Effects of a structured medical management intervention aimed at reducing medication complexity during hospitalization in inpatient and subsequent outpatient care

A controlled trial under routine clinical conditions in chronically ill patients

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"Take a little aspirin, add one part low-dose cholesterol medicine and three parts low-dose blood pressure medicine. Put it in a single pill and give to everybody older than age 45. What do you get?"

(John Fauber, Journal Sentinel, March 2009)

Abstract

„Medicine won't work if you don't take them"- this was a statement of the WHO report 2003 about adherence. According to this report, almost 50% of chronically ill patients do not take their medication as regularly as prescribed even though it is obligatory for a successful medication therapy. As a consequence non-adherence contributes to growing healthcare costs. In the present work a prospective, controlled study with chronically ill patients on medications against hypertension, diabetes and/or dyslipidemia was conducted. The objective was to analyze whether adherence increases through reducing medication complexity by (1) pharmaceutical counseling of the medical hospital staff in regards of simplifications and (2) additionally an information in the discharge letter for the general practitioner (GP) about the modified medication. The simplifications comprised reducing the dosing frequency as well as the total amount of dosages to take per day. The additional information explained the background of the simplification with a kind request to continue the medication unchanged if possible. The aim of it was to integrate the GP into the medication modification process and thus to provide a sustainable medication therapy across the interface between stationary and ambulatory care.

Furthermore, it was examined whether these interventions influence the health-related quality of life (QoL) and satisfaction of the patients.

Before running the study, the English Medication Regimen Complexity Index was translated into German and evaluated according to international approved guidelines, in order to have a validated instrument in German language for the assessment of complexity.

The study sample included 240 patients. Primary endpoint was patient adherence, using the German version of the Medication Adherence Rating Scale (MARS-D) as a self-reporting tool. Adherence was dichotomized into complete (25 points) and incomplete (< 25 points) adherence. Secondary endpoints were medication regimen complexity, quality of life and satisfaction of patients regarding the information about their drugs. Adherence and medication complexity were assessed at times of admission to hospital (T0), discharge (T1) and 6 weeks after discharge (T2); patients' quality of life and satisfaction with information

about the drugs were gathered at T0 and T2. Medical staff in hospital, caring for the patients of the intervention group, was pharmaceutically counseled about feasible simplifications of the cardiovascular medication before deciding on the discharge medication. After randomization of the intervention group, the GP of the patients of one sub group received the additional information in the discharge letter as mentioned above.

At T1 medication complexity was statistically significantly lower in the intervention than in the control group. This effect was partly reversed at T2 to statistically non-significant values. Propensity adjusted complete adherence rates at discharge and six weeks after discharge were slightly higher in the intervention group than in the control group, however, without reaching statistical significance.

The complexity at T2 was significantly lower when the GP had received additional information in the discharge letter. Especially the dosing frequency was reduced, as was the total number of medications. Complete adherence rates were also higher in that sub group, albeit without statistical significance.

Some of the changes in medication therapy done by the GP after discharge from hospital may be Germany specific due to healthcare system regulations that vary in between different countries.

The study showed that complexity of cardiovascular medication therapies can be reduced by counseling the medical staff in hospital. However, the effect is largely reversed in the ambulatory care if the GPs are not well informed about the modifications. Patient adherence was not significantly changed by this intervention. As adherence depends on various aspects, interventions to ameliorate adherence need to combine multifactorial strategies in order to accomplish significant clinical benefits.

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List of Abbreviations

ACE	Angiotensin Converting Enzyme
ADE	Adverse Drug Event
ANOVA	Analysis Of Variance
AT	Angiotensin
C	Control group
CHD	Coronary Heart Disease
CVD	Cardiovascular Disease
CI	Confidence Interval
e.g.	exempli gratia (*lat. abrev*.: for example)
est. means	estimated means
et al.	et alii (*lat. abrev*.: and colleagues)
Fig.	Figure(s)
I	Intervention group
ICC	Intraclass Correlation Coefficient
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10^{th} revision
I.U.	International Units
HCT	Hydrochlorothiazid
HIV	Human Immunodeficiency Virus
HRQoL	Health-Related Quality of Life
GP	General Practitioner
i.e.	id est (*lat. abrev*.: that is)
MARS (-D)	Medication Adherence Report Scale (German Version)
MEMS	Medication Event Monitoring System
mL	Millilitres
MRCI (-D)	Medication Regimen Complexity Index (German Version)

N	Number of patients
n.s.	Not significant
OR	Odds Ratio
OTC	Over the counter (medication)
p	Level of significance
QoL	Quality of Life
RR	Blood pressure according to Riva-Rocci [mmHg]
RR	Relative Risk
RCT	Randomized Controlled Trial
SD	Standard Deviation
SF (-12/-36)	Short Form (-12/-36)
SIMS (-D)	Satisfaction with Information about Medicine Scale (German Version)
SPSS	Statistical Package for the Social Sciences
UKE	University Medical Center Hamburg-Eppendorf (Universitätsklinikum Hamburg-Eppendorf)
WHO	World Health Organisation

1 Introduction

Medication is one of the most important healthcare interventions in the treatment of chronic diseases [1]. However, it strongly depends on patient adherence. In the setting of hospitals, clinical pharmacists are uniquely trained in medications and the provision of comprehensive drug management to patients and providers [2]. The role of clinical pharmacists in the care of hospitalized patients has evolved over time. Increased emphasis has been put on collaborative and pharmaceutical care and patient interaction, with pharmaceutical care defined as “the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient’s quality of life” [3]. Pharmacist intervention outcomes include economics, health-related quality of life, patient satisfaction, medication appropriateness, adverse drug events (ADEs) and clinical outcomes [2, 4, 5]. A review about clinical pharmacists and inpatient medical care concluded that the addition of clinical pharmacist services in the care of inpatients generally resulted in improved care, with no evidence of harm [2]. Their positive influence on adherence and the co-management of hypertension has been shown as well, however the effective interventions were complex and it was not possible to identify any particular intervention or combination that predicted success [6, 7].

The present work represents the development, performance and evaluation of a prospective controlled study of a pharmaceutical intervention to ameliorate patient adherence. Emphasis is on the medication regimen complexity. Furthermore, the quality of life of the patients and their satisfaction with information about medicines will be regarded.

1.1 Adherence

1.1.1 Definition

Adherence is defined as the extent to which a person’s behavior – taking medications, following a diet, and/or executing lifestyle changes – corresponds with agreed recommendations from a healthcare professional [8]. In contrast, the term *compliance*

describes the willingness of the patient to follow the therapeutic recommendations of the healthcare professional, whereas *persistence* is the continuation of therapy for the required period of time [9]. To underline the need of cooperation, partnership and equality in the patient–physician relationship, the term *concordance* is used – primarily in Great Britain [10].

1.1.2 Significance

Though it is known that medication intake is essential for a successful therapy that improves clinical outcomes, the WHO reported in 2003 that only 50 % of the patients take their medication as agreed with the prescriber [8, 11]. This contributes to the effect, that hypertension, a disease that should possibly be controlled with the antihypertensives that are available, blood pressure reaches the target range in just one third of the patients [9]. A similar situation is noted for diabetic patients: according to the CODE-2 study (Cost of Diabetes in Europe – type 2), solely 28% of the patients are under satisfying glucose control [12]. Poor adherence can decrease the effectiveness of treatment, leading to treatment failure, excessive morbidity, mortality [9, 13]. This, in turn, leads to an increase in the use of healthcare resources and an increase in overall expenditure and medical costs [14, 15]. Non-adherence was judged to be the cause of 69% of the adverse drug events (ADEs) causing admission to a four-hospital integrated academic health network in the United States [16] and approximately 1.7 % of healthcare expenditures in the USA were spent on hospital admissions following non-adherence [17]. Consistent adherence to antihypertensive or antidiabetic medication therapy, on the other hand, is associated with better health related outcomes, like better blood pressure control and less cardiovascular disease (CVD) and all-cause hospitalizations [13, 18]. In a large meta-analysis, increased treatment adherence improved health outcomes, including survival, readmission rates, cholesterol level, and hemoglobin A1c level [19]. Bramely et al. were also able to show that patients with high adherence have a 45% better chance to reach blood pressure control [20], and approximately 80% of the prescribed medications need to be ingested in order to lower the blood pressure successfully [21].

1.1.3 Non-adherence

Non-adherence can occur in two forms: intentional and unintentional. The latter is most often due to the oblivion of medication intake, possibly because of cognitive impairment, stress or being asymptomatic. Intentional non-adherence on the other hand can have various reasons, for instance ethical and/or moral issues, independency, life priorities and individualistic approaches to maintain and control one's health. Lack of motivation or deficient comprehension of the role of medication contribute to this phenomenon as do the development or anticipation of medication related side effects [22]. Complicated drug regimens and lack of symptoms favor both – intentional as well as unintentional non-adherence. Studies about CVD and related conditions have shown that poor adherence with medication is encouraged by the chronic and often asymptomatic nature of hypertension and hypercholesterolemia [23, 24].

