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

[PRIMUM *Pilot*]

Pilot study on ***PRI***oritising MUltiple medication in Multi-morbid patients

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

1.2 Signature Page

Attestation of Protocol

The trial protocol is herewith attested in its final version:

Leading investigator for the clinical trial: Dr. med. Christiane Muth, MPH

Place, Date	Signature

Co-Investigators

Prof. Dr. F. Gerlach, MPH:

Place, Date	Signature

Prof. Dr. med. Walter E. Haefeli:

Place, Date	Signature

Prof. Dr. med. Sebastian Harder:

Place, Date	Signature

Methods counselling during trial planning phase, counselling on evaluation and publication of the trial and supervision of statistical analysis

Dipl.-Psych. Justine Rochon:

Place, Date	Signature

1.3 Signature page for investigators

Acknowledgement of protocol

(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 the stipulations laid down in this protocol.

Investigator:

Name, first name: _____

Practice stamp:

_____ _____

Place, Date Signature

1.4 Synopsis of Protocol

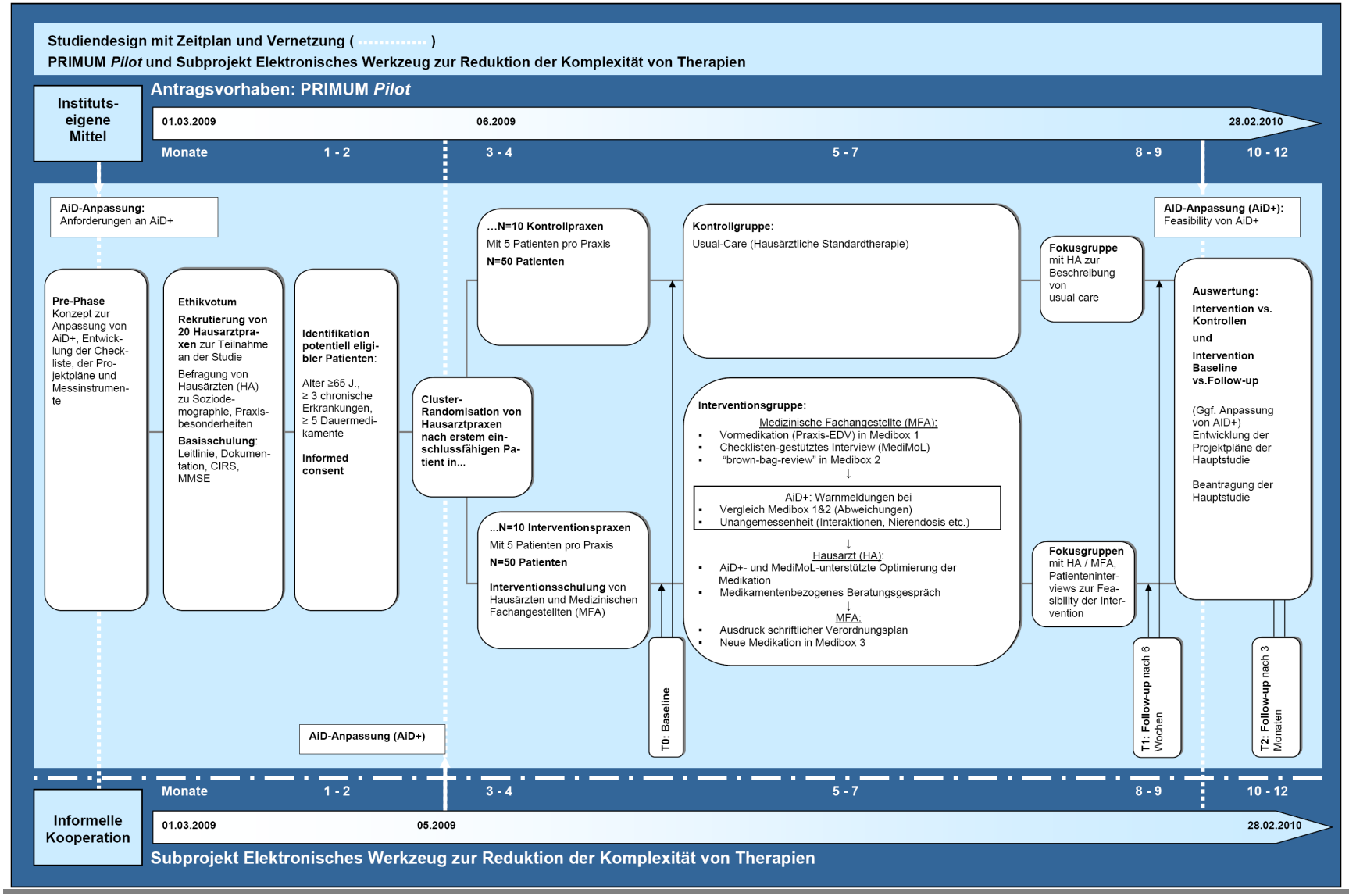
title of Trial:	Prioritization and Optimisation of Multimedication in elderly, multimorbid patients in general practice
Abbreviated name of trial	PRIMUM *Pilot* - Pilot trial on Prioritization of Multimedication in Multimorbid patients
Sponsor	Johann Wolfgang Goethe University, Frankfurt am Main
Head of Clinical Trial	Dr. med. Christiane Muth, MPH
Indication:	Multimedication in elderly, multimorbid patients: Age ≥ 65, ≥ 3 chronic diseases, ≥ 5 long-term medicines
Rationale	1. Multimorbidity, multimedication and increasing age raise the risk of inappropriate prescriptions and adverse drug events 2. Multimedication and high complexity of medication reduce adherence among patients 3. Doctor patient interviews on problems related to medicines are dominated by doctors in content and focus mostly on effectiveness 4. Patients do not generally inform doctors of adverse drug reactions and autonomous decisions to adjust medication dose (1) Use of pharmaceutical information system (AiD+) reduces number of inappropriate prescriptions (pharmaceutical interactions, renal dose adjustments, duplicate prescriptions) (1-4) Take records of medicines that were actually taken and problems relating to medicines (technical handling,potential adverse drug reactions) by medical assistant provides structured information for the family doctor and enables patients to discuss their problems with the doctor. → Prescriptions become more appropriate → Prescriptions become less complex → Prescriptions take the patient's perspective into account (avoidance of adverse drug reactions, patients' preferences are taken into account) and priorised → Patients are more satisfied with the information they receive and adhere to the doctor's therapy
Trial design:	Pilot trial, two armed, controlled, open, cluster-randomized (Randomization and intervention on the general practice level (HA-Praxen), measurement of outcomes on patient level, blind evaluation
Aim of trial:	(1) To ascertain the feasility of an intervention for the prioritization and optimisation of multimedication in elderly, multimorbid patients in general practice (2) To investigate the feasibility of the planned cluster-randomized main trial for the evaluation of the effectiveness of this intervention under the following aspects: - The practicability of the intervention, - The recrutability of practices and patients, - The randomisability of practices,

