correlation coefficient (ICC) will be estimated. To support the primary analysis, all potentially relevant baseline characteristics at practice level (e.g. practice status) and baseline characteristics at patient level (e.g. MAI score at T0) will be added as covariates to the model in sensitivity analyses. Further sensitivity analysis of the primary endpoint will include an unadjusted two-sample *t*-test on change in MAI from baseline to 6 months after baseline. Results from these sensitivity analyses will serve to explain and interpret the results of the primary analysis.

The primary analysis will be performed adhering to the intention-to-treat principle. An additional sensitivity analysis will be conducted on a per-protocol analysis set.

Baseline characteristics of participating practices and patients will be described by treatment arm. Categorical data will be presented as frequencies and percentages. For continuous data, N, mean, standard deviation, median, inter-quartile range (IQR), minimum, and maximum will be provided.

The statistical analyses of the secondary endpoints will use the same multilevel approach as the primary analysis. All statistical tests will be two-sided at the significance level of α=0.05. Because no adjustments for multiple endpoints are planned, findings will be interpreted with caution in view of the number of statistical tests undertaken. Only the result of the primary efficacy analysis will be interpreted in a confirmatory manner. Confirmatory subgroup analyses are not planned. No interim analysis with regard to efficacy will be done.

A complete case analysis will be performed. If any practices or patients are lost to follow-up, analyses will be done replacing the missing follow-up data with the last available or baseline data carried forward for that practice or patient.

12.3 Sample size

Sample size was calculated using the primary endpoint, the change in MAI score from baseline (T0) to 6 months after baseline (T1), i.e. MAI T1–T0. Because high MAI scores indicate inappropriate prescriptions, a negative difference MAI T1–T0 indicates an improvement in the appropriateness of prescriptions for the target population. The MAI T1–T0 difference is assumed to be normally distributed in each treatment arm population and the variances of the group specific differences T1–T0 are assumed to be equal. In the preliminary analysis of PRIMUM pilot with a total of 60 patients from 12 practices, a mean MAI of 4.2 was observed at baseline. Three months later (i.e. 6 weeks after the intervention), the MAI in the intervention group decreased by 0.9 units, while the MAI in the control group decreased by 0.5 units. Thus, the resulting between-group difference was 0.4 in favour of the complex intervention. In a previous study of a similar patient population, between-group differences of 3 and 4 for changes in MAI from baseline to 3 and 12 months after randomisation were reported.[32] However, the intervention in that study was even more intense than the intervention planned in PRIMUM. Thus, in the present study, a difference in the change values (MAI T1–T0) of at least 2 units between the treatment groups will be considered clinically relevant. In the PRIMUM pilot study, a pooled standard deviation of the MAI T1–T0 difference of 5.2 was observed. However, T1 was defined as 3 months from baseline, whereas in the present study, T1 is measured 6 months after baseline. Consequently, a greater standard deviation is expected for the MAI T1–T0 difference. Using the conservative assumption that the MAI scores at T0 and T1 are uncorrelated, we expect a standard deviation for MAI change of approximately 6 units. With this standard deviation, a between-group difference of 2 units corresponds to Cohen's effect size of d=0.3 and represents a small effect size.[63] Assuming an intracluster correlation coefficient (ICC) of 0.03 at practice level (which is also a conservative assumption because the ICC is assumed to be 0.01 in general practice setting[64]) and assuming an average cluster size of 7 patients, we estimated a design effect of DEFF = 1 + (7 – 1) x 0.03 = 1.18. Taking this design effect into consideration, a total of 62 practices and 434 patients (31 practices and 217 patients per treatment arm) will be required to detect a Cohen's d of 0.3 with a power of 1–β = 0.80 using a two-sample *t*-test at a two-sided significance level of α=0.05. The sample size calculation was performed using NCSS PASS 2008,

Inequality Tests for Two Means in a Cluster Randomised Trial. Assuming a drop-out rate of approximately 10%, the sample size was adjusted to a total of 70 practices and 490 patients (35 practices and 245 patients in each treatment group).

13 ETHICAL AND REGULATORY REQUIREMENTS

13.1 Ethical fundamentals

The project will be carried out in conformation with the Medical Association's code of conduct and good clinical practice (GPC) in line with the World Medical Association Declaration of Helsinki".[65] The trial will be checked and approved by the ethics commission of Frankfurt University Hospital. The original vote by the ethics commission will be kept in the Trial Master File at the Institute for General Practice. In addition, every participating practice will receive a copy to be kept in the investigator's file.

The voluntary participation of doctors and patients in the trial will be recorded in writing following an informed decision to do so. Patients in intervention practices who do not wish to participate will be treated without intervention and in accordance with usual care.

Data protection will be guaranteed for all person-related data: the data will be collected and stored separately from the other individual data in the trial, and deleted at the end of it. Participating patients will be separately informed about data protection in the trial and will give their consent by signing and dating a declaration to that effect. For data analyses, patient identifiers will be kept confidential and the data stored in a separate data base from the personalized one. The trial team are the only persons with access to trial data. Practice teams are also bound by the legal requirement to treat data confidentially.

The present trial will take ICH-GCP criteria into account, and all participants have undertaken an obligation to respect the Declaration of Helsinki and its amendments

The Ethics Commission is to be informed of all changes to the protocol and its renewed approval is to be sought if necessary.

Changes linked to the following points are regarded as requiring renewed approval:

- Necessary changes to the therapy regime, in particular:
  1. Intensification of intervention that is a burden to the patient or could be felt to be a burden by him,
  2. Reduction in intensity of intervention, in view of which a discussion on the likelihood of success must takes place,
  3. Inclusion of further elements in the intervention program about which the patient has not yet been informed,
  4. Changes in the therapy regime of the control arm,
  5. Revision in the risk estimate for participating patients;
  6. Additional examinations, data collection or analyses that necessitate a change in patient information and/or the consent form.

13.2 Subsequent changes to protocol

Changes to protocol may only occur with the prior agreement of all co-operation partners. All participating practices in the trial must be informed of such changes in written form. Changes must be dated and deposited in the Trial Master File.