1.1.4 Influences

According to the WHO report 2003 adherence is influenced by several factors (see Figure 1):

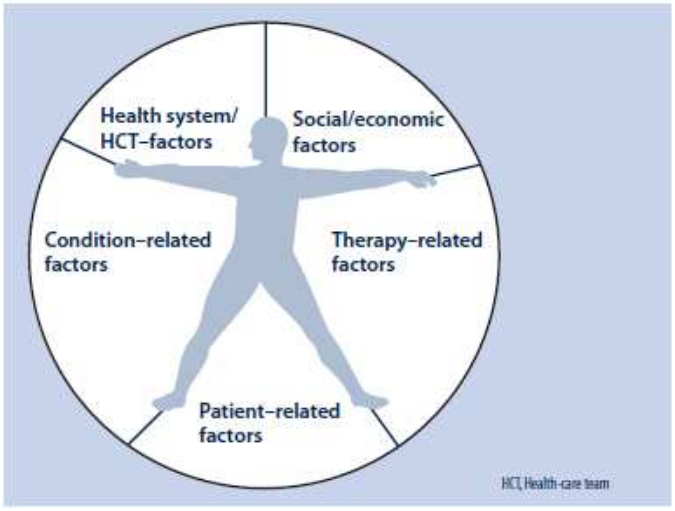

Figure 1 The five dimensions of adherence [8]

1. Social and economic factors
    - socioeconomic status
    - high cost of medication and tranport
    - age
    - educational status
    - family status
2. Healthcare team and system-related factors
    - patient-provider relationship
    - poorly developed health services
    - lack of knowledge of healthcare providers on managing chronic diseases
    - overworked healthcare providers
    - weak capacity of the system to educate patients
    - lack of knowledge on adherence and of effective interventions for improving it
3. Condition-related factors
    - severity of symptoms
    - level of disability
    - comorbidities
4. Therapy-related factors
    - complexity of the medical regimen
    - duration of treatment
    - previous treatment failures
    - frequent changes in treatment
    - the immediacy of beneficial effects
    - side-effects
    - the availability of medical support to deal with them

5. Patient-related factors

    - Resources (e.g. out of pocket cost of the medication, complicated prescribing and filling procedures)
    - Knowledge (e.g. the level of understanding of the importance of taking the medication)
    - Attitudes (e.g. cultural norms, motivation to manage the disease)
    - Beliefs/ Perceptions (e.g. tolerability, side effects, anxiety over the complexity of the drug regimen)
    - Expectations (e.g. the possible lack of discernible effects of the medication) [25]

1.1.5 Measurements

Several methods to assess adherence are available; they can be divided in direct and indirect methods. The former includes the measuring of drug concentration in body fluids. Of advantage is the high sensitivity and specificity. Nevertheless, the performance is complex and often costly to administer; a cost-effective drug assay is required. Patients who know that they will be tested may consciously take medication that they had been skipping so the tests will not detect individuals who have been nonadherent ("white coat adherence"). Examples where this method is frequently used are HIV medications, immunosuppressive or antiepileptic drugs. The second direct method is observing patients' drug intake. It is simple to perform, but not for daily routine since a hospital stay or close supervision is necessary.
One very precise indirect way of assessing adherence is electronic monitoring, using e.g. the Medication Event Monitoring System (MEMS). These are small medication boxes with a lid containing a microprocessor that records the exact date and time of each opening and closing. It is an accurate method that additionally allows getting chronological information about the medication use. A drawback is the elaborate filing procedure, which sometimes makes it too impractical and expensive for use in primary care settings. Therefore electronic monitoring is mainly used for clinical trials or the assessment of adherence to simple medication regimens or single drugs, like immunosuppressives [26]. Another simple and inexpensive approach is the pill count (with a pill usage of over 80 % being defined as adherent [27]). However, adherence rates may be overestimated if patients dispose of

unused medications. Also, count inaccuracies are common. The advantage of pharmacy refill data, used to calculate adherence is, that large-scale analyses can easily be performed once access to the necessary data is provided. On the other hand, it is dependent on complete pharmacy databases that capture all pharmacy refills without vacancies. Patients' self-report is the most feasible and inexpensive way to measure adherence and is therefore often used in primary care research. Of disadvantage is its limited reliability as patients tend to overestimate their adherence [28]. One example is the Morisky Scale which was developed in 1986 by Morisky, Green and Levine, consisting of four questions rated in "yes" or "no". Validity and reliability had been tested with 290 hypertensive patients [21]. For the concurrent validity the relationship between the individuals with their blood pressure under control and their score on the four-item medication taking scale was analysed. A significant relationship was found with a point biserial correlation of 0.43 ($P < 0.01$). The predictive correlation was obtained by comparing the baseline answers of the Morisky scale with the blood pressure after 24 months. The correlation coefficient was 0.58 ($p < 0.01$). Reliability was measured through internal consistence with a chronbach's alpha of 0.61. A correlation between the adherence and blood pressure had been shown, though without high correlation coefficients. Another self-report tool is the Medication Adherence Reporting Scale (MARS), which has also been translated into German (MARS-D) [28]. Originally, it was designed by Horne as a nine item scale in 2002. Further research then led to a reduction to five questions (MARS-5). The MARS-5 was validated in a renal transplant unit in the UK with 153 patients [29]. Patients were asked to score their own behaviour, regarding the frequency of the different aspects, on the following response scales: "always", "often", "sometimes", "rarely" and "never". Each item was scored with 1 ("always") to 5 points ("never"), leading to a sum score ranging between 5 and 25 points and a higher score indicating higher adherence to the prescribed medication regimen. For the validation of the German version, the MARS-D was part of two large-scale studies, including patients with chronic diseases and patients with risk factors of cardiovascular disease [28]. In the first study (n= 370) it was the aim to assess convergent validity between medication adherence (MARS-D) and satisfaction with information about medicines (SIMS-D). The correlation between the MARS-D score and the SIMS-D score showed a low value with statistical significance (Spearman's rho=0.26; $p<0.01$). The second study (n=1112) investigated divergent validity computing correlations between MARS-D and the SF-12 physical and

mental subscales. Correlation between the MARS-D score and the physical and the mental subscale of the SF-12 showed low values (Spearman's rho=0.06, p=0.34; Spearman's rho=0.19; p<0.01). Internal consistency (Cronbach's alpha: 0.60-0.69) and test-retest reliability (Pearson's r: 0.61-0.63) of the MARS-D were satisfactory [30].

1.1.6 Methods to ameliorate adherence

According to the five dimensions postulated by the WHO, interventions to ameliorate adherence can focus on the patient, his condition, his therapy, the socioeconomic situation or the health system. Examples for hypertensive patients are depicted in Table 1.

Table 1 Factors affecting adherence to treatment for hypertension and interventions for improving it, listed by the five dimensions and the interventions used to improve adherence [8]

Hypertension	**Factors affecting adherence**	**Interventions to improve adherence**
Socioeconomic-related factors	(–) Poor socioeconomic status; illiteracy; unemployment; limited drug supply; high cost of medication	Family preparedness; patient health insurance; uninterrupted supply of medicines; sustainable financing, affordable prices and reliable supply systems
Health care team/ health system-related factors	(–) Lack of knowledge and training for health care providers on managing chronic diseases; inadequate relationship between health care provider and patient; lack of knowledge, inadequate time for consultations; lack of incentives and feedback on performance (+) Good relationship between patient and physician	Training in education of patients on use of medicines; good patient–physician relationship; continuous monitoring and reassessment of treatment; monitoring adherence; non-judgmental attitude and assistance; uninterrupted ready availability of information; rational selection of medications; training in communication skills; delivery, financing and proper management of medicines; pharmaceuticals: developing drugs with better safety profile; pharmaceuticals: participation in patient

		education programs and developing instruments to measure adherence for patients
Condition-related factors	(+) Understanding and perceptions about hypertension	Education on use of medicines
Therapy-related factors	(–) Complex treatment regimens; duration of treatment; low drug tolerability, adverse effects of treatment (+) Monotherapy with simple dosing schedules; less frequent dose; fewer changes in antihypertensive medications; newer classes of drugs: angiotensin II antagonists, angiotensin converting enzyme inhibitors, calcium channel blockers	Simplification of regimens
Patient-related factors	(–) Inadequate knowledge and skill in managing the disease symptoms and treatment; no awareness of the costs and benefits of treatment; non-acceptance of monitoring (+) Perception of the health risk related to the disease; active participation in monitoring; participation in management of disease	Behavioral and motivational intervention; good patient–physician relationship; self-management of disease and treatment; self-management of side-effects; memory aids and reminders

(+) Factors having a positive effect on adherence; (–) factors having a negative effect on adherence

Interventions addressing the patient either aim to improve his knowledge about the medication and its use, to remind him to take the medication or to motivate him. Regarding a tailored therapy, dosing regimens can be simplified, dosage forms be adapted to the needs of the patient and medications with as little side effects as possible be chosen, since studies of therapy-related interventions revealed that the main barriers to adherence was the dose frequency and the incidence of side-effects [8]. In terms of the condition, comorbidities that influence the adherence might be treated. An example is the incidence of depression with its

negative impact on adherence, which might be approached with additional psychotherapy. Concerning social or economic issues, additional charge for the medications could be reduced or the access to medicinal resources facilitated. Regarding the healthcare system, interventions to ameliorate the doctor-patient relationship can be performed. Doctors might continuously be educated about adherence and its enhancement measured or the work load of healthcare providers can be reduced.

1.2 Medication Regimen Complexity

The complexity of medication therapies belongs to the therapy related factors influencing patient adherence. Novel therapeutic options as well as the increasing need of pharmacotherapy due to the changing age profile of the population and the concomitant increase in chronic diseases result in *polypharmacy* and thus, in highly complex therapies for some patients [31]. The doctor prescribing the medication therapy has a key role in this issue and therefore the WHO demanded that doctors should be trained to make rational decisions when selecting the medication therapy: it should have a simple dosing regimen, be financeable and ideally not interfere with patient's quality of life [8]. Hitherto few interventions addressing the prescribers can be found in the literature.