	- A check of the suitability of the Medication Appropriateness Index as a potential, primary outcome criterium for the planned main trial and, based on that, the sample size estimation for the main trial.
Further aims of the trial:	- To investigate the suitability of further target variables for the main trial; - A description of usual care among family doctors when adjusting medication for elderly, multimorbid patients
Number of trial sites and patients	To test a criterium, 30 patients per group are sufficient for a good estimate of mean and standard deviation. In order to achieve this aim with certainty, 50 patients will be recruited for the intervention group and 50 for the control group, making a total of N=100. Therefore five patients will be recruited from each of k=20 practices.
In- and exclusion criteria for trial sites (practices)	Inclusion criteria - Doctor's practice accepts patients covered by statutory health insurance - 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 - Agreement of the investigator to train a medical assistant from the practice for the intervention, as required by the trial (brown bag review, patient interviews on basis of checklist) Exclusion criteria - Practice focuses on unconventional medical treatments - Practice focuses on special indications (e.g. HIV)
In- and exclusion criteria for patients	<u>Inclusion criteria:</u> - Age ≥ 65 and - ≥ 3 chronic diseases - ≥ 5 long-term medicines and - Health care provided by family doctor (at least one contact in most recent quarter) 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 consent to participate in trial <u>Exclusion criteria:</u> - Diseases cause life expectancy of < 6 months - Abuse of alcohol or illegal drugs and visible clinical signs or symptoms therof - Cognitive disability that prevents trial participation (MMSE < 26) or - emotional stress that prevents participation in trial or - not legally competent or - Participation in a clinical investigation over the following 30 days - -

Therapy	Intervention: computer assisted optimization of multi-medication using recommended standard controls: Usual care in accordance with recommended standards
Visits:	Visit T0 (Baseline), Visit T1 (Follow up after 6 weeks), visit T2 (Follow up after 12 weeks)
Primary and secondary outcomes:	A) Practicability of intervention ▪ Estimation of time / cost of intervention including training for GPs and medical assistants B) Feasibility of trial ▪ Reasons for non-participation of patients ▪ Proportion of patients with loss to follow up compared to entire population ▪ Feasibillity of taking measurements T0, T1 (Time required by GP and medical assistant for documentation, content and duration of patient interviews) C) Test potential outcome criteria for the main trial: 1. ***Appropriateness of medication*** (*potential primary outcome criterium in the main trial*): the appropriateness will be rated by two experts independently and blinded with regard to the group to which the patient belongs by means of the Medication Appropriateness Index (MAI) and selected scales from the PiDoc©-classification system. The feasibility (quantity of trial data required, time consumed by medication review) will be checked and the effect size of the intervention will be calculated before and after, as well as between groups. ***2. Medication complexity:*** ▪ Sum of prescriptions ▪ Number of single doses / day ▪ Complexity of the medication regimen (Medication Regimen Complexity Index, MRCI) ***3. Adherence and other factors*** ▪ Adherence as observed from discrepancies between intake (patient interviews) and the prescription (doctor's documentation) at T0, T1 and T2. - Discrepancy score, DIS (Sum of all discrepancies in medicine, time of intake, frequency and dose / sum of all prescriptions, DIS >0.2=1 - Overestimate/Underestimate of actual intake by doctor: Drug Score (DS, Sum of all drug intake / sum of all prescriptions) DS<0.8 or DS>1.2=1. - Dose Score (DoS): DoS = d1(a1) + d2(a2) + d3(a3) + … /n d = patient's intake (0.1) of prescribed medicines, n = sum of all prescriptions, a = variance (actual dd intake/prescribed dd); DoS<0.8 or DS>1.2=1. - Regimen Score (RS): RS = d1(b1) + d2(b2) + d3(b3) + … /n d = patient's intake (0.1) of prescribed medicines, n = sum of all prescriptions, b = variance (actual intake frequency per day / prescribed frequency per day); RS<0.8 or DS>1.2=1. ▪ Self reported adherence of patients (Medication Adherence Report Scale, MARS and adherence according to Morisky) ▪ Attitude of patients to medicinal therapy (Beliefs about Medicines Questionnaire, BMQ)

	▪ Satisfaction of patients with information provided on medicines ***4. Quality of life, preservation of functional status*** ▪ General quality of life (EuroQuoL) ▪ WHO Disability Assessment Schedule (WHO-DAS II) ***5. Pain*** ▪ Verbal Rating scale (VRS) ***6. Days in hospital*** 7. ***Number (and type) of adverse drug reactions(ADR))***
Potentally disruptive factors	▪ Age ▪ Gender ▪ Additional prescribers in treatment process ▪ Depressivity (Geriatric Depression Scale, GDS) ▪ Co-morbidity: Cumulative Illness Rating Scale (CIRS), Charlston-Comorbidity-Index ▪ Infirmity (Sherbrooke Questionnaire)
Biometrics	- Descriptive and according to the intention to treat principle - Additional evaluation per protocol in form of sensitivity analyses - Regression for effects of covariables - All analyses include correction for cluster effect
Schedule:	- Begin of pre-phase for the development of Drug Information Service +, all trial plans and implemented instruments 01.01.09 - Begin of practice recruitment 01.02.09 - Beginof trial (sponsorship begins) 01.03.09 - Vote from Ethics Commission 16.03.09 - Begin of patient recruitment 01.05.09 - Duration of trial three months per patient - Deadline for interim report 01.12.09

1.5 Flow chart



1.6 Investigation procedure for control and intervention group

Week	**Before trial begin**	**0**	**6**	**12**
Visits		**T0**	**T1**	**T2**
Trial measures for *control and intervention group*				
Documentation training, doctor	•			
Profile of practices participating in trial	•			
Sociodemographic characteristics of medical assistants	•			
Identification of potentially eligible patients – Pre-randomizations lists	•			
Randomization lists	•			
Patient registration sheet (In- and exclusion criteria, reasons for non-participation of patients; If informed consent available: name, first name, telephone number, MMSW score	•			
CRF, doctor's documentation				
• Detailed sociodemographics, patient		•		
• Patient's current diagnoses		•	•	•
• Patient's current medication		•	•	•
• Height and weight of patient		•	•	•
• Laboratory results of patient (Serum electrolytes K, Na, Serum creatinine)		•	•	•
• Degree of patient's multimorbidity (CIRS)		•	•	•
• Existing co- and multimorbidity of patient (Charlston Comorbidity Index)		•	•	•
• Hospital stays (duration, reason)		•	•	•
Patient questionnaire:				
• General quality of life of patient (EuroQuoL)		•	•	•
• WHO Disability Assessment Schedule (WHO-DAS II)		•	•	•
• Self reported patient adherence (Medication Adherence Report Scale, MARS)		•	•	•
• Attitude of patients to medicinal therapy (Beliefs about Medicines Questionnaire, BMQ)		•	•	•
• Satisfaction of patients with information provided on patients		•	•	•
• Pain: Verbal rating scale		•	•	•