If in the course of the trial it becomes clear that changes or additions must be made to the present trial protocol, then these must be laid down in the form of an amendment and signed by the principal investigator, the investigators and by those responsible for approving the trial protocol.

Changes to the timetable that may influence the safety of trial participants or the scientific analysis of the trial necessitate renewed approval by the responsible Ethics Commission. The Commission is to be informed of changes to the trial protocol that occur solely for logistical or administrative reasons.

13.3 Trial registration

The trial has been registered as a clinical, scientific based non-AMG-non-MPG-trial in the international trial register "The Current Controlled Trials (CCT)" (URL: http://controlled-trials.com) and - as far as possible - at the German Register of Clinical Trials (DRKS; http://www.germanctr.de) before it begins. The registration notice will be kept in the Trial Master File (TMF) in the IGP.

13.4 Finance and Insurance

No patient insurance is necessary for this trial, as it represents no health risk to patients.

13.5 Responsibility for preparing reports to the funding organization

Joint reports were agreed upon due to the networked nature of the project structure (PRIMUM trial and sub project E within a joint research project). The coordinator of the joint research project and head of the IGP, Prof. Ferdinand M. Gerlach, MPH, will be responsible for the coordination and composition of the reports in a standard format. To this end he will receive the full support of all participants in the project and the co-investigators will provide all required information in a timely fashion.

The reporting process includes

(1) Interim reports to the funding organisation about the trial management in April 2010, and 2011.

(2) A final report following the completion of the trial.

13.6 Publication agreements

The specifications laid down in the CONSORT Statement for cluster-randomised trials must be taken into account when the results of the trial are published.[66]

In principle, the publication should adhere to the suggestions made by the German Research Community (Deutsche Forschungs-Gemeinschaft DFG) to ensure good scientific practice, January 1998 which correspond to the uniform requirements for manuscripts submitted to biomedical journals, NEJM 336: 309 ff, 1977:

"Authorship credit should be based only on substantial contributions to (a) conception and design, or analyses and interpretation of data; and to (b) drafting the article or revising it critically for important intellectual content.; and on (c) final approval of the version to be published"

Conditions (a), (b), and (c) must all be met.

- Names and the sequence of authors' names will be determined collectively for every publication, and by means of asterisks, all particpating persons and their functions will be named at the end of each article.

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15 APPENDIX A

15.1 Abbreviations

ADR	Adverse Drug Reaction
AMG	Medication law
AS	Discrepancy score
BMQ	Beliefs about Medicines Questionnaire
CDSS	Computerized Decision Support System
CIRS	Cumulative Illness Rating Scale
CR	Center registration
CRF	Case Report Form
DEGAM	German Society of General Practice and Family Medicine
DS	Drug Score
DoS	Dose Score
GCP	Good Clinical Practice
GDS	Geriatric Depression Scale
GP	General Practitioner
HCA	Health Care Assistant
ICC	Intra-Cluster Correlation-coefficient
ICH	International Conference on Harmonisation
ID	Identifier
IGP	Institute for General Practice, Goethe university Frankfurt, Coordinating centre of the study
ITT	Intention To Treat
MAI	Medication Appropriateness Index
MSH	Man-Son-Hing scale
MediMoL	Medication Monitoring List
MMSE	Mini Mental Status Exam
MRCI	Medication Regimen Complexity Index
OTC	Over The Counter
PP	Per Protocol
PZN	National Drug Code
RS	Regimen Score

SOP	Standard Operating Procedure
SPSS	Statistical Package for Social Sciences (Software)
TMF	Trial Master File
VES-13	Vulnerable Elderly Survey, 13 items
VFT	Verbal Fluency Test
VRS	Verbal Rating Scale on pain

15.2 Instructions on the content of the investigators file

- Trial protocol (plan) incl. all data collection instruments (sample)
- Geriatrics Guideline from the Hesse Guideline Group (short versions parts 1 and 2)
- Copy of the Ethics Commission vote
- Center Registration (CR)
- Screening list
- Random list
- Original of the signed patient information and consent form to the trial
- Original of the signed data protection declaration
- Patient registration form
- Flow chart on the trial
- Guideline on data flow

Intervention group only:

- Appendix B of the study protocol
- Medication Monitoring List
- AiD+ user manual
- Training material for intervention

15.3 MAI manual

(follows)

16 APPENDIX B

16.1 Description of the intervention (for intervention group, only)

The intervention in the PRIMUM trial is a complex intervention and consists of the following elements:

1. Pre-consultation interview of the HCA with the patient based on a checklist (Medication Monitoring List, MediMoL)
2. Brown bag review: medication reconciliation by the HCA of what drugs are taken by the patient
3. Use of an internet-based, user-initiated computerised decision support system 'AiD+', which alerts in case of
   - discount contracts,
   - duplication with other drugs,
   - drug-drug interactions,
   - renal dose adjustments
   - incompatibilities of parenteral applied drugs

   and provides further information on divisibility of tablets, medication regimen complexity, and maximal dosage
4. Physician-patient-consultation on medication related problems

16.1.1 Intervention – Tools

- Web-based pharmaceutical information system: AiD+ (further information materials will be distributed during intervention training)
- Checklists to track medication-related problems and patients therapeutic aims: Medication-Monitoring-Lists (MediMoL, will be issued during intervention training)

16.1.2 AiD+ development for use in the trial

AiD+ has been developed on the basis of the existing AiD clinic by the Department of Clinical Pharmacology and Pharmacoepidemiology, Heidelberg, for use in the PRIMUM trial, whereby the functionality of AiD+ has been agreed upon with the Institute for General Practice, Frankfurt. With the exception of the features "medication regimen complexity", and "maximal dosage" AiD+ has been tested in the pilot study and has shown a suitable feasibility. The new features have been developed prior to the start of the trial in the practices. All further changes of the functionality of AiD+ will take place after agreement between IGP and AiD developers.

For each trial site, a study employee of the IGP will set up 15 patient files using the patient identification codes from the random list in the password-protected area of the system. If the trial site demands a second random list then the IGP will set up a further 15 patient files.