1.2.1 Definition

Definitions of the complexity of medication regimens vary. Some researchers confine complexity to the number of drugs and the dosage frequency, while others include additional factors [31, 32]. These are, for example, the number of dosage units to be taken at a time, the total number of doses per day or the need to follow specific instructions for administration (such as administration relative to mealtimes), since these were found to have an influence on adherence as well [33]. As George et al. pointed out, it is conceivably more difficult for the patient to manage a drug therapy with four different agents in four different dosage forms with four different specific directions for use than to manage a regimen with four different tablets taken at the same time of the day without any further instructions, although both result in the same number of tablets being taken and the same dosage frequency [34]. Studies addressing the consequences of medication regimen

complexity have been carried out with patients suffering from various diseases [32, 35]. Especially for the treatment of HIV a lot of research has been realized, including dosing frequency and medication intake related to mealtimes as factors contributing to medication regimen complexity. It has demonstrated that patients were more likely to have missed doses if they were taking their HIV-medications three or more times per day or had to take them on an empty stomach. A multivariate logistic regression model further revealed that patients with less complex regimens (twice daily or less in frequency, no food-dosing restrictions), who correctly understood the dosing and food restrictions of their regimen, were less likely to have skipped doses in the past three days than those with more complex regimens [33]. Similar were the results for patients with Type 2 diabetes. Evaluating the predictors of adherence, it was shown that one tablet per day administration was associated with greater adherence than multiple tablets [36]. However, the lack of a uniform definition for medication regimen complexity and instruments for its validated assessment impede the comparability of results.

1.2.2 Significance

Complexity of medication regimens is considered as one of the main reasons for poor adherence [20, 37, 38]. Its inverse correlation with adherence has been verified by a multitude of studies [27, 36, 39-41]. The more medications a patient has to take at different times during the day, the more likely he is to forget the medication intake or to see his quality of life negatively affected by the amount of tablets and the impact on daily activities [9, 42]. Comparing a three-time daily regimen with a once-daily regimen, Eisen et al. were able to show an increase in adherence from 59.0% to 83.6%. They concluded that probably the single most important action that health care providers can take to improve adherence is to select medications that permit the lowest daily prescribed dose frequency [41]. Observing the persistence to a single pill (n=4146) versus two pills (n=6204) of amlodipine and atorvastatin over a period of four years, 11% of patients failed to fill the first repeat prescription vs. 23% in the two pill group. After 12 months treatment was ceased by 33 and 59% of the patients, respectively [39]. Nevertheless, hardly any guideline addresses the coherence of medication complexity and adherence. Only recently fixed combination pills have been accepted as recommendation for the first-line therapy of stage 2 hypertension in

order to profit from their faster and more efficient blood pressure control [43]. The implementation of this novel treatment approach has been investigated in a cluster randomized study in Canada. Existing "Canadian Hypertension Education Program Guidelines" were compared to a simpler therapy, starting initially with a combination pill. In the end, the number of patients under blood pressure control was higher in the intervention group, as were the number of doctors, satisfied with their prescribed therapy [44].

1.2.3 Measurements

For a reliable measurement of medication complexity, George et al. developed the *Medication Regimen Complexity Index (MRCI),* which considers numeric aspects (dose, frequency) as well as additional criteria, i.e. the dosage form or specific directions for the medication intake [34]. The MRCI can be regarded as advancement of the *Medication Complexity Index* (MCI), which has been used by some researchers either in its original or in a modified form, but which showed unsatisfactory results in terms of validity and reliability [45]. In contrast, the MRCI showed a high inter-rater reliability, test-retest reliability and construct validity, as assessed with 134 medication regimens in Australia [34]. So far, the MRCI is the only instrument with high psychometric quality for the assessment of medication regimen complexity described in literature.

The index consists of the sections A, B and C, covering aspects like dosage form, dosage frequency and additional directions for the administration, respectively. Each section yields a score that is ultimately summed to the Medication Regimen Complexity Index. The original version of this instrument was published in English [34] and translated subsequently into Portuguese [46]. Since therapeutic recommendations and habits may differ considerably between countries, the availability of the MRCI in German language for the measurement of medication regimen complexities is highly desirable, both for national use and international comparison.

1.2.4 Methods to reduce complexity

According to the MRCI, there are different options to reduce the complexity of medication regimens. One could address the dosage form, frequency or additional directions that complicate the intake. The strategies that are investigated in the present study are further explained:

- Reducing the dosing frequency

Several studies confirmed the positive impact of the reduction of the dosing frequency on patient adherence [47, 48]. In general two approaches to reach this are available. First of all, short acting substances that need to be taken several times per day can be substituted by long acting ones with a once daily dosing. An example is the switch from captopril (2-3x/d) to ramipril (approved for 1x/d). Secondly, extended release/depot preparations instead of ones with normal release can be prescribed. Thus, Albert et al. proposed the switch to once-daily dosing substances like carvedilol extended release, metoprolol-succinat or bisoprolol for the treatment of heart failure instead of medications with repeated daily intakes [49]. Further investigations pertaining to the dosing frequency are listed in Table 2.

Table 2 Interventions changing dosing frequency for long-term medication (modified by Gorenoi et al.[10])

Patients	Intervention	Results
Men < 65 years, high risk for CHD, after 12 month therapy with lovastatin, colestipol and niacin (4 times/d)	- 2 times/d Niacin extended release (n = 31) - 4 times/d Niacin regular release (n=31) (crossover after 8 of 16 months)	Compliance 95 % with extended vs. 85 % with regular release (p < 0,001, pill count), significant improvement of lipid profile after 16 months
Moderate essential hypertension (diastolic RR 90 - 110 mmHg), control with monotherapy	- enalapril: 1 time/d 20 mg (A) - enalapril: 2 times/d 10 mg (B) regime after initial phase in 4 study arms (phase - 4 weeks): ABB, BAA, ABA, BAB (n = 4 * 27)	Compliance significantly better with 1 time/d, no difference in therapy success after 16 weeks
Moderate essential hypertension, control with metoprolol or propranolol	- Beloc Zok: 1 time/d 200 mg (n = 196) - Beloc Zok: 2 times/d 100 mg (n = 193)	Compliance significantly better, no difference in therapy success after 10 weeks

- Reducing the pill burden

The total amount of tablets to take – also denoted as pill burden – has a negative influence on adherence. A way of reducing it is to combine various drugs in only one tablet – the so-called combination drug. It has been described that patient adherence can be improved by approximately 20 % through the prescription of combination versus single drugs [50-52]. For the first time approved in 1974 as a combination of trimethoprim and sulfamethoxazole (Bactrim), fixed-dose combinations evolved ever since for the treatment of various diseases [53]. Particularly for the treatment of HIV and hypertension, many combinations are available in Germany nowadays. In the United Stated of America, combinations of cholesterol and blood pressure medicine are already available and in India the first "polypill" combining low doses of thiazide, atenolol, ramipril, simvastatin and aspirin has been tested [54]. Of disadvantage are the high costs for some combinations. However, investigations have shown that overall healthcare costs can be decreased by the reduction of non-drug costs through fewer medical events when adherence is increased [15]. Less variability for dosage modifications of each component in the combination drug is attempted to be avoided by a variety of different strength of the respective product that is available.

Still more studies are needed that investigate clinical outcomes rather than adherence as endpoints for the evaluation of combination drugs or extended release ones as better adherence does not automatically mean better clinical outcome. Additionally, if the patients forget the intake of a combination product, the therapeutic consequence might be greater that the omission of just one drug.

- Avoiding halving tablets

In Germany, nearly every second outpatient needs to halve his tablets in order to obtain the dosage that is prescribed. Sometimes halving is not even approved and therefore inappropriate [55]. Especially for elderly people the procedure might implicate difficulties in the medication handling, frustration and decreasing adherence [56, 57]. Prescribing the right tablet strength may thus facilitate the medication process for the patient.

1.3 Health related Quality of Life

Over the last decades substantial emphasis has been put on the health related quality of life (HRQoL) as an outcome of health interventions. The term was coined in the 1980s and has evolved to cover many aspects of the overall Quality of Life (QoL) that refer to the physical, psychological and social dimensions of health [58]. HRQoL is influenced by a person's experiences, beliefs, expectations and perceptions [59, 60]. For the term Health Related Quality of Life no clear definition exists. Holistic definitions emphasize e.g. the social or emotional well-being of the patient [61], whereas others focus on the ability to have a fulfilled life depending on the health status [62]. The term "health" itself was defined in the preamble to the World Health Organisation constitution in 1948 as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity." Health measures in general may be classified into four levels:

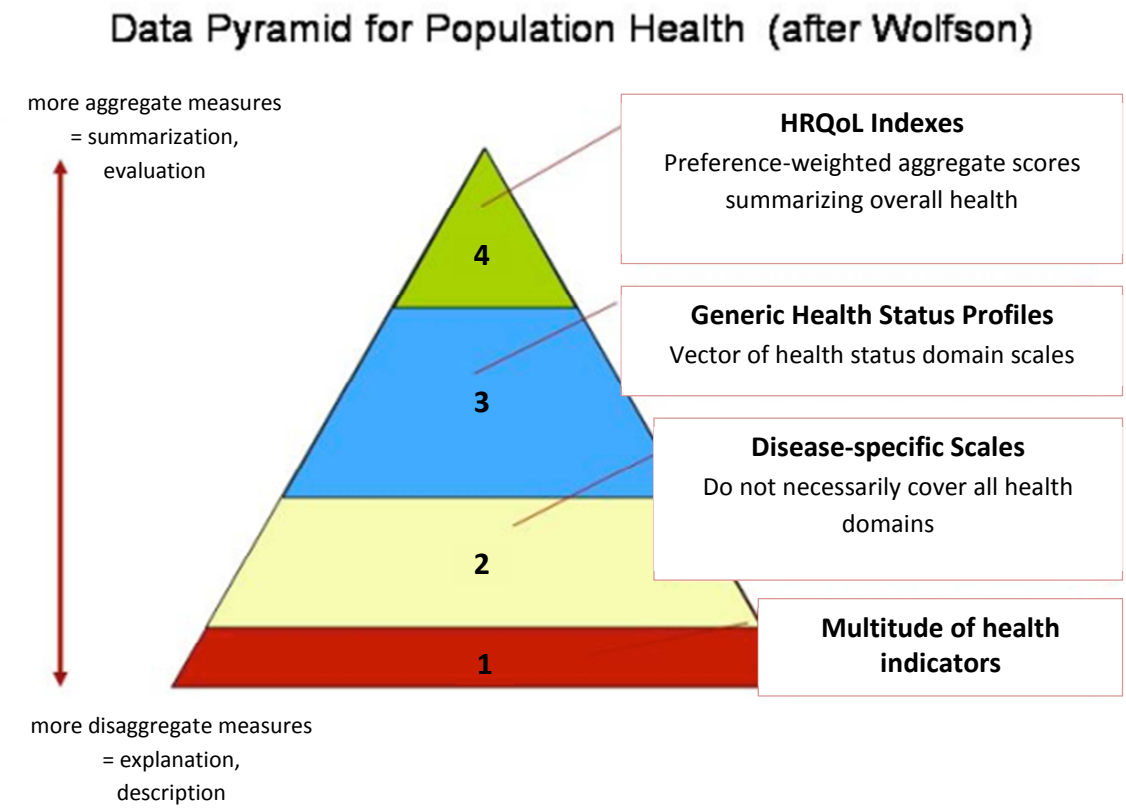

Figure 2 A hierarchal classification of population health measures (modified after [63])

Health indicators focus on only one particular aspect of health in the population, e.g. smoking rates or the prevalence of overweight. They are important measures and offer a detailed view of health; however, they do not allow summarisation or evaluation of overall changes in health. The next level of the pyramid presents the *disease specific scales*. Often in forms of questionnaires, they are used in clinical research data sets to evaluate treatment progress for specific diseases or the burden of particular diseases. *Generic health status profiles* are used to summarise each important domain of health of an individual in order to obtain an overall picture of the respective health status. The scales mentioned above *describe* health, rather than *valuing* it. As a solution, *health-related quality-of-life indexes* were designed, which combine the two different aspects of morbidity and mortality in one, summarized single number. Examples are the EQ-5D (EuroQoL) or SF-6D [64, 65].

Level two and three of the pyramid (Figure 2) depict ways to measure patient's quality of life. They can be classified as [66]:

- specific instruments that focus on problems associated with single disease states, patient groups, areas of function or individuals (e.g. quality of life instruments for breast cancer patients undergoing adjuvant therapy or the "Minnesota Living With Heart Failure questionnaire" [67])

- generic instruments that provide a summary of quality of life (e.g. "The Medical Outcomes Study Short Form 36 (SF-36)" [68], or Sickness Impact Profile (SIP)[69])

The SF-12 is yet a shortened form of the SF-36. Bullinger and Kirchberger were mainly responsible for the validation and implementation into the German-speaking world of the two questionnaires [70, 71]. Compared to the SF-36, reliability and validity of the SF-12 (including the German version) were almost equally satisfying [72]. The SF-12 consists of two summary scales, assessing physical function and mental well-being. It is highly accurate and quicker for the respondent to fill [73]. The physical and mental health scores (QoL psychic, Qol somatic) are computed using the scores of the twelve questions in four defined steps in order to obtain comparable, standardized results [70]. The score ranges from 0 to 100 – zero indicating the lowest and 100 the highest level of health. The SF-12 has been widely used in the world for numerous ethnic groups, which allows for comparisons between study results with the average population or even healthy cohorts. A score of 50 corresponds with the

average score of a population-based cohort; 5 scores of difference reveal a clinical relevant shift [74, 75].

The evidence for a correlation between adherence and QoL has been modest [76]. Depending on the type of medication, the QoL can be influenced in either way – e.g. antihypertensives with side effects might be associated with lower QoL, whereas analgesics, that relief patients from their pain, might improve QoL. Even though many studies analysed adherence, QoL or both, only a few studies evaluated the relationship between the two. Populations that have been investigated are e.g. patients taking anti-psychotics [77], HIV medication [78], lipid-lowering medication [79] or hypertensive geriatrics [80]. Results concerning the associations between QoL and adherence were inconsistent. Whereas data of 772 patients on antihyperlipidemic medications revealed that patients reporting high SF-36 vitality scores were less likely to adhere to their medications, the SF-36 failed to predict compliance behaviour in the geriatric population [79, 80].

1.4 Satisfaction

In order to aid the patients to follow their pharmacotherapy correctly they need to be supplied with the right amount of information about the use, risks and benefits of their medication [81, 82]. The depth and quantity may differ between the individuals, as every person is handling his disease in a distinct way. Some people avoid any information that exceed the minimum of information needed, in order to get the own illness out of mind; others are striving for as much information as possible to understand and cope with the disease and its consequences. In short, patients need to be satisfied with the information they receive about their medication – otherwise they are more likely to become non-adherent [83]. As to that Horne et al. developed and piloted the first questionnaire to assess patient's satisfaction with prescribed drugs information in a valid and reliable way: the "Satisfaction with Information about Medicines Scale" (SIMS). It is a 17-item tool consisting of several questions which assess whether the patient understands action and usage of his medication (sub score a; items 1–9) and whether he knows its potential risks (sub score b; items 10–17). The patient is asked to rate the amount of information he has received from his doctor, using the answers "too much", "about right", "too little", "none received" or "none needed". The ratings "about right" or "none needed" display satisfaction and are

given a score of 1. “Too much”, “too little” or “none received” – showing dissatisfaction – get a score of 0. Scores range from 0 to 17 with higher scores indicating a better overall satisfaction with the amount of medication information received. By examining each item individually, detailed information profiles can be gained about the types of information patients are lacking. The scale has been proved to show adequate reliability and validity and also to correlate with self-reported adherence [83, 84].

Published in 2001, it can be used to quantify information requirements, with potential applications in clinical care, audit and research. The English version has been translated into German (SIMD-D, Appendix H) and its psychometric properties tested [30].

1.5 Influences of a hospital stay on medication therapy and adherence

Medication therapy, -complexity and patient adherence may vary when patients are transferred from ambulatory to hospital care and back. In Germany, the healthcare system is characterized by a rather strict separation between the ambulatory and the hospital sector, resulting in considerable discontinuity in medical care, including pharmacotherapy: It has been described that the on-going medication is modified at hospital admission for 83% [85, 86] and at discharge for 72% of the patients (3). Modifications after return to ambulatory care have often been attributed to economic reasons [87] or lack of information about the discharge medication [88, 89]. These alterations can cause drug-related problems and decrease patient adherence [8]. Medication complexity increases [47, 90-92], patients might get confused by the varying names and appearances of drugs [85, 93] and the trust between patient and physician may suffer owing to frequent modifications [86, 94]. Finally, polypharmacy and poor adherence may result as complications from a hospital stay [95, 96].

Yet, little is known about the magnitude of medication complexity alterations and concomitant adherence variations at the interfaces between hospital and ambulatory care in Germany. Concerning changes in therapy, Himmel et al. found that about 50% of the used medications for chronic treatment were changed during hospitalization [86, 97]. Mansur et al. investigated the association between changes of medication regimens and the adherence following hospital discharge: Non-adherence correlated with the number of medication

regimen changes and was more common in patients discharged with prescriptions for seven or more drugs per day [93]. Therefore, he concluded that the number of long-term drugs should be reduced in order improve the adherence to a medication regimen [93].

Modification of the discharge medication is frequently necessary, e.g. because a drug is intended for short-term treatment, the dose titration is completed after discharge or the brand is switched, e.g. for financial reasons. However, also careful optimization of medication complexity might be short-lived when general practitioners (GP) are not informed about the background of the treatment modifications. A lack of communication between hospital and community healthcare providers has frequently been described and the need for explicit and detailed discharge letters discussed [98]. Nevertheless, information about the effect of additional information for the GP in regards of continuity of intentionally simplified medication regimes from hospital is scarce.

2 Objectives

A lot of research has focused on patient adherence in the last decades, but up to this date no gold standard for improving adherence has been found. To the best of my knowledge, no study has investigated a putative correlation between the reduction of medication complexity and adherence in chronically ill patients at the interfaces of in- and outpatient care yet.

Purpose of this study was to analyze the effects of structured medical management interventions during hospitalization on patient adherence and other outcomes in inpatient and subsequent outpatient care.

In a first step, the MRCI was translated into German, following international recommendations, and to run a pilot test with the new German MRCI instrument.

Secondly, it was the aim to analyse the magnitude of medication complexity alterations and concomitant adherence variations at the interfaces between hospital and ambulatory care in Germany and to collect data on patients' attitudes towards their pharmacotherapy and on reasons for the GPs to either accept or modify hospital discharge prescriptions.

Main objectives of the study were to investigate whether

i.

ii. the complexity of medication therapies at discharge from hospital can be reduced by pharmaceutical counseling of the medical staff in hospital

iii. the patient adherence can be ameliorated by this intervention

iv. the quality of life or satisfaction with information about medicines of the patients is influenced by this intervention

v. an additional information letter for the GP ensures maintenance of the discharge medication in the ambulatory sector.

3 Material and Methods

3.1 Development of the study design

3.1.1 Pharmaceutical Intervention

The aim of the intervention was to simplify the medication regimens of the patients in hospital. Since cardiovascular medications (i.e. antihypertensive, anti-diabetic and lipid-lowering medications) offer various opportunities for simplifications, these medications were focused on and further termed as “study medications”. Feasible simplifications included prescribing combination drugs or long acting formulations and dosing without the need to split tablets. In contrast to other countries, pharmacist do not have prescribing right by German law [99]. Therefore the intervention focused on counseling the doctors in hospital about the respective medication change recommendations.