Week	**Before trial begin**	**0**	**6**	**12**
Visits		**T0**	**T1**	**T2**
Telephone interview with patient				
• Sociodemographics		•		
• Current patient medication		•	•	•
• Adverse drug reactions (ADRs according to general list of adverse events in German Medicines Law trials)		•	•	•
• Patient's hospital stays		•	•	•
• Infirmity index (Sherbrooke Questionnaire)		•	•	•
• Depressivity (Geriatric Depression Scale, GDS)		•	•	•
• Self reported adherence of patient (Morisky)		•	•	•
Measures for *intervention group only*				
• Intervention: Training for doctors and medical assistants	•			

2 INTRODUCTION

2.1 Current situation and problem

Care for chronically ill patients is a central challenge for medical care in developmed industrial countries. Increasingly problems arise as a result of co- and multimorbidity and associated multimedication – the intake of five or more medicines at the same time – something which is exacerbated by the aging population. Multimedication is associated with substantial risks in the form of adverse drug reactions (ADR) and concomitant hospitalization and increased mortality.

2.2 Background

The risk of inappropriate prescriptions (interactions, non-observance of renal dose adjustments, non-observance of contraindications, inappropriate choice of of medicines with regard to age and sex and associated discrepancies in terms of pharmaco-kinetics and -dynamics) rises in line with increasing age, multimorbidity and multimedication.[1],[2],[3],[4],[5],[6] 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 optimized..[8]

Multimedication und highly complex medication regimes are associated with poor therapy adherence among patients, whereby modern schools of medicine 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.[9]

Discussions between doctor and patient concerning mediction 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 interview has been understood by the patient. Patients often fail to inform their doctor when they have changed the dosis of a medicine autonomously, or if they have ceased taking a prescribed medicine.[10],[11]

Evidence from previous studies shows that in order to avoid inappropriate prescriptions

- Regular checks of what medicines have been taken (including OTC medicinal products and dietary supplements – a so-called *brown bag review*) and

The use of *computerized decision support systems*, CDSS, that automatically generate warnings in case of potentially inappropriate prescriptions and present suitable strategies to prevent them.[12]

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. This effect could also be demonstrated for interventions carried out be medical assistants and was also true for elderly patients. As a result patients showed higher medication and appointment adherence.[10],[13]

2.3 Rationale

Based on the assumptions that

1. Multimorbidity, multimedication and increasing age increase the risk of inappropriate prescriptions and adverse drug events
2. Multimedication and high medication complexity reduce patient adherence.
3. Discussions between doctor and patient on medication-related problems generally focus on the benefit of a therapy and are dominated by the doctor
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) Collection of information on the actual medication intake *(brown bag review)* and medication-related problems (technical handling, potential adverse drug reactions, patient preferences) by means of a checklist (MediMoL) in a pre-consultation interview conducted by a medical assistant.

(2) The use of a medication information system (AiD+)

(3) Consultations between family doctor and patient on medication-related problems.

Brown bag review and MediMoL provide the family doctor wih structured information. This can then be checked by means of the AiD+, that warns the doctor of potentially inappropriate prescriptions, the need for renal dose adjustments and of unintended duplicate prescriptions.

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

The family doctor and patient then discuss necessary changes in the therapy and decide on a new medication. We expect that after taking into consideration the AiD+ warnings and the patient's problems taking the medicine, as well as his or her dislikes and preferences of the patient, the adapted medication will be more suitable, leading to a reduction in potentially inappropriate prescriptions and medication complexity. Furthermore, we expect a prioritization of the medication will take place (as a result of directly asking and taking into account the patient's perspective.

In consequence it is to be expected that patients are more satisfied with the information they have received on their medication and are more likely to adhere to the doctor's instructions. Their health can be improved through the avoidance of undertreatment in pain therapy and possibly through a reduction in adverse drug reactions and associated events. As a result their functional situation and general quality of life should be improved.

2.4 Risk assessment

The risk to the patients of the intervention and collection of data for study purposes is low, as in the case of the intervention group detailed information on a patient's medication will be made available thus ensuring that worse treatment than previous to the trial is not possible. In the control group, the treatment provided by the family doctor will not be changed at all, so

that the trial cannot result in any deterioration in treatment in this case either. The trial centre (Institute for General Practice, Johann Wolfgang Goethe-University, Frankfurt am Main) has no influence on the diagnostic-therapeutic decision-making of the family doctors and their patients. The results of the analysis of the appropriateness of the medication will only be available to the trial HQ after a substantial time lag, so that no timely feedback to the participating doctors will be possible. In addition, it is rather unlikely that results will indicate any real danger to patients, as due to the limited nature of the clinical data being collected, only potential risks to patients can be identified. In the unlikely event of the identification of any clinically relevant potential danger to a patient, the family practice concerned will be immediately informed (within two working days of danger to the patient becoming known), and all necessary measures taken to eliminate the danger.

3 AIMS OF TRIAL

The aims of this pilot trial (PRIMUM *Pilot*) are

(1) To ascertain the ***feasibility of an intervention*** for the prioritization and optimization of multimedication in multimorbid, elderly patients in general practice and

(2) To ascertain the ***feasibility of a planned cluster-randomized controlled trial*** for the evaluation of the effectiveness of this intervention. Taking into account the recommendations for the preparation of a program for clinical trials of 1999 [14] and 2001 [15],[16] the pilot trial will focus on the following aspects

- the practicability of the intervention,
- the recrutability of practices and patients,
- the ease with which practices can be randomized,
- estimated sample size for the controlled trial.

The ***practicability of the intervention*** will be examined mainly on a qualitative level. The examined quantitative factors will be the time involved and the costs of the intervention including training for family doctors and medical assistants.

For the ***feasibility of the planned controlled trial*** reasons for the non-participation of both patients and practices and the loss to follow up will be documented, along with the time involved for documentation by the family doctor and medical assistant and for patient interviews by phone. In addition, further potential outcome criteria will be looked at very closely.

3.1 Primary Aim

In preparation for estimating the sample size for the planned clinical trial the criterium appropriateness of the medication will be calculated and evaluated on the basis of the *Medication Appropriateness Index* (MAI)[17], [18] . Furthermore, problems associated with medications will be encoded using the PiDoc©-classification system[19] .