16.1.3 Schedule of the intervention

In the intervention arm, patients will be looked after by the GP and a trained HCA from the general practice. The practices in the intervention group will receive the simplified version of parts I and II of the latest geriatrics guideline from the Hessen guideline group as a "recommended standard".[1] All study patients from the intervention group will receive the following structured intervention:

	Procedural step	Content
1	HCA arranges appointment	The HCA arranges an appointment with the patient to visit the practice. The patient will be asked to bring all drugs to the appointment that he or she takes, whether occasionally or regularly (also including OTC drugs phytopharmaceuticals and nutrition supplements) including the original packaging wherever possible.
2	HCA enters patient's core data and "practice medication" into Medibox 1 (AiD+)	The HCA logs into the web-based AiD+ (Internet address and password for the protected area are kept in the investigator file. On the trial site's page she calls up the patient by entering the patient's ID and compares the patient's reference code with that of the practice EDP. She confirms that the written declaration of informed consent is dated, has been signed personally and is present in the investigator file. She enters the date of birth, size and weight and the most current laboratory values (serum-potassium, -sodium and -creatinine) in the core data page of AiD+. Then she enters the prescribed medication from the most current therapy plan into AiD+, (entered in practice software) (Medibox 1: "practice medication"). After entering the data she logs out of AiD+.
3	HCA interviews patient on basis of checklist (MediMoL)	The patient arrives at the practice at the arranged time with all the drugs currently being taken. The HCA systematically asks the patient on the basis of a checklist (Medication Monitoring List, MediMoL) about pain, common symptoms of ADRs, need for information on the drugs, reasons for not taking drugs (including technical reasons such as the need to split tablets), adherence aspects such as neglecting to take long-term medication, objections to specific medication and about preferred therapy goals. The MediMoL includes the possibility to answer in free text as well as in pre-provided response categories that take the form of a traffic light pattern, enabling quick comprehension, and more sophisticated reactions according to severity: ▪ Red response category ("Emergency"): in case of this answer, the interview with the patient will be interrupted and the HCA will contact the GP immediately who will then decide how to proceed. ▪ Orange response category ("potentially serious and with a high probability of a clinically relevant problem"): the interview with the patient will be continued as planned. The HCA will inform the GP of the findings on the same day (at the latest within the next 24

	Procedural step	Content
		hours). The GP will decide what to do next. · Yellow response category ('*potentially* a clinically relevant problem'): the interview is continued as planned. If the category yellow is the most serious answer the HCA puts the MediMoL into the general findings tray that is looked at by the GP. · Green response category ('no problem'): the GP is informed of the MediMoL by means of the general findings tray.
4	HCA enters "house medication" into Medibox 2 *brown bag review*	The HCA logs into the password protected area of AiD+ and opens the patient's file (compare patient ID and date of birth with the data in the investigator's file). The HCA enters all drugs (regular medication, medication to be taken as needed, prescriptions from co-treating doctors, OTC products including phytopharmaceuticals and nutrition supplements) using its trade name, the name of the active ingredient or National Drug Code. In addition she records the dosage. After entering the information she stores it under home medication (Medibox 2).
5	GP checks the medication and problems associated with the medication with the support of AiD+ and MediMoL	The GP logs into the password protected area of AiD+ and opens the patient's file. He checks AiD+, "home medication" and "practice medication" for agreement in terms of the active ingredient (on the ATC code level) and dose. Both home and practice medication appear in a shared AiD+ window (Medibox 3: "coordinated medication", sorted according to ATC group (groups of active ingredients), whereby the origin of the medication – whether home or practice medication – can be recognized by the coloured background. Thus if there is total agreement between home and practice medication (the prescribed medication is the same as the medication actually taken), Medibox 3 will contain drug pairs with identical active ingredients. The GP then deletes the drug pairs and checks the warnings (drug interactions, duplication with other drugs) and pointers (renal dose adjustment, tablet divisibility, exceeding maximal dose) for clinical relevance. He identifies patient problems using MediMoL. He prepares necessary therapy adjustments in „Medibox 3".
7	Consultation between GP and patient on medication	The GP discusses the identified problems and any necessary changes in the medication with the patient. He saves the prescription plan he has discussed with the patient in the practice computer and makes a note of other arrangements (further appointments, transfer to a specialist etc.) on the MediMoL. He ends the interview with the patient and gives the MediMoL back to the HCA.
8	HCA ends the intervention	The HCA prints out the updated prescription plan and gives it to the patient. She follows any other instructions that have been made on MediMoL by the GP (e.g. makes an appointment for further interviews, laboratory checks, transfers to a specialist).

Medication Monitoring List (MediMoL)

PRIMUM

Date of interview

Name of the patient ..... ID .....

Name of health care assistant .....

	Contact GP	Follow-up consultation within	Report to the GP	Normal findings

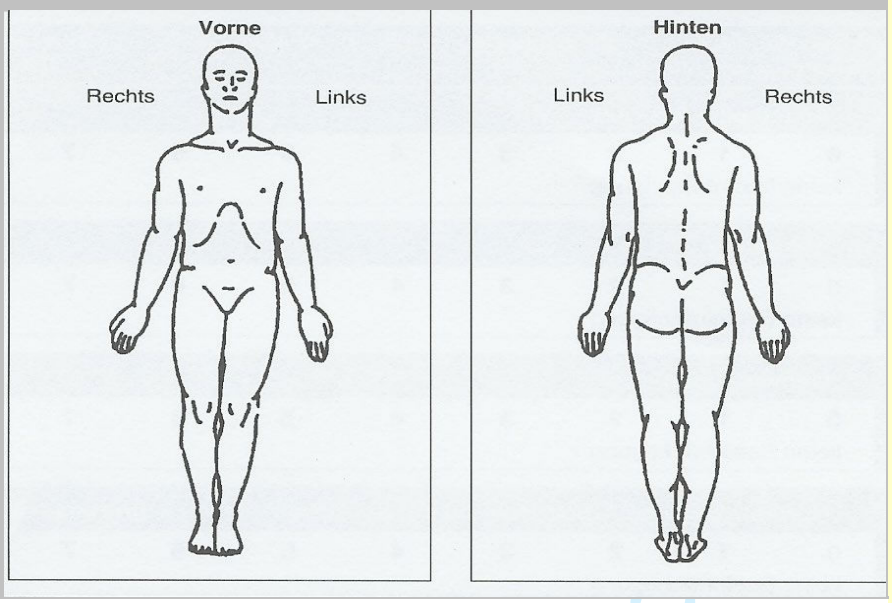
Pain: potential underuse?