3.1.1.1 Pre-analyses

In order to quantify the potential extent of simplifications of medication regimes in the setting of the University Medical Center Hamburg-Eppendorf (UKE) and define the exact pharmaceutical recommendations thereafter, two pre-analyses were conducted.
First, the medical histories from urology patients that were routinely sent to the hospital pharmacy via fax were collected for a period of two months. All histories were included and retrospectively analysed with regards to combination pills prescribed and their (dis-)continuation at the time of hospital admission. The medical histories were chosen from the urology department because of various (practical) reasons: first of all the department agreed to cooperate for the study, secondly the patients displayed well an average elective patient admitted to hospital and thirdly the medical histories were sent to the pharmacy anyway in order to enter the patients’ home medication into the electronic medication program according to the pharmacy stock list by a pharmacist.

The second pre-analysis was a point prevalence analysis, examining the dosing frequency of the four long-acting antihypertensives amlodipine, bisoprolol, ramipril and metoprolol-succinat, prescribed on 27 wards of the UKE at one defined day in March 2009. Data was retrieved from the computerized physician order entry system "ATC-Host" (Baxter, Netherlands) which is used at the UKE.

The first pre-analysis revealed that 21.3% of the medications from the medical histories were antihypertenisves. From these 20.9% were prescribed as combination pills, of which the UKE pharmacy had listed 21.4%. This means that 78.6% of the combination pills were discontinued and substituted by single pills at times of admission to hospital. The second pre-analysis showed that approximately one fifth of the long-acting substances were prescribed twice daily, even though the drug information suggested a once-daily dosing.

3.1.1.2 Final standards

Based on the information gained from these analyses a list of combination pills, that were to be stocked in the hospital pharmacy additionally, was generated. These included for example triple combination pills containing amlodipine, valsartan and hydrochlorothiazide (HCT) as well as further double combination pills:

Listed combination pills in the UKE:

- Delix plus® 2,5/ 12,5 ; 5/25 (Ramipril/ HCT)
- Renacor® (Enalapril/ HCT)
- CoDiovan® 80/ 12,5 (Valsartan/ HCT)
- CoDiovan forte® 320/ 25 (Valsartan/ HCT)
- Lorzaar plus® 50/ 12,5 (Losartan / HCT)
- Dytide H® (Triamteren/ HCT)
- Inegy® 20/ 10 (Simvastatin / Ezetimid)
- BiPreterax® 5/1,25 (Perindopril/ Indapamid)
- Dehydrosanol tri® 20/10 (Triamteren/ Bemetizid)
- Amilorid® HCT 5/50
- Eucreas® 50/ 1000 (Vildagliptin/ Metformin)

Further possible combination pills for the study:

- Metoprolol/ HCT
- Bisoprolol/ HCT
- Enalapril/ HCT
- Arelix ACE® 5/6 (Ramipril/ Piretanid)
- Delmuno® (Ramilpril/ Lercanidipin)
- Atacand plus® (Candesartan/ HCT)
- CoDiovan® 80, 160, 320/ 12,5, 25 (Valsartan/ HCT; further strength than already listed)
- Rasilez/ HCT®
- Exforge® 5/ 80, 160; 10/160 (Amlodipin/ Valsartan)
- Exforge/ HCT®, different dosages (Amlodipin/ Valsartan/ HCT)
- Eucreas® 50/ 850 (Vildagliptin/ Metformin)
- Avandamet® 2/ 500; 4/ 1000 (Rosiglitazon/ Metformin)
- Inegy® 10, 40, 80/10

Besides the reduction of the amount of medications, the intervention targeted the dosing frequency. Long acting-substances, approved for the once-daily dosing, were expedited not to be given twice a day and a list of the respective medications was compiled (Table 3).

Table 3 Medications listed in the UKE pharmacy and approved for the once-daily dosing (according to the official drug information)

German Brand Name	Active ingredient(s)
Ca-Antagonists	
Adalat Eins 60®	Nifedipin
Amlodipin	Amlodipin
Carmen®	Lercanidipin
(Nitrendipin)	Nitrendipin
ß-Blocker	
Betapressin®	Penbutololsulfat
Accupro®	Quinapril
Beloc-Zok® *	Metoprololsuccinat
Carvedilol **	Carvedilol
Atenolol ***	Atenolol
Concor®	Bisoprolol
Nebilet®	Nebivolol
Selectol®	Celiprolol
ACE-Inhibitor	
Coversum®	Perindopril
Fosinorm®	Fosinopril
Delix®	Ramipril
AT1-Antagonists	
Aprovel®	Irbesartan
Atacand®	Candesartan
Diovan®	Valsartan
Lorzaar protect®	Losartan
Rasilez®	Aliskiren
Others	
(Moxonidin)	
(Lonolox®)	
Doxazosin	

German Brand Name	Active ingredient(s)
Diuretics	
Natrilix®	Indapamid
Arelix®	Piretanid
(Furo)*	Furosemid
HCT	Hydrochlorothiazid
(Hygroton®)	Chlortalidon
(Aldactone®)	Spironolacton
Inspra®	Eplerenon
Combinations	
Amilorid HCT®	Amilorid + HCT
Dehydrosanol®	Triamteren+ Benserazid
Delix plus®	Ramipril+HCT
CoDiovan®	Valsartan +HCT
Bipreterax®	Perindopril+ Indapamid
Lorzaar plus®	Losartan + HCT
Atacand plus®	Candesartan+ HCT
Coronary medication	
(Corangin Retard)®	Isosorbidmononitrat
MonoMack 50 Retard®	Isosorbidmononitrat
Oral antidiabetics	
Actos®	Pioglitazon
Amaryl®	Glimepirid
Diamicron®	Gliclazid
(Euglucon®)	Glibenclamid
(Glurenorm®)	Gliquidon
Januvia®	Sitagliptin
Glavus®	Vildagliptin

*Exceptions 1-2 times/d: (); *Heart failure; ** Stable angina, heart failure; *** Arrhythmias*

Also, short-acting substances like enalapril were recommended to be substituted by long-acting ones with a once-daily dosing like ramipril. As many elderly patients have difficulties in dividing their tablets another focus was put on the avoidance of prescribing half tablets. An overview of the simplifications is given in

Figure 3.

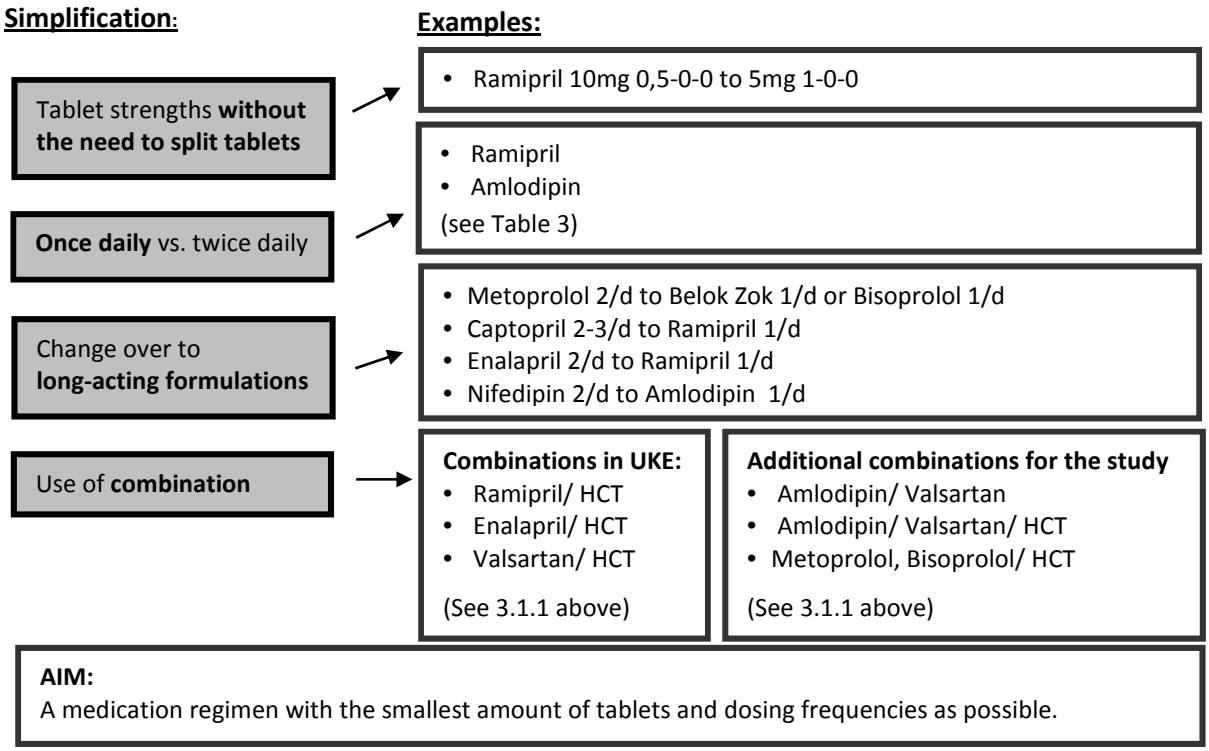

Figure 3 Recommended simplifications

3.1.2 Additional Information for the GP

A lack of communication across the stationary and ambulatory care has been criticised by general practitioners before. In order to evaluate the effect of more information for the GP in the discharge letter pertaining to the discharge medication, an additional text about the changes done in hospital was prepared. It was a standardized paragraph that explained the background of the intervention/ simplification of the medication regimen with the kind request to continue the therapy if possible or to keep the regimen as simple as possible (see Appendix M). The text was written and saved as a text module – ready for the integration in the discharge letter – in the electronic patient record "Soarian" (Siemens), used in the UKE.