- The MAI consists of 10 items which are rated in line with regulations concerning medicinal products: (1) Indication for a drug, (2) Efficacy for the condition, (3) Suitability of medication (regarding all prescribed medication for a 24 hour period), (4) Accuracy of dosage instructions, (5) Practicability of dosage instructions, (6) Clinically relevant

drug-drug interactions, (7) Non-observance of drug-disease/condition interactions, (8) unnecessary prescription of two or more drugs from the same group, (9) Correctness of the duration of the therapy, (10) Choice of the most favourably priced treatment among drugs of comparable efficacy and safety. 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". [17,18] In the trial it is not possible to cover all imaginable types of inappropriateness. It is rather the case that the trial is limited to the most commonly observed combinations in the cross-sectional studies summarized in a manual (deposited in the trial master file). Prospective definitions for the rating values were defined for each criterium. Furthermore an evaluation of criterium 10 relating to the most favourably priced alternative will not take place as a rating does not appear possible due to the new discount contracts between the pharmaceutical industry and the various statutory health insurance companies. Therefore only nine of the orginal 10 items will be evaluated.

- The PiDoc©-classification system, which is based on German empirical studies and takes account of Strand's classification[20] and the PAS-System [21] - developed to encode problems associated with medication. Formally it is a "categorization system for standardized observance" [22] and is constructed in a hierarchical manner with two classification levels in six main problem groups ((A) Inappropriate choice of medication, ***WHERE IS B?*** (C) inappropriate intake by patient (incl. compliance), (D) inappropriate dosage, (E) Drug interaction, (F) ADR, (G) Other, which may be patient-, doctor- or communication-linked), relevant intervention suggestions and result codes following a completed intervention[19] As a direct interview with the patient is envisaged, only selected items will be used for the qualitative description of medication problems in the trial (see appendix).

In Prof. Harder's trial group, an MAI Rating incl. the evaluation of individual PiDoc©-criteria will be carried out independently of the project and blinded for the patient's group membership (intervention vs. control) in order to improve the reliability of the results.

3.2 Secondary Aims

The following parameters were determined in order to identify further suitable target variables for the clinical trial:

1) Complexity of the medication:

- Total numer of prescriptions
- Number of single doses / day
- Complexity of the medication regimen (*Medication Regimen Complexity Index*, MRCI [23])

2) Adherence and associated variables:

- Observed adherence reported as the difference between what medication was taken (*brown bag review*) and what was prescribed (doctor's files) [24]

- Reported adherence by the patient (according to Morisky [25], *Medication Adherence Report Scale*, MARS [26])
- Patient's attitude towards medication (*Beliefs about Medicines Questionnaire*, BMQ [27])
- Patient's satisfaction with information on medication

3) Quality of life and maintenance of functional status

- General quality of life (EuroQuoL) [28]
- Functional status in accordance with WHO Disability Assessment Schedule (WHO-DAS II)

4) Intensity of pain

- Verbal Rating Scale (VRS)

5) Days in hospital, or death (regardless of cause)

6) Adverse drug reaction (ADR)

4 PRIMÄARY AND SECONDARY OUTCOMES OF THE TRIAL

4.1.1 Primary Outcome

The primary target criterial of the PRIMUM pilot trial is the change in the MAI scores, i.e. the difference between the base value (T0) and the value after six weeks (T1).

4.1.2 Secondary outcomes

Secondary outcomes are:

1) Change in MAI score after 12 weeks

- Difference between base value (T0) and value after 12 weeks (T2)

2) Change in complexity of medication after 6 and 12 weeks

- Total number of prescriptions
- Number of single doses / day
- Medication regimen complexity (Medication Regimen Complexity Index, MRCI)

3) Change in adherence and associated variables

- Observed adherence measured as the difference between intake (*brown bag review*) and prescribed medication (physician's records) after 6 to 12 weeks.
    - Discrepancy score, DS (Sum of all differences in drug, time of intake, frequeny and dose) / Sum of all prescriptions,,AS>0.2=1
    - Overestimate / underestimate of actual intake by the doctor:
      Drug Score (DS, Sum of all drugs taken/sum of all prescriptions), DS<0.8 oder DS>1.2=1.31
    - Dose Score (DoS)
      DoS = d1(a1) + d2(a2) + d3(a3) + … /n

d = Patient intake (0.1) of prescribed medication
n = Sum of all prescriptions
a = Discrepancy rate (actual intake dd / prescribed dd)
DoS<0.8 or DS>1.2=1.31

- Regimen Score (RS)
  RS = d1(b1) + d2(b2) + d3(b3) + … /n
  d = Patient intake (0.1) of prescribed drugs
  n = Sum of all prescriptions
  b = Discrepancy rate (actual frequency of intake per day / prescribed frequency of intake per day)
  RS<0.8 oder DS>1.=1.31

- Change in reported patient adherence (Medication Adherence Report Scale, MARS) *after 6 and 12 weeks*
- Change in the attitude of patients to medicinal therapy (Beliefs about Medicines Questionnaire, BMQ) *after 6 and 12 weeks*
- Change in patient satisfaction with information received on medicines *after 6 and 12 weeks*

4) Change in quality of life and maintenance of functional status after 6 and 12 weeks

- Change in general quality of life (EuroQuoL)
- Change in or maintenance of functional status in accordance with WHO Disability Assessment Schedule (WHO-DAS II)

5) Change in intensity of pain after 6 and 12 weeks

- Verbal rating scale (VRS)

6) Days in hospital for whatever reason

7) Death for whatever reason

8) Adverse drug reaction (ADR)

5 DESIGN AND DURATION OF TRIAL

5.1 Type and design of trial

A two armed, controlled, open cluster randomized pilot trial in the Rhein-Main region has been planned in order to achieve the aims mentioned above (compare schematic presentation in section 1.5). In the design used here groups of people rather than individuals will be allocated to the various categories (intervention vs. control). The evaluation of the Medication Appropriateness Index (MAI) will take place without knowledge of group membership.

5.2 Expected duration of trial

The recruitment of participating practices is expected to take one month as this phase will be commenced in the trial preparation phase. After the successful recruitment of practices, training for the investigators will begin and participating family doctors (investigators) made familiar with all the documents in the investigator files including the documentation requirements.

The recruitment phase for patients will not take longer than three months. Directly following the decision on the randomization status of each practice (intervention or control) the intervention practices will begin intervention training. For this purpose, the family doctors and one medical assistant per practice will take part in group training and after access to the internet-based RandomizationAiD+ has been activated also in local training with all intervention instruments incl. software functionality. Each patient (in both intervention and control groups) will be tracked for three months following successful basis documentation. Excluding evaluation, the planned duration of the trial will be around 9 months.

6 SELECTION OF TRIAL SITES AND TRIAL PARTICIPANTS

6.1 Criteria for trial sites (Family practices)

6.1.1 Inclusion criteria (Trial sites)

- 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 medical assistant
- Investigating physician agrees to the contractual obligations of the trial
- Investigating physician agrees to train a medical assistant from the practice as part of the trial for intervention (*brown bag review*, patient interview on basis of checklist).