1. Did you suffer from pain during the past 2 weeks?

Please take the time frame into consideration! If the patient reports pain, let him/her show the area that hurts. Circle all the aching regions on the map. If more than one area hurts, ask where the pain is most severe and mark the respective circle with an additional arrow.

Yes

Where?



Please present the verbal rating scale (VRS) to the patient and ask him/her about the intensity of the pain. If the patient reports pain in more than one place, ask him/her to describe the intensity at the location where it is most severe.

How intense was the pain during the past week?

- Worst imaginable pain
- Severe pain — 24h
- Moderate pain
- Mild pain
- No pain

Did the pain limit your ability to perform activities of daily living (e.g. shopping, gardening, etc.)?

- Yes
- No

No

Potential ADR

2. Did you suffer from the following complaints/symptoms during the past 2 wks?

Please take the time frame into consideration!

2.1 Nausea or vomiting? *Please underline as applicable.*

Yes
- Almost every day — 24h
- On a number of days
- Once

No
- Never

Did you suffer from the following complaints or symptoms during the past two weeks? (cont.)

Potential adverse drug reactions (ADR) or symptoms of underlying diseases

		Contact GP	Follow-up consultation within	Report to the GP	Normal findings
2.2 Dizziness?					
Yes	Almost every day		24h		
	On a number of days				
	Once				
No	Never				
2.3 Shortness of breath?					
Yes	Almost every day		24h		
	On a number of days				
	Once				
No	Never				
2.4 Abnormally rapid heart rate or irregular heartbeat? *Please underline as applicable.*					
Yes	Almost every day		24h		
	On a number of days				
	Once				
No	Never				
2.5 Swollen legs / edema?					
Yes					
No					
2.6 Do you think, your tendency to bleed has increased?					
Yes	Did you suffer from one of the following **more than once** during the past two weeks?				
	Bleeding gums?				
	Nosebleed?				
	Prolonged bleeding after a mild injury (e.g. when shaving or after a light cut)?				
	You have bruises that are more than 3 cm in diameter but you do not remember bumping yourself?				
	None of these problems.				
No					
2.7 Did you notice any black feces / melena during the past three months?					
Please take the time frame into consideration!					
Yes	Did the feces really look black and "tarry" (like tar) or was it just dark?				
	Yes, black and tarry. When did you last notice it?				
	Within the past three days				
	Within the past three weeks but not the past three days		24h		
	More than three weeks ago				
	No, only dark				
No					

Was the green box selected to answer questions 2.1 to 2.7? If so, go to question 3. If a different colored box was chosen to answer at least one question, go to question 2.8.

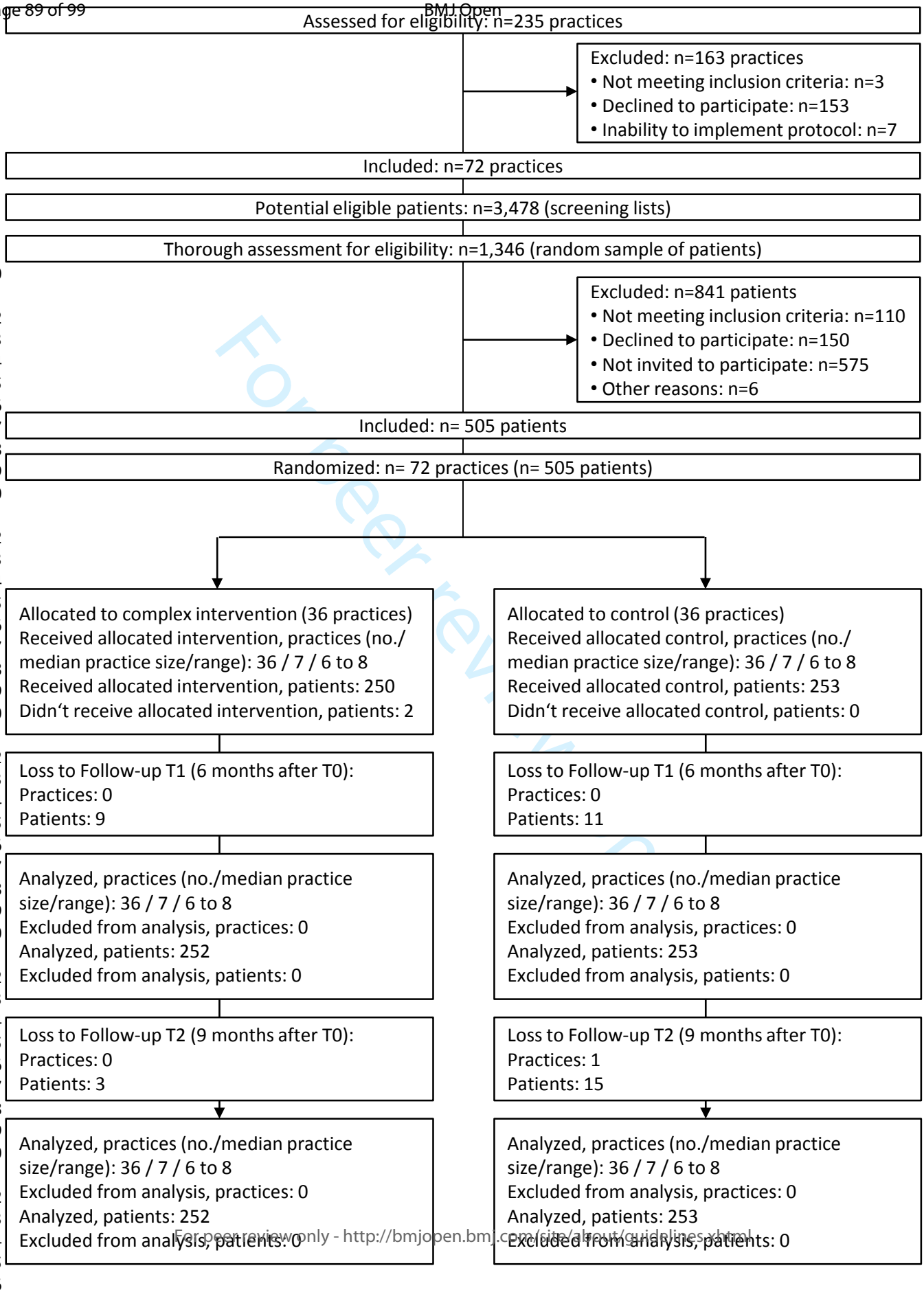
2.8 Do you think your symptoms/complaints are caused by your medication?					
Yes	What makes you think so?				
	_____				
	_____				
No					

