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**

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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

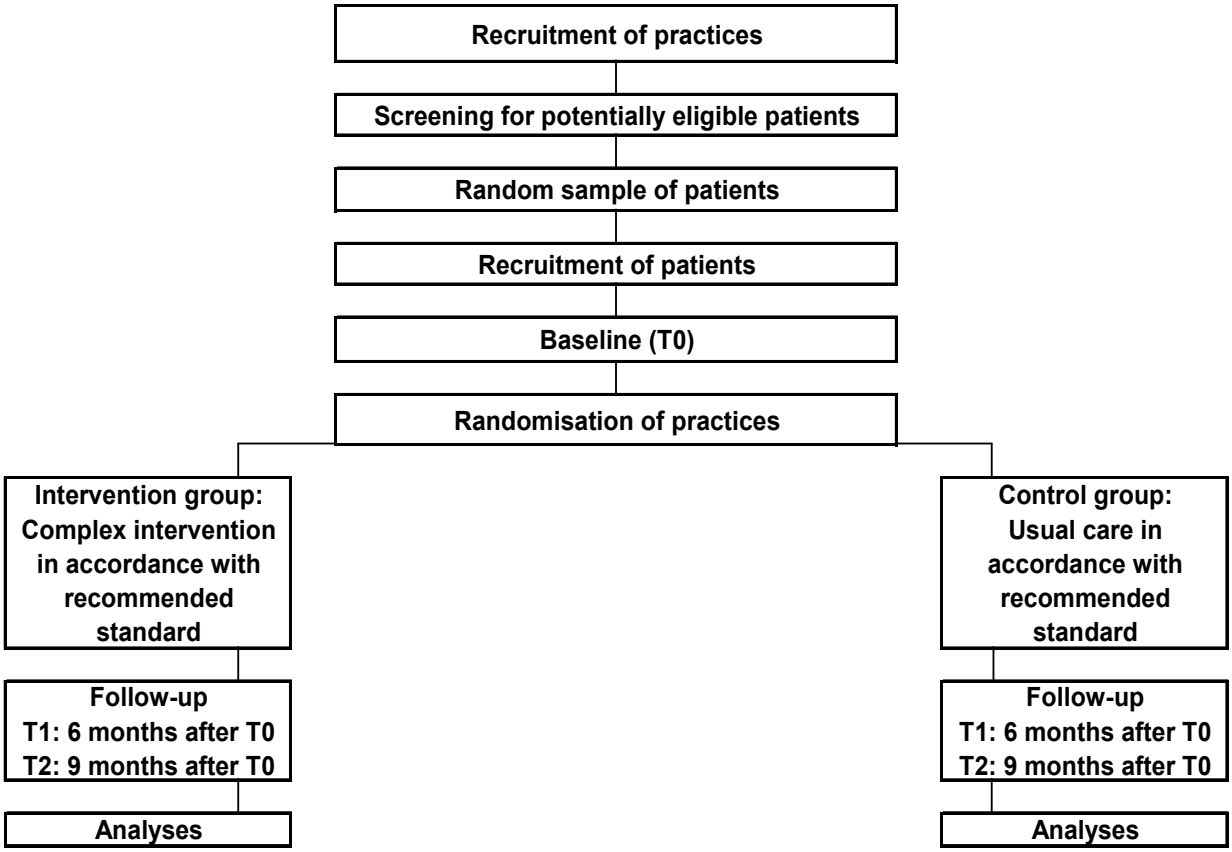
In- and exclusion criteria for trial sites (practices)	Inclusion criteria - General practice cares for patients covered by statutory health insurance and is active in primary care - Specialist doctor for general practice or internal medicine, or doctor with no specialist field. - Practice has internet 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]

o 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.

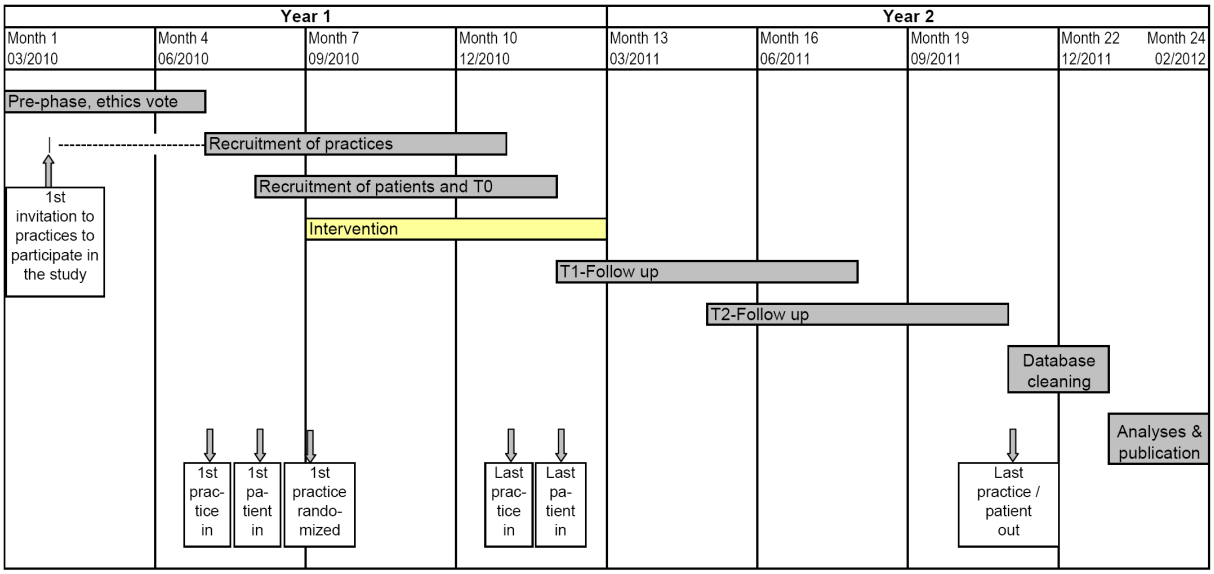
11.8.3 End of treatment

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).