3.1.3 Outcomes

Following endpoints and leading questions were defined for the study in order to investigate the respective objectives:

Primary endpoint:

- Medication adherence

Secondary endpoints:

- Medication Regimen Complexity
- Quality of Life
- Satisfaction with Information about Medicines

Further leading questions:

- How do the outcomes change across the interface outpatient / inpatient /outpatient care?
- What is the impact of additional information for the GP in the discharge letter?

3.1.4 Measurements

3.1.4.1 Adherence

Various ways to assess adherence are available. However, for antihypertensive patients – comparable to patients with heart failure [100] – no gold standard for the measurement of adherence has been defined yet. For the present study, certain methods were ruled out from the beginning. Measuring plasma levels did not come into account as it is unpractical for assessing adherence to a whole medication regimen. There are no standardized methods for the respective drugs and it would be too complicated to develop for the variety of eligible drugs. Observing the patients' medication intake, as another direct method, was impossible as adherence was assessed retrospectively at times of admission to hospital. During hospitalisation it would have been possible, but with too much personnel expenditure. As no data from the insurances about pharmacy refill or doctor consultations were available, these indirect methods were not taken into consideration. The obtaining of

these data obliges strict data privacy regulations of the insurances and often passes through time-consuming bureaucratic ways. Also, no study personal was provided to conduct pill count, which would have implied home visits after discharge from hospital. Even though electronic monitoring is assumed to be one of the most exact ways to measure adherence, the expenses and complexity were too high in this setting: for each patient the whole medication would have had to be filled into the small medication boxes – in hospital as well as in the following ambulatory care. Due to its economic performance and widespread use in primary research, the indirect method of patients self-report was chosen for the present study. A disadvantage of self-reports in general is that their reliability might be limited due to social desirability (e.g. not to admit non-adherence in order to please the doctor) and therefore manipulation. Nevertheless, self-reports are regarded as a reliable method for assessing adherence [101, 102]. In order to find an appropriate instrument, a literature research was performed. The Morisky Scale (Appendix F) [21] and the Medication Adherence Reporting Scale [103] were the questionnaires matching the research aims the best, even though low sensitivity and specificity and an overestimation of patient adherence of both had been criticised [104]. The main reason for not selecting the Morisky Scale was that – at the time of developing the study design – no validated German version was available [104].

The Medication Adherence Reporting Scale (MARS) on the other hand had been translated into German (MARS-D, Appendix G) according to guidelines for translation and cultural adaptation of patient-reported outcome measures [105]. Therefore it was used for the presented study.

Data distribution in other studies using the MARS-D for the measurement of patient adherence had been skewed, with a tendency to very high adherence scores. For some investigations results have been dichotomized into adherence and incomplete adherence, but without defining a consistent cut-off point yet; cut-offs range from 20 to 25 [28]. As specificity of the MARS increased with a higher cut-off value [104], a cut-off point of 25 was defined for the present work, as chosen in a previous study [106]. Additionally, each item of the MARS-D was dichotomized separately (score of 5 = adherent; < 5 = incompletely adherent).

3.1.4.2 Medication Regimen Complexity

The Medication Regimen Complexity Index (Appendix D), designed by George et al. in 2004, was the instrument found in literature that quantified the complexity of general medication regimens in the most comprehensive way [34]. Its reliability and validity have been proved, thus it was chosen for the measurement of medication complexity for the present study. The index consists of three sections (A, B, C) and incorporates the total number of medications to be taken, the dosage forms, dosage frequency as well as additional directions pertaining to the administration. According to strictly defined rules, each section yields a score for the respective component of complexity. These scores are ultimately summed up to express the MRCI as a single number. At times of planning the study, no German version was available. Therefore, in a first step, the MRCI was translated into German and a pilot test with the new German MRCI instrument was performed.

Referring to international guidelines [105, 107] the English instrument was independently translated into German by two German pharmacists, fluent in English and aware of the objectives. The two versions were compared and after discussion of the discrepancies, involving a medical psychologist, a German consensual version was generated. In the second phase, this version was back-translated into English by two British pharmacists and native English speakers, who were fluent in German language. Both were uninformed of the underlying objectives, and they did not know the English original MRCI. Discrepancies between the two back-translations regarding the original were pin-pointed and discussed. The two British co-workers commented on the relevance of the discrepancies and after minor modifications of the first draft, the first German version was drawn up. It was reviewed by two other German pharmacists, who looked specifically at language and comprehensibility. Unclear vocabulary or instructions that led to inconsistent interpretations when using the new tool for first-cut tests were modified in accordance with the opinions of an expert in psychometric assessment and the author of the original MRCI to yield the final German version of the Medication Regimen Complexity Index (MRCI-D).

For the testing of the first and final version, the MRCI-D was applied to the medication regimens of 20 patients. All patients were being treated with cardiovascular medications on the ward for internal medicine of the University Medical Center Hamburg-Eppendorf and gave their written informed consent prior to involvement. Scoring was not restricted to the cardiovascular medications, but encompassed the whole regimen, including medicines used

on an 'as needed' basis. The medication regimens of the 20 patients were analysed independently by two pharmacists using the first version of the MRCI-D. After the previously mentioned small changes of the first version, the 20 therapy plans were again rated by three pharmacists, this time with the final version. Based on these results the inter-rater reliability of the instrument was determined. Three weeks later, one of the pharmacists repeated this process with the same medication plans in order to calculate the test-retest reliability.

The final version of the MRCI-D was then determined as instrument for the measurement of medication regimen complexity in the present study. In line with other trials, including the original validation of the MRCI, no cut-off values were defined [34, 46, 108]. For the analysis of the magnitude of medication complexity alterations at the interfaces between hospital and ambulatory care, the whole medication regimens of the patients were included in the calculation. For the main research question (evaluation of the effect of the pharmaceutical counseling) only “study medications” (see 3.1.1) were regarded. In cases of discrepancies between the medication lists returned from the patients and their GP at T2, the information from the GP was considered correct and used for the calculation of medication regimen complexity.

3.1.4.3 Health Related Quality of life

For the measurement of the patient’s quality of life, a generic instrument was needed as the study population was not completely coherent concerning their diagnoses. This excluded the usage of disease specific instruments. The SF-36 (Short Form-36) might have been considered as the most widely used health status tool in the world. Starting originally with a 250-items questionnaire in the 1970s, Ware and colleagues shortened it to only 36 questions covering 8 scales in 1992. This was formally known as the Medical Outcome Study Short Form-36, or “MOS Short Form-36,” and is now just the “SF-36” for short [63]. Still, for the present work, the consideration of the length of the questionnaire led to choosing the 12 item short form health survey (SF-12).

3.1.4.4 Satisfaction with Information about Medicines

For gathering how satisfied patients are with the information they received from their doctor about their medications, the only suitable instrument that was found in literature was the "Satifaction with Information about Medicines Scale" (SIMS) [84]. It was tested in a variety of studies between 1995 and 1998, including in- and outpatient settings and various diagnoses. The SIMS was evaluated in terms of its acceptability (ease of use), internal consistency, test-retest reliability, and criterion related validity using existing self-report measures of adherence and patient beliefs about medicines [84]. The English version was then translated into German (SIMS-D, Appendix H) and its psychometric properties tested and published in 2009 [30]. This version was used for the present study.

3.1.4.5 Patient Questionnaires

In order get the needed information from the patients bundled and in an organized way, the self-report tools mentioned above were integrated into self-designed patient questionnaires (see Appendices I, J, K).

Patient questionnaire N°1 covered the MARS-D, the SIMS-D and the SF-12. Besides, sociodemographic aspects and questions about the medication intake in general were asked as follows:

- Does the number of tablets to take influence your quality of life?
  ("Beeinträchtigt die Anzahl an einzunehmenden Tabletten Ihre Lebensqualität?")
- Is it important for you to take as few tablets as possible?
  ("Ist es Ihnen wichtig, möglichst wenige Tabletten einzunehmen?")
- Are you willing for a co-payment if it helps reducing the number of tablets?
  ("Wären Sie bereit eine Zuzahlung für die Medikamente zu leisten, wenn sich dadurch die Tablettenzahl reduziert?")
- Are you concerned about forgetting medication intake/ taking medication incorrectly?
  ("Haben Sie Angst, versehentlich Tabletten zu vergessen oder falsch einzunehmen?")
- Do varying appearances of tablets complicate the correct intake for you?
  ("Erschwert Ihnen ein Wechsel des Aussehens die richtige Einnahme?")

- Are the shape and color of tablets helpful for the correct intake?
  ("Hilft Ihnen die Form oder Farbe von Tabletten zur Orientierung?")
- Do you have problems with splitting tablets?
  ("Bereitet Ihnen das Teilen von Tabletten Schwierigkeiten?")

Patient questionnaire N°2 included the MARS-D plus the following two questions, all in reference to the medication intake in hospital:

- Are you aware of the different drugs you receive during hospital stay?
  ("Achten Sie auf die einzelnen Medikamente, die Sie im Krankenhaus bekommen?")
- Does a change of these drugs compared to your home medication have an influence on your medication intake?
  ("Beeinflusst ein Präparatewechsel Ihrer Medikamente im Krankenhaus Sie dort in Ihrem Einnahmeverhalten?")

Patient questionnaire N°3 covered the MARS-D, the SIMS-D and the SF-12. Moreover the patient was asked to write down his actual medications with drug name, strength and dosing frequency.