		Contact GP	Follow-up consultation within	Report to the GP	Normal findings
Information	**3. Do you need more information on your medication?**				
	Yes What in particular would you like to know? _____			☐	
	No				☐
Problems to take medicines in	**4.1 Did you have any of the following problems handling your medication during the past two weeks?**				
	Getting medicine out of the box or blister pack?				
	Yes Which drugs? _____			☐	
	No				☐
	Splitting, crushing or dissolving tablets?				
	Yes Which drugs? _____			☐	
	No				☐
	Counting the drops of a solution or applying plasters?				
	Yes Which drugs? _____			☐	
	No				☐
	Inserting suppositories?				
	Yes Which drugs? _____			☐	
	No				☐
	Administering inhalers or nebulizers?				
	Yes Which drugs? _____			☐	
	No				☐
	4.2 Did you have any difficulties swallowing a medicine during the past two weeks?				
	Yes The medicine is too large			☐	
	The taste is bad			☐	
	I have always had difficulties swallowing tablets			☐	
	Other reasons: _____			☐	
	No				☐
Adherence	**5.1 Did you try a medicine which was recommended by relatives, friends, neighbors etc. during the past two weeks ?**				
	Yes Which drugs?			☐	
	No				☐
	5.2 During the past two weeks, did you only take certain medicines when you felt worse?				
	Yes Which drugs? _____			☐	
	No				☐
	5.3 During past two weeks, did you neglect to take your prescribed medicine now and then?				
	Yes Which drugs? _____				
	When do you neglect to take your medicine?				
	_____			☐	
	No				☐
	5.4 Would you like to take fewer medications?				
	Yes Would you like to discuss this with your physician?				
	Yes Anything in particular?			☐	
	No				☐
	No				☐

		Contact GP	Follow-up consultation within	Report to the GP	Normal findings
Adherence	**5.5 Do you take a medicine that you would prefer not to take?**				
	Yes — Which medicine?			☐	
	What don't you like about it?				
	I can't tolerate it.			☐	
	I don't believe it is effective.			☐	
	It is too expensive			☐	
	Because I have to take so many other medications.			☐	
	Other reasons: _____			☐	
	No				☐
Patientent's preferences & treatment goals	**6.1 What are your medications supposed to achieve in your current situation?**				
	Please answer by ticking the blue boxess. ***Several answers possible*** *.*				
	☐ Prolonged survival?			☐	
	☐ Fewer hospitalizations?			☐	
	☐ Less pain?			☐	
	☐ Improved functional status (e.g., able to go shopping)			☐	
	☐ More enjoyment of life?			☐	
	☐ Others: _____			☐	
	6.2 What is most important to you?				
	Please tick one of the yellow boxes above (6.1). *Please note:* ***one answer only!***				
Communication within the practice team	**7. Making an appointment for a consultation with the physician (depending on find**				
	If you ticked any orange boxes, please inform the patient that after checking with the GP, you may well call him up and ask him to come to the practice. If you ticked only yellow and / or green boxes: please follow the procedure you have agreed upon in your practice for dealing with study patients.				
	Date of appointment with the physician: ..... **End of interview**				
	8. Health care assistant's assessment				
	Was there anything striking about the patient, e.g., exceptional circumstances or conflicts?				
	9. Information provided to the health care assistant by the physician after the physician-patient consultation on medication-related problems				
	Order lab tests: _____				
	☐ Electrolytes, creatinine				
	☐ Blood count				
	☐ Others				
	☐ Referral				
	☐ No changes to treatment				
	Treatment changes:				
	☐ Changes in medication				
	☐ Others				
	☐ Next consultation (follow up)				
	☐ Others				

Acknowledged:

Date Physician ..... Date Health care assistant .....