6.1.2 Exclusion criteria (Trial sites)

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

6.2 Criteria for medical assistants

6.2.1 Inclusion criteria

- Completed training as medical assistant or similar
- At least one year of professional experience as medical assistant and
- Written agreement to complete the necessary qualification measures and to perform the tasks associated with the trial.

6.2.2 Exclusion criteria (MFA)

- Expected to work for the practice for fewer than nine months when no regular takeover has been agreed with the trial headquarters
- Less than 18 years of age

6.3 Patient criteria

6.3.1 Inclusion criteria (patients)

- At least 65 years of age
- At least three chronic diseases
- Regularly takes at least five medicines (long-term medication
- Care is provides by a GP working at a trial site (at least one contact in most recent quarter)
- Capable of free and informed trial participation, of filling in questionnaires and of participating in telephone interviews
- Written agreement to take part in trial

6.3.2 Exclusion criteria (patients

- Diseases that mean the patient's life expectancy is under six months
- Alcohol or drug abuse with recognizable clinical signs or symptoms
- Cognitive impairment (MMSE < 26), that would prevent participation in the trial
- Emotional stress that would prevent participation in the trial
- Limited contractual capability
- Participation in a clinical trial within the last 30 days.

6.4 Patient selection

1. The participating practices (trial sites) will be asked to prepare a list of potentially eligible patients in accordance with the procedure (a – c) described below. (Pre-rRandomization list):

    a. Using the practice computer, the investigator calls up the most cost-intensive patients in the practice and prints the patient's reference number (from the practice EDP) to create a screening list.

    b. The investigator deletes all reference numbers from the screening list that in his or her preliminary view belong to patients who do not fulfil the in- and exclusion criteria.

    c. The trial site faxes the resulting list (=Pre-randomization liste) with at least 30 reference numbers (corresponding to 30 potentially eligible patients) to the Institute for General Practice. As no informed consent will yet have been given, the names must be sent in pseudonymous form i.e. the pre-randomization list only includes information relating to the provided reference numbers. Further information is not permitted and may have to be blackened out by the trial site before they are faxed.

2. A simple random sample of 10 patients will then be drawn from the pre-randomization list by the trial headquarters. This random sample will then make up the randomization list and will be faxed back to the family practice.

    Each of the 10 patients in the randomization list will then receive a patient-ID exclusive to the trial. This will be made up of a three digit practice ID (to be provided by the trial HQ)

and the patient's reference number as used in the practice's EDP, which will be of variable length. This patient ID will be used for documentation purposes throughout the the trial.

3. At the general practice, patients included in the randomization list that have been invited to participate in the trial will be asked to provide their informed consent until five patients are included in the trial. Reasons not to participate in the trial should be in a pseudonymous form (see below). Randomization
4. If it is not possible to include five patients from the randomization list in the trial a fax will be sent to the trial HQ. A further 10 patients will then be taken from the pre-randomization list by means of simple random selection and then faxed to the trial site in the form of a second randomization list. The patients in this list will then be treated in the same way as those in the first randomization list.

6.5 Non-includable patients in the randomization list

If a patient from the first randomization list (or the second randomization list) does not agree to participate or cannot be included for any other reason, then the following data will be documented on the patient registration form – 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 Trial HQ and the originals will remain on the files of the investigator and checked by the monitor after completion of the trial.

7 REGISTRATION AND RANDOMIZATION

7.1 Trial registration

The trial will be registered as a clinical, scientifically based non-AMG-non-MPG-trial in the international trial register "ClinicalTrials.gov" (http://clinicaltrials.gov/) as well as 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 trial HG, and a copy will be sent to all the trial sites and placed in the investigator's file.

7.2 Randomization algorithm and determination of practice status

The first trial patient from each practice reported to the Institute for General Practice (Trial HQ) will serve as the basis for randomization. The investigator will check the in- and exclusion criteria for the patient and fax the patient registration form to the Trial HQ.

If all necessary criteria for the patient's inclusion in the trial are fulfilled the practice is centrally randomized at the trial HQ. The status as either an intervention or a control practice is determined through the randomization of the first patient from each practice. All the patients registered thereafter will be dealt with according to the practice's status. The randomization will take place in one trial arm in the ratio 1:1. Block randomization with a variable block size will be used, as this will ensure that 10 family practices will be allocated to each arm. The

necessary randomization code will be generated by the Centre for Clinical Studies in Regensburg.

8 TREATMENT PLAN FOR INTERVENTION AND CONTROL GROUPS

8.1 Description of trial therapy (intervention arm)

a) Preparation of AiD+ for use in the pilot trial

AiD+ will be developed on the basis of the existing AiD clinic by the department of clinical pharmacology and pharacoepidemiology, Heidelberg, for use in the PRIMUM pilot trial, whereby the functionality of AiD+ will be agreed upon with the Institute for General Practice, Frankfurt.

For each trial site, the Trial HQ will set up 10 patient files using the patient identification codes from the randomization list in the password-protected area of the system. If the trial site demands a second randomization list then the Trial HQ will set up a further 10 patient files.

b) Intervention

In the intervention arm, patients will be looked after by the family doctor as well as a systematically trained medical assistant 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".[29] All test persons from the intervention group will receive the following structured intervention:

	Procedural step	**Content**
1	Medical assistant arranges appointment	The medical assistant 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	Medical Assistant enters patient's core data and "practice medication" into Medibox 1 (AiD+) durch MFA	The medical assistant logs into the web-based AiD+ (Internet address and password for the protected area are kept in the investgator 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 medication from the most current therapy plan into AiD+, if possible including the pharma reference numbers* (PZN, entered in practice software (Medibox 1: "practice medication").