3.1.4.6 General Practitioner Questionnaire

The questionnaire for the GPs (Appendix L) included following questions about the medication recommendations in the discharge letter of the respective patient, their reasons for acceptance or modifications of the discharge medication and their attitude towards the complexity of therapeutic regimens in general:

- How to you assess the medication therapy from hospital compared to the medication therapy before hospital stay?
  ("Wie beurteilen Sie die im Krankenhaus angesetzte Therapie im Vergleich zur vorherigen Hausmedikation?")

- Did you make modifications? (“Haben Sie Veränderungen vorgenommen?“)
- If yes, why? (economic, therapy insufficient, no long-term medication, patient’s request, adverse events, insufficient information from hospital, others)
  (“Wenn JA, Gründe für Veränderungen (ökonomisch, keine ausreichende Einstellung des Patienten, fehlende persönliche Erfahrung, keine Dauermedikation, Wunsch des Patienten, Nebenwirkungen, unzureichende Infos aus dem Krankenhaus, andere“)
- If no, why not? (therapy successful, patient satisfied, good discharge letter, patient’s request, others)
  (“guter Therapieerfolg, Patientenzufriedenheit, guter Entlassbrief, Wunsch des Patienten, andere“)
- How often are you willed to accept recommendations from hospital?
  (“Bereitschaft zur Übernahme einer Krankenhaus-Verordnung“)
- For how important do you consider a small amount of tablets for the patient?
  (“Für wie wichtig halten Sie eine möglichst geringe Anzahl an Tabletten für den Patienten?“)
- When choosing the medication therapy do you consider that…
  (“Ziehen Sie bei der Therapieauswahl in Betracht, dass…“)
    - …halving tablets might be a problem for the patient?
      (“…Tablettenteilen oftmals ein Problem für den Patienten darstellt?“)
    - …adherence can be enhanced by reducing the number of medications?
      (“…die Adhärenz durch eine geringere Anzahl an Tabletten erhöht werden kann?“)
- I prescribe more expensive medications if they are considered more effective.
  (“Wären Sie bereit, teurere Medikamente zu verordnen, wenn dadurch bessere Therapieerfolge erzielt werden könnten?“)
- Financial issues restrict me in choosing the appropriate medication.
  (“Sehen Sie sich durch gesetzliche Vorschriften hinsichtlich Ihres Arzneimittelbudgets in Ihrer Therapiewahl eingeschränkt?“)

3.1.5 Study design

The investigation was planned as a prospective, semi-randomized controlled study with a study design as pictured in Figure 4, divided in phase 1 and phase 2.

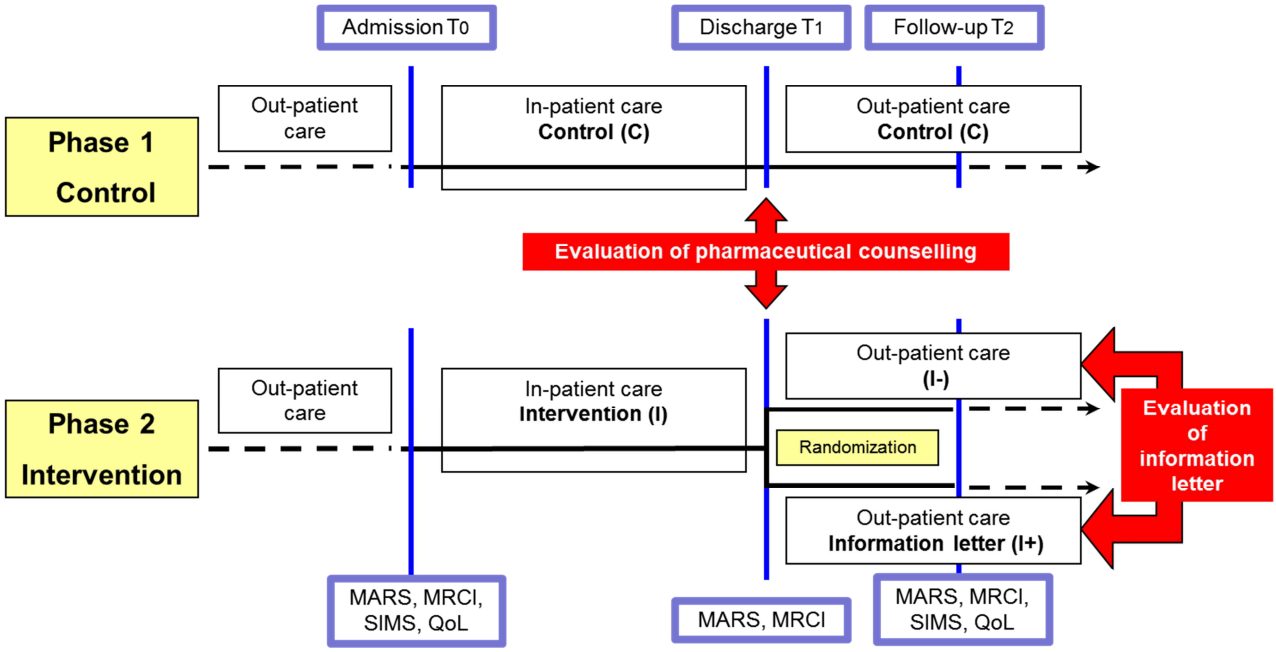

Figure 4 Study design

The first cohort of patients was assigned to the control group (C; phase 1), the second cohort to the intervention group (I, phase 2). The latter was randomised into the two subgroups (I-) and (I+). As a randomisation of the entire study population would have required a parallel design, knowledge bias of the counseled prescribers in hospital and a resulting "carry-over-effect" on the control group would have been inevitable. Thus complete randomisation of the study population was waived.

In the intervention group the doctors in hospital were counseled by a pharmacist about possible simplifications (see 3.1.1.2) of the "study medication" in the regimens of the included patients. Recommendations were given during daily ward rounds and directed personally towards the doctors in charge. Concerning the further discharge management, the intervention group was randomised into two subgroups: I- received the intervention and was discharged from hospital with the normal discharge letter; I+ received the intervention and a discharge letter with an additional information text explaining the background of the

simplification and the request to continue the therapy unchanged if possible (3.1.1.1 and Appendix M).

The randomisation of the intervention group was conducted with closed numbered envelopes, containing the concrete allocation of the respective patient to either the intervention group (I-) or (I+). The envelopes had been prepared by an independent person before conducting the study. After receiving written consent the envelopes were opened according to their numbering. Neither the patient nor the hospital medical staff were aware of the allocation. Patients were enrolled and assigned to their respective group by the pharmacist conducting the study.

Four wards of the University Medical Center Hamburg-Eppendorf (UKE), a tertiary care university hospital in Germany, were included. Two were internal medicine wards, in particular nephrology and endocrinology, and two were urology wards. The internal medicine ones were chosen as many patients treated for their hypertension, diabetes or dyslipidaemia were admitted to these wards. The urology wards were chosen in order to include a surgery unit, where medication therapy was not as much in the focus of the hospital stay as on internal medicine wards. This was to avoid a selection bias by only including internal medicine wards.

Following inclusion criteria were defined:

- Age above 18 years
- Patient on the internal medicine or urology wards
- Receiving medications to treat chronic cardiovascular and/or metabolic diseases with potential simplifications (“study medication”)
- Capability to fill out questionnaires
- Written informed consent

Exclusion criteria:

- Cognitive impairment
- Inability to communicate in German
- Transfer to wards not included in the study

All patients who met the inclusion criteria and gave their written consent were enrolled consecutively between March 2010 and October 2011. Follow-up lasted to December 2011.

3.1.6 Data collection

Data was collected at three points of time: admission to hospital (T0), discharge from hospital (T1) and 42 ± 7 days after discharge (T2). The different times were chosen in order to evaluate outpatient care *before* the hospital stay (T0), inpatient care (T1) and outpatient care *after* the hospital stay (T2).

- Admission to hospital (T0)

At times of admission to hospital, clinical and demographic aspects were compiled from the electronic hospital files with a standardized data sheet (see Appendix N). The pharmacist recorded the necessary information after the patients had given their written informed consent. The diagnoses of the patients were registered using the tenth version of the International Classification of Diseases (ICD-10). The ICD is a code published by the World Health Organisation (WHO) and originally designed to promote international comparability in the collection, processing, classification and presentation of mortality statistics. Periodically, the ICD is revised in order to incorporate changes in the medical field. Thus, compared to the ninth version, the ICD-10 has almost twice as many categories, now classified with alphanumeric names. ICD-10 was endorsed by the forty-third World Health Assembly in May 1990 and came into use in WHO member states as of 1994.

The medication regimens were obtained from different sources, depending on the ward's organisation. At the internal medicine ward they were extracted from scanned medication plans in the electronic hospital files. For the urology patients admitted through the admission office, the home medication was routinely recorded by the responsible medical staff and directly sent to the pharmacy via fax. These plans were collected for the patients participating in the study. Patient questionnaire N°1 (socio-demographic data, pre-admission adherence, QoL, SIMS, additional questions concerning their attitudes towards their medication) was filled out by the patient independently. It was handed to him on the ward after he had signed the consent and recollected before discharge from hospital.

- Discharge from hospital (T1)

Before discharge, the patients filled out questionnaire N°2 (in-hospital adherence), that was handed over and recollected together with the first questionnaire. Discharge medication was retrieved from the discharge letters.

- Post-discharge (T2)

42 ± 7 days after discharge questionnaires were sent to the patient (N° 3: post-discharge adherence, QoL, SIMS, current list of prescribed medications) and his GP, including a stamped addressed envelope. If questionnaires were not returned, no further reminder (by phone or written) was scheduled in order to avoid bias through social pressure.