Characteristics of non-responding practices

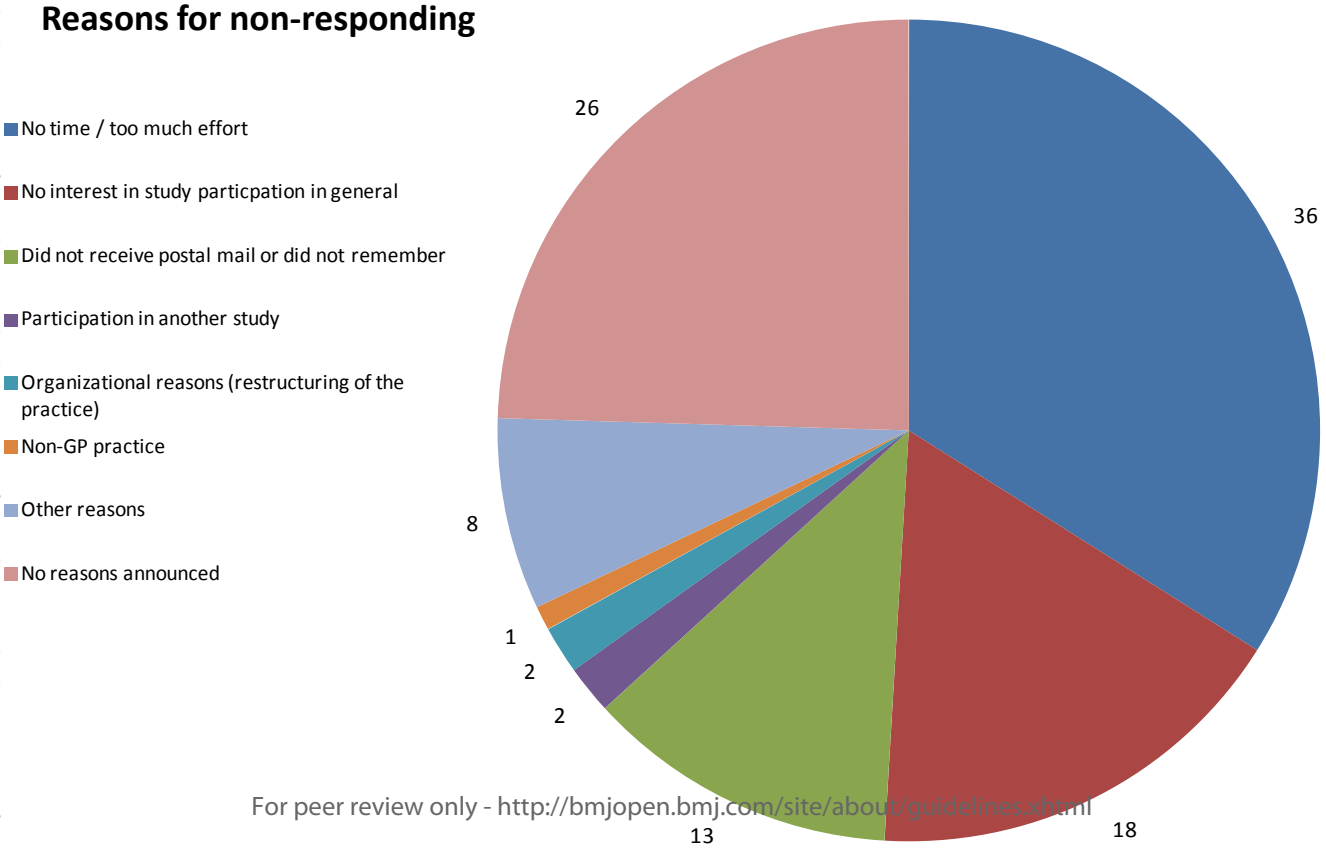
In total, 132 practices were called up to three times, of them 6 did not answer the phone.

107/126 were active general practices, 7 were not, and 12 practices did not provide information about it at the phone.

55/107 (51%) of the general practices had internet access, 50/107 had not, 2 did not provide details.

	Participating practices (total)	Non-responding practices
Practices	**N=72**	**N=132**
Location: no. (%)	N=72	N=132
City (>100,000 inhabitants)	22 (31%)	46 (35%)
Middle size town (20,000 to 100,000)	16 (22%)	37 (28%)
Small town (5,000 to 20,000)	25 (35%)	47 (36%)
Rural area (<5,000 inhabitants)	9 (13%)	2 (2%)
Practice type: no. (%)	**N=72**	**N=126**
Single handed practices	41 (57%)	75 (60%)
Group practice	27 (38%)	27 (21%)
Practice community	4 (6%)	6 (5%)
Not announced	-	18 (14%)

Reasons for non-responding



Effectiveness of a complex intervention on PRIoritising MUltimedication in Multimorbidity (PRIMUM) in primary care: results of a pragmatic cluster-randomised controlled trial.

Christiane Muth, Lorenz Uhlmann, Walter E. Haefeli, Justine Rochon, Marjan van den Akker, Rafael Perera, Corina Güthlin, Martin Beyer, Frank Oswald, Jose M. Valderas, André Knottnerus, Ferdinand M. Gerlach, Sebastian Harder

Web-appendix 4: Symptoms for potential adverse drug reactions (ADR) - descriptive analysis

Symptom† *(number, percentage)*	T0		T1		T2	
	Control group (n=253)	Intervention group (n=252)	Control group (n=237)	Intervention group (n=238)	Control group (n=225)	Intervention group (n=231)
Bleeding diathesis#	44 (17)	33 (13)	28 (12)	43 (18)	34 (15)	39 (17)
Ankle edema	78 (31)	84 (33)	79 (33)	87 (37)	67 (30)	90 (39)
Dizziness#	54 (21)	54 (21)	61 (26)	52 (22)	59 (26)	46 (20)
Dyspnea#	86 (34)	70 (28)	62 (26)	68 (29)	55 (24)	53 (23)
Difficulties urinating	51 (20)	64 (25)	56 (24)	54 (23)	43 (19)	47 (20)
Abdominal pain#	36 (14)	37 (15)	29 (12)	24 (10)	38 (17)	30 (13)
Tachycardia or palpitation#	36 (14)	36 (14)	28 (12)	26 (11)	21 (9)	21 (9)
Nausea or vomiting#	16 (6)	11 (4)	22 (9)	10 (4)	8 (4)	15 (6)

†for details see Figure 1, item "h", #symptoms appeared on at least several or almost every day

Manuscript: "Effectiveness of a complex intervention on PRIoritising MUltimedication in Multimorbidity (PRIMUM) in primary care: results of a pragmatic cluster-randomised controlled trial."