	Procedural step	**Content**
		After entering the data she logs out of AiD+.
3	Medical assistant 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 medical assistant 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 medical assistant 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 medical assistant will inform the GP of the findings on the same day (at the latest within the next 24 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 medical assistant 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	Medical assistant enters "house medication" into Medibox 2 *brown bag review*	The medical assistant 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 medical assistant enters all drugs, regular medication, necessary medication, prescriptions from co-treating doctors, OTC products including phytopharmaceuticals and nutrition supplements. She enters every drug using its trade name, the name of the active ingredient or National Drug Code. In addition she records the dosage and the name of the doctor who prescribed the drug. Where possible the entry should be simplified by scanning the barcode using a document reader. After entering the information she stores it under home medication (Medibox 2) She prints the results from AiD+ from "Practice medication" (Medibox 1)

	Procedural step	**Content**
		and “Home medication” (Medibox 2) and logs out of AiD+.
5	The 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 (possibly using the pages printed out by the medical assistant). 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, duplicate prescriptions) and pointers (renal dose adjustment, tablet divisibility, exceeding maximal dose) for clinical relevance. He identifies patient problems using MediMol. He prepared necessary therapy adjustments in „Medibox 3“.
6	Medical assistant prepares interview between doctor and patient	The medical assistant prepares the AiD+-printouts and the completed MediMoL for the consultation.
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 medical assistant.
8	Medical assistant enters information into Medibox 3 (“coordinated medication) and ends the intervention	The medical assistant prints out the updated prescription plan from the practice computer 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). The medical assistant logs into the password protected area of AiD+, opens the patient’s file, checks “Medibox 3“ using the current practice prescription plan and makes any necessary changes. She gathers up all documentation on the intervention (printouts of all 3 Mediboxes and the completed MediMol and places them in the investigator’s file. .
9	GP concludes intervention	Finalization of “Medibox 3” (“coordinated medication”)

[*] *The inclusion of the central pharmaceutical number serves to ensure data validity*

8.2 Description of therapy in 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 simplified version of the current geriatrics guideline, parts I and II, published by the Hessen guideline group.[29] Practices and patients in the control group have no access to the Drug Information System AiD+ and do not use the 'MediMoL' checklist. In addition, the description of "usual practice" is the object of qualitative research in the pilot trial.

8.3 Observation and Documentation

Examinations and documentation take place regularly during the aforementioned visits 1-3. **v**Visits 1-3 take place in weeks 0, 6 and 12 following the inclusion of the patient in the trial. An overview of the individual examinations is given in the visit table on page 14. The content of the individual examinations to be documented is described in detail in section 9 (see below).

The trial documentation (case report form – CRF) completed by the investigators and their medical assistants, as well as the completed patient questionnaires are promptly sent to the trial HQ (self-addressed envelopes will be supplied to the trial sites in sufficient quantities and postage will be paid by the recipient).

As soon as the patient registration documents arrive (if possible within three working days), trial employees will conduct telephone interviews with the patients. 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 3 to 5 working days. After the fifth unsuccessful attempt, the responsible trial site will be contacted by the trial assistant and asked for information on the wherabouts of the patient.

8.4 Regular end of treatment / trial participation

Trial participation will generally be over for a patient when:

- Documentation of the last planned visit has been completed (T2)
- Death: if possible the date and the circumstances of the death (cause of death, location) should be documented.
- Hospital treatment that begins before documentation of the final planned visit has been completed and is in progress when the trial is over.

9 TRIAL EXECUTION AND INVESTIGATION METHODS

9.1 Training for GPs and medical assistants

9.1.1 Investigator training

GPs in both trial arms are trained in documentation in the same way. If possible, one medical assistant per practice should also participate in order to be in a position to support data documentation and to carry out the Minimental Status Test (MMSE).

The necessary training module will be available when the trial begins. The training will include basic training lasting around three hours.

Content:

1. Introduction to the PRIMUM*Pilot* trial and outlook for the main PRIMUM trial
2. Introduction to the execution of the trial including qualitative appraisals
3. Introduction to "recommended standards" (Geriatrics guideline, parts I and II by the Hesse guideline group[29])
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

9.1.2 Intervention training

The intervention training in the intervention practices will begin after the first patient from each practice has been included and the randomization status as an intervention practice fixed. Randomization

1. Group training: GPs and one medical assistant per intervention practice will be familiarized with the intervention content and procedures. The operation of AiD+ will be introduced and medical assistants will be trained to use the MediMoL-Checklists.
2. Individual and on-site training: The intervention practices will be visisted by an employee from the Trial HQ. This visit will be used to teach the investigator and the medical assistant how to use AiD+. Additional intervention training will be provided on an individual basis where necessary.
3. Additional training: This will be provided on an individual basis when Trial HQ employees regard it as necessary

The necessary training modules are available at the beginning of training. Three hours will be scheduled for the group training.

9.2 Intervention – Tools

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

9.3 Description of data sets

9.3.1 Data set to determine practice profile

- Single-handed practice / group practice (incl. Ambulatory healthcare center, with the number of doctors and their specialist areas,
- Location: Town / Country
- Clinical specialization of practice
- Number of registerd patients in most recent quarter [in categories: 0 – 499, 500 – 999, 1000 – 1499, 1500 – 1999, 2000 and over]
- Age of investigator
- Investigator's professional practice experience (Year doctor commenced private practice)
- Years of clinical experience in total
- Investigator: Specialist in general practice, specialist in internal medicine, GP / doctor with no specialist area

9.3.2 Data collection to determine medical assistant's profile

- Age, gender
- School leaving certificate, professional qualifikation and additional qualifications
- Years of professional experience as medical assistant and at trial site
- Type of employment
- Previous participation in clinical trial

9.3.3 Patient registration form

Registration form for every patient on pre-randomization listrandomization with

- Patient-ID, Age, gender
- Checklist for in- and exclusion criterial (items to be marked with a cross, initally without giving 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 declaration of consent is on hand)
- If declaration of consent on hand:
  - Name, first name, Patient's phone number
  - MMSE Score

9.3.4 Case report forms (see appendix)

9.3.4.1 Sociodemography and basic clinical data

Gender, year of birth, insurance status, family situation, home care situation, height, weight, current diagnoses, allergies / intolerances and hospital stays during the last six months (date of admission to / release from hospital; inpatient, day hospital care, outpatient, inpatient rehabilitation, admission diagnosis or reason for treatment)..

9.3.4.2 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.

9.3.4.3 Medication

Current medication, including both prescription drugs and OTC drugs recommended by the doctor (including National Drug Code if possible), name of active ingredient or trade name, strength, dosage form, dosage, indication (if possible all treatment indications), 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-step Likert scale: very important – important – of little importance – not important.

9.3.4.4 Modified Cumulative Illness Rating Scale (CIRS)

Assessment of organs / organ systems / areas (15 items in total) according to severity of impairment (5-step Likert scale: no impairment to extreme impairment)[30], [31], with one supplementary item “chronic pain syndrome) and a reponse category entitled “not applicable“ if the named organ (system) is not affected.

9.3.4.5 Expanded Charlston Comorbidity Index

List of underlying diseases in the Charlston Comorbidity Index[32] plus relevant diseases and situations that often result in contraindications to specific medication.