Table 1: CONSORT 2010 checklist of information to include when reporting a cluster randomised trial

Section/Topic	Item No	Standard Checklist item	Extension for cluster designs	Page No.*
Title and abstract				
	1a	Identification as a randomised trial in the title	Identification as a cluster randomised trial in the title	✓ - p. 1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)[i,ii]	See table 2	✓ - p. 1
Introduction				
Background and objectives	2a	Scientific background and explanation of rationale	Rationale for using a cluster design	~~7~~ p.6 (lines 119-125), p. 7 (132-134 and 144-146) Introduction section for scientific background and publication of the pilot trial [35][iv]
	2b	Specific objectives or hypotheses	Whether objectives pertain to the cluster level, the individual participant level or both	p. 7 (lines 134-140 and 147-148)
Methods				
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	Definition of cluster and description of how the design features apply to the clusters	p. 7 (lines 144-145), p. 8 (lines 184-188)
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons		**none**
Participants	4a	Eligibility criteria for participants	Eligibility criteria for clusters	p. 7 (lines 153-156), p. 8 (lines 167-181)
	4b	Settings and locations where the data were collected		7
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Whether interventions pertain to the cluster level, the individual participant level or both	p. 8~~-~~ (lines 196-206, 209-211) plus PaTplot (figure 1, icons "2" to "5" and "j" to "k"), provision of an instrument (web-appendix 2)
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	Whether outcome measures pertain to the cluster level, the individual participant level or both	p. 9-11~~0~~ (lines 214-265) plus PaTplot (figure 1, icons "f" to "h")
	6b	Any changes to trial outcomes after the trial commenced, with reasons		**none**
Sample size	7a	How sample size was determined	Method of calculation, number of clusters(s) (and whether equal or unequal cluster sizes	p. ~~10~~ 11 (lines 268-278)

Section/Topic	Item No	Standard Checklist item	Extension for cluster designs	Page No.*
			are assumed), cluster size, a coefficient of intracluster correlation (ICC or *k*), and an indication of its uncertainty	
	7b	When applicable, explanation of any interim analyses and stopping guidelines		n.a.
Randomisation:				
Sequence generation	8a	Method used to generate the random allocation sequence		p. 8 (lines 186-188) plus PaTplot (figure 1: icon "i")
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Details of stratification or matching if used	p. 8 (lines 186-188) plus PaTplot (figure 1: icon "i")
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Specification that allocation was based on clusters rather than individuals and whether allocation concealment (if any) was at the cluster level, the individual participant level or both	p. 8 (lines 188-189)
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Replace by 10a, 10b and 10c	
	10a		Who generated the random allocation sequence, who enrolled clusters, and who assigned clusters to interventions	p. 8 (lines 186-189) plus PaTplot (figure 1: icon "i")
	10b		Mechanism by which individual participants were included in clusters for the purposes of the trial (such as complete enumeration, random sampling)	p. 8 (lines 167-168) plus PaTplot (figure 1: icons "c" to "e")
	10c		From whom consent was sought (representatives of the cluster, or individual cluster members, or both), and whether consent was sought before or after randomisation	PaTplot (figure 1: icons "a", "b", "e")
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how		p. 8-9 (lines 189-192)
	11b	If relevant, description of the similarity of interventions		~~8~~ p. 9 (lines 203-206 and 209-211): both groups received practice guidelines for older adults~~)~~
Statistical methods	12a	Statistical methods used to	How clustering was taken into	p. 12~~1~~ (lines 287-296,

Section/Topic	Item No	Standard Checklist item	Extension for cluster designs	Page No*
		compare groups for primary and secondary outcomes	account	301-303)
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses		p. 1~~1~~2 (lines 297-301)
Results				
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	For each group, the numbers of clusters that were randomly assigned, received intended treatment, and were analysed for the primary outcome	Web-appendix 3 (Flow chart)
	13b	For each group, losses and exclusions after randomisation, together with reasons	For each group, losses and exclusions for both clusters and individual cluster members	p. 1~~1~~2-1~~3~~2 (lines 311-324) plus web-appendix 3
Recruitment	14a	Dates defining the periods of recruitment and follow-up		PaTplot (figure 1)
	14b	Why the trial ended or was stopped		N.a., trial was completed.
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Baseline characteristics for the individual and cluster levels as applicable for each group	p. 13 (lines 327-337) and Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	For each group, number of clusters included in each analysis	Table 1; web-appendix 3 (flow chart), table 1 and 2; web-appendix 4,
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Results at the individual or cluster level as applicable and a coefficient of intracluster correlation (ICC or k) for each primary outcome	p. 13-14 (lines 342-348, 372-379), Table 2; Figure 3; ~~W~~web-appendix 4~~,~~ (table) ~~1 and 2~~; web appendix 3~~,~~ (flow chart)
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended		n.a.
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory		p. 14 (lines 353-359) and Figure 2 (2a and 2b)
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms[iii])		n.a.
Discussion				
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses		p. ~~14~~ 15-16 (lines 398-437)
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	Generalisability to clusters and/or individual participants (as relevant)	p. ~~22~~15-16 (lines 406-417)
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other		p. 17 (lines 462-473) ~~23~~p. 18 (lines 481-487)

Section/Topic	Item No	Standard Checklist item	Extension for cluster designs	Page No.*
		relevant evidence		
Other information				
Registration	23	Registration number and name of trial registry		p. 4 (lines 76-78)
Protocol	24	Where the full trial protocol can be accessed, if available		Web-appendix 1
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders		p. 197 (lines 521-522)

** Note: page and line numbers refer to the numbers within the original WORD file with track changes (2nd revision)*

Table 2: Extension of CONSORT for abstracts[i1,ii2] to reports of cluster randomised trials

Item	Standard Checklist item	Extension for cluster trials	Page No*
Title	Identification of study as randomised	Identification of study as cluster randomised ✓	p. 1 (lines 1-2)
Trial design	Description of the trial design (e.g. parallel, cluster, non-inferiority)	✓	p. 3 (line 49)
Methods			
Participants	Eligibility criteria for participants and the settings where the data were collected	Eligibility criteria for clusters ~~We did not apply inclusion criteria of major relevance for practices and provided this information with main text.~~	We did not apply inclusion criteria of major relevance for practices and provided this information with main text.
Interventions	Interventions intended for each group	✓	p. 3 (lines 54-58)
Objective	Specific objective or hypothesis	Whether objective or hypothesis pertains to the cluster level, the individual participant level or both ✓	In accordance with a reviewer's comment (Q26), we have removed the sentence from the abstract (p. 3, line 6): „Outcomes were measured at patient level"
Outcome	Clearly defined primary outcome for this report	Whether the primary outcome pertains to the cluster level, the individual participant level or both ✓	In response to a reviewer (Q26), we have removed the sentence from the abstract (p. 3, line 6): „Outcomes were measured at patient level"
Randomization	How participants were allocated to interventions	How clusters were allocated to interventions ✓	We used a common allocation ratio (1:1) and did not report it in the abstract due to the limit of the word count.
Blinding (masking)	Whether or not participants, care givers, and those assessing the outcomes were blinded to group as-	✓	We reported in the main text: "Owing to the character of the