9.3.5 Patient questionnaires (see appendix)

9.3.5.1 Patient questionnaire on quality of life and maintenance of functional status

- General quality of life: EuroQoL
- WHO Disability Assessment Schedule (WHO-DAS II)

9.3.5.2 Patient questionnaire on medication adherence

- Medication Adherence Report Scale (MARS)

9.3.5.3 Patient questionnaire on patient’s attitude to medicinal therapy

- Beliefs about Medicines Questionnaire (BMQ)

9.3.5.4 Questions on satisfaction with information provided on medication

- Two questions on sources from which information is a) obtained and b) mostly obtained

- Six questions on whether patients felt they had sufficient information on:
    - Effect of medicines
    - Application of medicines
    - Side effects (adverse drug reactions) of medication and instructions on how to act if they occur
    - Behaviour guidelines if medication dose is forgotten
- Two questions on satisfaction with doctor-patient interviews on medication-related problems

9.3.5.5 Pain

- Verbal rating scale (VRS)

9.3.6 Telephone interview with patients

A trained employee from Trial HQ conducts interviews with patients using an interview guide (see appendix) and enters the answers directly into an Access-Databankstaff.

9.3.6.1 Medication

Long-time medication and OTC drugs (trade name, National Drug Code, dose, prescribed by whom, duration of intake more or less than three weeks) currently being taken, acute medication, 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, adverse drug reactions.

9.3.6.2 Hospital Stays

Inpatient treatment (inpatient day and night, day hospital care, inpatient rehabilitation) during the last six months (number of stays, reason for treatment as inpatient).

9.3.6.3 Sherbrooke Questionnaire

Five items to identify positive trigggers (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). [33]

9.3.6.4 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)

9.3.6.5 Patient interview on depression

- Geriatric depression scale[34]

9.3.6.6 Patient interview on adherence

- Self reported adherence according to Morisky[35]

9.3.7 Documentation of monitoring of trial by medical assistant

After completion of the trial the information from the completed medication monitoring lists compiled by the medical assistants (MediMol) in the trial sites will be centrally recorded and can be analyzed in terms of practice and patient.

Furthermore, the Department of Clinical Pharmacology and Pharmacoepidemiology, Heidelberg, will provide the medical boxes stored in AiD+ in an electronic and readable fashion for analysis. Further related commitments will be unanimously agreed by the participants during the trial.

10 EVALUATION OF FEASIBILITY

10.1 Assessment of Feasibility of Intervention

- In order to assess the feasibility of the intervention, the following questions must be answered: “Is the intervention tested in the pilot trial realizable, was it accepted by participants and considered usable (see below)?” To answer these questions, the following persons’ points of view were examined:

Medical assistant’s point of view: A focus group will be conducted on the realizability of the intervention. The content of a tape recording of the group meeting will be analyzed in terms of the main question: “What problems cropped up with the intervention, how severe were they considered to be and what changes did participants consider needed to be made to the intervention?“ Further questions concerned the usability (usability: easy to learn, easy to memorize, efficient usability, low error rate, provides satisfaction to user [36]).

GP’s point of view: Short interviews will be held with the GP which concern the feasibility of the intervention and important changes in comparison to standard treatment. These interviews will be recorded and their content analyzed in terms of the main questions. “Is the intervention in its current form usable (see above), what barriers can be identified and what changes need to be made to the intervention?“

Patient’s point of view: At the T1 time of collecting data and as part of the telephone interview, a short guideline based survey takes place of the imposition caused by the intervention, the acceptance of the interview with the medical assistant as part of the brown bag review, and the perceived content of the doctor-patient interview. Pre-formulated answer categories will be quantitatively measured and analyzed. Open answers will be combined to create categories on the basis of content analysis.

11 DURATION OF TRIAL / TRIAL DROP-OUTS

11.1 End of Trial

The regular end of the trial is reached when the post-procedure observation period of three months is over for all patients participating in the trial.

11.2 Trial drop-outs

11.2.1.1 Patients drop out of trial

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

If the patient only wishes to end the therapy measures foreseen in the trial but is happy for the further documentation of the course of his illness(es) to take place, then it is regarded as a drop out of therapy. The documentation will continue in accordance with the protocol(intention-to-treat principle).

11.2.1.2 Belated detection of exclusion criteria

If it belatedly turns out that a patient satisfied an exclusion criterium at the time of recruitment, then the fact must be documented on the relevant patient registration form. The protocol will nevertheless be continued for the patient as long as the newly discoverd circumstance does not represent a risk or unacceptable stress for the patient.

11.2.1.3 Drop out of trial for individual patientsThe investigator 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 organizationally 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.

The Trial HQ must be informed of the withdrawal 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.

11.2.2 Withdrawal of trial site from trial

The trial administrators can decide to withdraw a trial site (GP practice) from the trial if:

- It does not satisfy the protocol's technical requirements (e.g. organizational problems in implementing the protocol))
- The implementation of the trial is inadequate for the trial
- The quality of the data is inadequate
- The investigator withdraws his agreement to participate in the trial protocol

12 STATISTICAL METHODS

12.1 Description of the populations to be analyzed

Two differing analysis datasets have been defined for the analysis:

Intention-to-Treat (ITT) Set: includes all randomized practices and their patients.

Per-Protocol (PP) Set: includes all randomized practices and their patients that have been treated in accordance with the protocol. The criteria for the exclusion of practices or patients from the PP population will be determined by the trial arm before the databank is closed for further participants.

12.2 Statistical analysis

The primary analysis takes place for all target criteria according to the Intention-to-Treat (ITT) principle. Additional per-protocol analyses will be undertaken as sensitivity analysis.

The primary comparison between the intervention and the control group will be made on the basis of the difference between the MAI score at baseline (T0) and the MAI score after 6 weeks (T1). The primary comparison will thus be performed using a comparison between 2 mean values. Assuming a normal distribution and the same standard deviation in both groups, a two-tailed, unpaired t-test with a significance level of $\alpha = 0.05$ will be used. For the difference between mean values, a two-tailed 95% confidence interval will be specified. Furthermore, in order to quantify a possible cluster effect an intra-class-correlation (ICC)-coefficient (ICC) wil be estimated. The ICC will be used for adjustment purposes as part of a multilevel regression analysis. The ICC estimate will also serve to prepare the sample size calculation for the planned main trial.

As this is a so-called pilot trial, the analysis of all result parameters will remain primarily descriptive. At the same time, the p-values will only have a descriptive character. Statistically significant differences (with a significance level of $\alpha = 0.05$, two-tailed) between the control and intervention groups will not be interpreted as proof of the effectiveness of the intervention. They serve merely to provide indications of irregularities in order to evaluate the suitability of the MAI score as a main target criterium and possibly identify further suitable target parameters for the planned main trial.

The statistical and biometric approaches and procedures to be used will be determined in detail in the statistical analysis plan.

12.3 Reason for the sample size

The suitability of the Medication Appropriateness Index as a potential primary outcome criterium in the planned main trial should be checked. According to Browne[37] in Lancaster et al.[38] In order to have a good estimate of mean and standard deviation, 30 patients per group should be sufficient to test the suitability of a criterium. To ensure this target is definitely achieved, 50 patients will be recruited for the control group and 50 for the intervention group, thus making a total of 100 samples N=100.