Item	Standard Checklist item	Extension for cluster trials	Page No*
	signment		intervention, it was not possible to blind GPs, HCAs, patients, and the study team. Treatment allocation was blinded to the clinical pharmacologist conducting medication reviews for the primary outcome (MAI - medication appropriateness index) and to the statistician." Due to the limited word count, we did not report these details in the abstract.
Results			
Numbers randomized	Number of participants randomized to each group	Number of clusters randomized to each group ✓	p. 3 (lines 64-65)
Recruitment	Trial status[1]	~~N.a.~~	N.a.
Numbers analysed	Number of participants analysed in each group	Number of clusters analysed in each group ✓	p. 3 (lines 64-65)
Outcome	For the primary outcome, a result for each group and the estimated effect size and its precision	Results at the cluster or individual participant level as applicable for each primary outcome ✓	p. 3 (lines 65-67)
Harms	Important adverse events or side effects	~~n.a.~~	n.a.
Conclusions	General interpretation of the results	✓	p. 3 (lines 70-75)
Trial registration	Registration number and name of trial register	✓	p. 4 (lines 76-78)
Funding	**Source of funding**	~~Due to the word limit, we provided the source of funding with the plain text~~	Due to the word limit, we provided the source of funding with the plain text

Note: page and line numbers refer to the numbers within the original WORD file with track changes (2nd revision)

[1] Relevant to Conference Abstracts

The TIDieR (Template for Intervention Description and Replication) Checklist*:

Information to include when describing an intervention and the location of the information

Item number	Item	Where located **	
		Primary paper (page or appendix number)	Other † (details)
	BRIEF NAME		
1.	Provide the name or a phrase that describes the intervention.	The title: "complex intervention in PRIoritising MUltimedication in Multimorbidity (PRIMUM) in primary care"	_____
	WHY		
2.	Describe any rationale, theory, or goal of the elements essential to the intervention.	Abstract: objectives Main text: introduction (p. 6-7)	Pilot study [35] [iv]
	WHAT		
3.	Materials: Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (e.g. online appendix, URL).	Abstract: interventions Main text: p. 98, ~~last~~ paragraph on "Intervention and control groups" Figure 1 (icons "j" and "3" to "5") web-appendices 1 (study protocol) and 2 (checklist MediMoL)	_____
4.	Procedures: Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities.	Abstract: interventions Main text: p. ~~8~~ 9 Figure 1 (icons "j" and "3" to "5") web-appendices 1 (study protocol) and 2 (checklist MediMoL)	_____
	WHO PROVIDED		
5.	For each category of intervention provider (e.g. psychologist, nursing assistant), describe their expertise, background and any specific training given.	Abstract: interventions Main text: methods section; for expertise and background of health care assistants (introduction: p. 6-7, last paragraph); Figure 1 (icon "2~~i~~"	_____

		for intervention training)	
	HOW		
6.	Describe the modes of delivery (e.g. face-to-face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group.	Figure 1 (icons "j" and "3" to "5")	_____
	WHERE		
7.	Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features.	Figure 1 (icons "j" and "3" to "5")	_____
	WHEN and HOW MUCH		
8.	Describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity or dose.	Methods section p. 98, last paragraph	_____
	TAILORING		
9.	If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how.	N/A	_____
	MODIFICATIONS		
10.‡	If the intervention was modified during the course of the study, describe the changes (what, why, when, and how).	N/A - the intervention was not modified during the study.	_____
	HOW WELL		
11.	Planned: If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them.	N/A	_____
12.‡	Actual: If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned.	N/A	_____

** **Authors** - use N/A if an item is not applicable for the intervention being described. **Reviewers** – use '?' if information about the element is not reported/not sufficiently reported.

† If the information is not provided in the primary paper, give details of where this information is available. This may include locations such as a published protocol or other published papers (provide citation details) or a website (provide the URL).

ǂ If completing the TIDieR checklist for a protocol, these items are not relevant to the protocol and cannot be described until the study is complete.

* We strongly recommend using this checklist in conjunction with the TIDieR guide (see *BMJ* 2014;348:g1687) which contains an explanation and elaboration for each item.

* The focus of TIDieR is on reporting details of the intervention elements (and where relevant, comparison elements) of a study. Other elements and methodological features of studies are covered by other reporting statements and checklists and have not been duplicated as part of the TIDieR checklist. When a **randomised trial** is being reported, the TIDieR checklist should be used in conjunction with the CONSORT statement (see www.consort-statement.org) as an extension of **Item 5 of the CONSORT 2010 Statement.** When a **clinical trial protocol** is being reported, the TIDieR checklist should be used in conjunction with the SPIRIT statement as an extension of **Item 11 of the SPIRIT 2013 Statement** (see www.spirit-statement.org). For alternate study designs, TIDieR can be used in conjunction with the appropriate checklist for that study design (see www.equator-network.org).

REFERENCES

[i] Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG, et al. CONSORT for reporting randomised trials in journal and conference abstracts. *Lancet* 2008, 371:281-283

[ii] Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG at al (2008) CONSORT for reporting randomized controlled trials in journal and conference abstracts: explanation and elaboration. *PLoS Med* 5(1): e20

[iii] Ioannidis JP, Evans SJ, Gotzsche PC, O'Neill RT, Altman DG, Schulz K, Moher D. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Ann Intern Med* 2004; 141(10):781-788.

[iv] Muth C, Harder S, Uhlmann L, Rochon J, Fullerton B, Guthlin C, et al. Pilot study to test the feasibility of a trial design and complex intervention on PRIoritising MUltimedication in Multimorbidity in general practices (PRIMUMpilot). BMJ Open 2016;6(7):e011613.