With targeted cluster sizes of 5 patients per cluster, 10 GP practices will be needed for the intervention and 10 for the control group. This sample size will also make possible the calculation of intra-class-correlation coeffizients (ICC) that is required for planning the sample size calculation.

12.4 Missing data

Missing data will not be replaced.

13 DOCUMENTATION, DATA MANAGEMENT AND ARCHIVING

13.1 Documentation concept

13.1.1 Patient registration forms and patient inclusion

The patient registration form will be faxed to the Trial HQ. It includes the patients' names and telephone numbers (so that the interviews can be conducted in a timely manner) as well as other information on in- and exclusion criteria and on the availability of informed consent.

At Trial HQ, these data will be entered into a separate databank (Access™) from which personal data will be deleted after conclusion of the trial.

13.1.2 Data collection following patient inclusion

1. Case Report Form (CRF)

The CRF is a paper-based document that is completed at visits T0, T1 and T2 and records the following variables:

- **Basic clnical data**: Sociodemographic detail, physical examination (height, weight), cuurrent diagnoses, allergies / intolerances and hospitalization during the last six months, laboratory tests (serum electrolytes, serum creatinine)
- **Current medication:** prescription drugs and OTC drugs recommended by the doctor (active ingredient or trade name, strength, dosage form), indications, duration of therapy and estimation of importance of the medication relative to the therapy concept as a whole.
- **CIRS-Value:** modified Cumulative Illness Rating Scale (1 extra Item, 1 additional answer category)
- Expanded **Charlston Comorbidity Index**

The CRF is completed by the investigator[1]. Every CRF includes a sheet of paper with information on filling in the form and a checklist on how to send the to data (see below). Necessary correction to the CRF must take place in the following manner: invalid data should be crossed out whereby crossed-out details should be authorized with the date and the investigator's initials.

[1] Werden klinische Basisdaten, Scores psychometrischer Instrumente und Medikation durch eine dafür geschulte MFA erhoben, bestätigt der Prüfarzt die Richtigkeit der Angaben mit seiner Unterschrift.

2. **Patient questionnaire**

The patient questionnaire is also on paper and is also filled in at visits T0, T1 and T2.. It covvers the following information:

- Quality of life (EuroQoL)
- WHO Disability Assessment Schedule (WHO-DAS II)
- Beliefs about Medicines Questionnaire (BMQ)
- Medication adherence (MARS)
- Verbale rating scale on pain (VRS)

The patient questionnaires, including an envelope, will be issued by the medical assistants. 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 medical assistants provide help filling in the patient questionnaires and keep 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 returned to the Trial HQ.

3. Patient telephone interview

After the arrival of the patient registration forms, the participating patients will be called on the telephone by a trained trial employee - firstly at the time of the T0 visit and then at the regular T1 and T2 - visits and asked about the following:

- Medication, Allergies, adverse drug reactions
- Hospitalization
- Sherbrooke questionnaire
- Depression (GDS)
- Medication adherence according to Morisky

The information will be entered directly into an SQL-database (Access™).

13.2 Data management

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

The data whose receipt has been confirmed will then 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 specific 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 Trial HQ (see below, Query management). With the exception of the patient registration form which is recorded separately, 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

13.3 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 Trial HQ. 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 Trial HQ in paper-form. Changes to the Access database should be documented in an audit trail if possible. The necessary programming instructions will be developed along with the data management concept.

13.4 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 Trial HQ will archive the central trial documents, the original CRF (including patient questionnaires, the final report and further reports where necessary.

14 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Monitoring

Trial HQ will be responsible for monitoring the trial. All data will be checked for completeness, plausibility and consistency. Any discrepancies will be followed up by means of queries.

All trial employees will sign a written declaration agreeing to treat all personal data as confidential.

As part of the trial, the investigator guarantees to allow trial employees access to the files of those patients included in the trial and to support them and their monitoring work

A certain as yet unspecified percentage of source data will be monitored on site (Responsible persons, see p. 5). The patients and source data to be checked will be selected by Trial HQ.

The SOPs (yet to be developed) will be used for monitoring and data management during the trial.

15 ETHICAL AND REGULATORY REQUIREMENTS

15.1 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" [39]. The trial was 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 analyisis, 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.

15.2 Subsequent changes to protocol

Changes to protocol may only occur with the prior agreement of all cooperation partners. All participants 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 head of the clinical trial, 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 adminstrative reasons.

15.3 Patient Information and Declaration of Consent

When the patients in the randomization list appear in the practice, the investigator 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, 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 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.

15.4 Finance and Insurance

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

15.5 Responsibility for preparing Interim and final Reports

Joint reports were agreed upon due to the networked nature of the project structure (PRIMUM-pilot trial and sub project E). The head of the clinical trial will be responsible for the coordination and composition of the reports in a standard format. To this end she 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) An interim report due nine months after sponsoring has begun. The positive appraisal of the interim report is the condition for a successful application to conduct the main trial and

(2) A final report following the conclusion of the pilot trial unless the sponsor decides to suspend this requirement until the main trial has been completed.

15.6 Publication agreements

The specifications laid down in the CONSORT Statement for cluster-randomized trials must be taken into account when the results of the trial are published.[40]

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.

16 APPENDIX

16.1 Abbreviations

AiD	Medication information service
AMG	Medication law
AS	Dicrepancy 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
FA	Specialist doctor
FU	Follow-up
GCP	Good Clinical Practice
GDS	Geriatric Depression Scale
ICC	Intra-Cluster Correlation-coefficient
ICH	International Conference on Harmonisation
ID	Identifier (Kennziffer)
ITT	Intention To Treat
HA	Family doctor (GP)
LKP	Clinical Trial Director
MAI	Medication Appropriateness Index
MARS	Medication Adherence Report Scale
MediMoL	Medication monitoring list
MFA	Medical assistant
MMSE	Mini Mental Status Test
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
UAE	Adverse Drug Event
ADR	Adverse Drug Reaction
VO	Prescription(s)Verordnung(en)
VRS	Verbal rating scale on pain
WHO-DAS II	WHO Disability Assessment Schedule

16.2 Hinweise auf Inhalte des Prüfarztordners

16.2.1 Trial protocol (plan) incl. all data collection instruments (sample)

16.2.2 Geriatrics Guideline from the Hesse Guideline Group (Full versions parts 1 and 2)

16.2.3 Copy of the Ethics Commission vote

16.2.4 Copy of the trial registration form

16.2.5 Center Registration (CR)

16.2.6 Pre-randomization list

16.2.7 Randomization list

16.2.8 Original of the signed patient information and consent form to the trial

16.2.9 Original of the signed data protection declaration

16.2.10 Patient registration form

16.2.11 Flow chart on the trial

16.2.12 Guideline on data flow

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