Table 4 Time point of data collection

	T0		**T1**		**T2**		
Outcome	Patient	Pharmacist	Patient	Pharmacist	Patient	Pharmacist	GP
Adherence	**X**		**X**		**X**		
Complexity		**X**		**X**		**X**	
Qality of Life	**X**				**X**		
Patient satisfaction	**X**				**X**		
GP Questionnaire							**X**

3.2 Ethical Review Committee vote

Before running a clinical study, the responsible ethical review committee has to review and approve the respective proposal. It is to safeguard the dignity, rights, safety and well-being of the research participants. All ethical aspects of the research proposal are reviewed and evaluated – free of bias and influences – before carrying out the study.

Therefore a detailed application with information about the study design, performance and further analysis was submitted to the Ethical Review Committee Hamburg. It was accompanied by the required patient information (Appendix A) that insures that the patient is well-informed about the study before consenting to it and the respective informed consent (Appendix B). Of importance was also the information of data protection, which was integrated as a text passage into the patient information. On December 3rd, 2009 the Ethical Review Committee Hamburg approved the study (Appendix C).

3.3 Statistical analysis

3.3.1 Sample size calculations

In order to obtain sufficient statistical power sample size calculations were conducted. Background is the aim of empirical studies to transfer results from a sample to a population. The larger the sample size, the more surely do the answers truly reflect the population. However, because of economic and ethical reasons, the sample is often kept as small as possible.

Two terms that are important to know before calculating a sample size are **confidence interval** and **confidence level**. A ***confidence interval*** gives an estimated range of values which is likely to include an unknown population parameter, the estimated range being calculated from a given set of sample data [109]. The ***confidence level*** is the probability value associated with a confidence interval. The selection of a confidence level determines the probability that the confidence interval produced will contain the true parameter value. Common choices for the confidence level are 0.90, 0.95, and 0.99. Two types of errors can occur:

- Type I error (α) is often referred to as a 'false positive' and reflects the probability of rejecting the null hypothesis (H_0) when it is true
- Type II error (β) is the opposite of a Type I error and might be referred to as a 'false negative' and reflects the probability of not rejecting the null hypothesis (H0) when it is false

The power (1- β) represents the probability of rejecting the null hypothesis (H0) when it is false. A power of >0.80 is desirable for clinical research and it correlates directly with α, the sample size and the expected effect size.

		Reality	
		H_0 False	H_0 True
Test	Reject H_0	Correct rejection H_0 = Power = 1 - β	Type I error = α
	Accept H_0	Type II error = β	Correct acceptance of H_0

Figure 5 Statistical errors [110]

The required sample size for the present study was planned to enable the detection of small to medium effects, with a Cohen's d of 0.40 for metric outcomes. Cohen's d is defined as the difference between two means divided by a standard deviation for the data and is frequently used in estimating sample sizes. An effect size of 0.2 to 0.3 might be a "small" effect according to Cohen's d, around 0.5 a "medium" effect and 0.8 to infinity a "large" effect. The Cohen's d of 0.40 as in the present calculation corresponds to an odds ratio of approximately 2.0 for dichotomous outcomes in two-tailed analyses with a power of 0.80 and a type I error probability of 0.05 in two-group comparisons. This resulted in a required sample size of 300 patients, with 100 patients in each group (control group C, intervention group I+ and intervention group I-).

3.3.2 Evaluation of the MRCI-D

For the validation of the German version of the Medication Regimen Complexity Index (MRCI-D) several statistical analyses were performed. The psychometric evaluation included the calculation of inter-rater reliabilities and a test-retest, as well as the assessment of convergent validity.

For the inter-rater reliability of the MRCI-D (pre-version/final version), the complexity calculations for 20 different medication regimens by two/three different raters were the basis for quantifying the agreement, using the intraclass-correlation-coefficient (ICC). The same method (ICC) was used for the test-retest reliability, based on the results of one pharmacist rating the same medication regimens twice, with three weeks in-between.

Correlations between the scores of the MRCI-D (A, B, C and the total score) and the number of medications were checked to obtain information about convergent validity of the instrument. Statistical tests were carried out using SPSS ver. 15.0 (Chicago, Illinois).

3.3.3 Control group at the interfaces between hospital and ambulatory care

For the analysis of the magnitude of medication complexity alterations and concomitant adherence variations at the interfaces between hospital and ambulatory care, adherence, regimen complexity and number of prescriptions of the entire long-term medication therapy of the patients were analysed at T0, T1 and T2 using descriptive statistics. Additionally, each of the five items of the MARS-D was analysed separately. Means and standard deviations were calculated for continuous outcomes (regimen complexity, number of prescriptions and adherence) and frequencies were assessed for dichotomous outcomes (i.e. single MARS-D items). In a second step, univariate analyses of variance (ANOVA) with repeated measures were conducted for each outcome using time as a factor (admission, discharge, post-discharge) and the specific outcome as dependent variable. Results with a type I error rate of $p < 0.05$ were considered statistically significant. According to the conventions values for the F-test (F) and the number of degrees (df) are given within the results for the ANOVA. Values for the Friedman test, Chi-squared are also listed.

Patients' attitudes towards their medication as well as practitioners' attitudes towards prescriptions and reasons for the GPs to either accept or modify hospital discharge medications were analysed using absolute and percentage frequencies. The relationship between categorical variables (gender, education, employment-status) and incomplete adherence was evaluated using chi-squared tests. T-tests were used to assess differences between adherent and incomplete adherent patients in terms of age. Additionally, multicollinearities (pairwise correlations) between patient characteristics were studied. All analyses were performed using SPSS ver. 18.0 (IBM Corp., Armonk, NY).

3.3.4 Main objectives

The evaluation of the *effects of pharmaceutical counseling of hospital medical staff* was based on an observational (controlled but not randomised) design. This included comparison of the control group (C) and the intervention group (I) at discharge (T1). For this comparison, both intervention subgroups were used (I- and I+), as the additional intervention (detailed discharge letter for the GP; I+) took an effect only after discharge. For comparisons of outcomes six weeks after discharge (T2), the control group (C) was compared only to the usual discharge letter subgroup (I-), in order to avoid confounding with the effects of the discharge letter intervention, which were evaluated separately.

In order to adjust for imbalance between the control and intervention groups, propensity score stratification was applied [111, 112]. The propensity score matching reduces the confounding effects of covariates and allows differences of responses to be attributed to differences of treatments. In other words, the propensity score for an individual, defined as the conditional probability of being treated given the individual's covariates, is often used to balance the covariates in two non-randomized groups and thus to reduce bias [111]. Based on propensity scores predicted from demographic and clinical characteristics as well as from baseline level of outcomes, five propensity strata were built in the present analysis. Within these strata, patients were therefore comparable according to their demographic and clinical characteristics. Comparisons between the cohorts were made within these strata and results were pooled in a fixed-effect model. This was done for the dichotomous outcome (completely vs. incompletely adherent) by logistic regression and for interval-scaled outcomes (scales) by analysis of covariance with inclusion of the stratum as covariate. In each model, the baseline level of the investigated outcome was included. Thus error variance was reduced and the power increased as differences between the groups were better identified and the effects attributed to the intervention and not to the fact that the two groups already had different characteristics at baseline.

The evaluation of the *effects of additional information on medication in the discharge letter for the GP* was performed through the comparison of two randomly allocated groups six weeks after discharge (T2). Analyses were performed as described above, but without propensity score stratification since the two groups were well balanced due to successful randomisation.

The analyses followed a per-protocol design than intention-to-treat since last values were not carried forward. A drop-out analysis was executed in order to check for systematic errors: all patients having at least one evaluable outcome at T2 vs. all patients not having evaluable outcomes at T2. Additionally, baseline differences between control and intervention after stratification were controlled.
All analyses were performed using SPSS ver. 18.0 (IBM Corp., Armonk, NY).

3.3.5 Missing values

Every patient with at least one evaluable outcome was included into the analyses. If one or more questions of the questionnaires were missing, the questionnaire was still included and missing values were not substituted. Exceptions were validated tools integrated into the questionnaires, like the MARS-D, SIMS-D and SF-12. Calculations were done according to the respective instructions for the adequate use of the tool. Missing values of the MARS-D and SIMS-D were replaced by the average value of the answered questions. For the use of the SF-12 it was recommended not to exploit questionnaires if one value was missing [70].

4 Results

4.1 Translation and evaluation of the MRCI-D

Like the original tool, the MRCI-D (Appendix E) is composed of three sections: section A *dosage forms*; section B *dosage frequency* and section C *additional instructions*. The guidelines for the raters given on the first page were expanded by an additional point 9: “Drugs that are administered as mL, drops or units do not score points for “multiple units at one time” (e.g. insulin 20-0-23 I.U., tramadol drops 20°- 20°- 20°, lactulose 15mL once daily"), since pilot-testing of the first version showed wide variations due to different interpretations of the raters. This resulted in a low inter-rater agreement for medication regimens containing such prescriptions. The Latin abbreviation “mdu” in point 6 seemed not sufficiently common in German language prescriptions and was therefore replaced by the German equivalent of “according to the directions”. The examples “Marcumar™ according to INR” und “insulin according to blood glucose” were added as well. The equally uncommon terms “mane/nocte” that are given as examples in section C under the heading “Take/use at specified time(s)” led to several misunderstandings and were replaced by the more specific timing instruction “at bedtime”. Further, the dosage form "effervescent tablets" was added to section A since pre-test ratings were inconsistent regarding the classification and varied between tablets, liquids and granules. It was added to the group "powders/granules" because these dosage forms also need to be solved in water before ingesting at times and were therefore considered as similar.

For the pilot-testing of the psychometric properties of the tool, the medication regimens of 20 patients (14 men and 6 women) were included. The mean age was 58.9 years (SD 13.8, range 29 to 78). Eight patients were treated for endocrine disorders and twelve for renal conditions. Reasons for hospital admission were metabolic disturbances, surgery of endocrine tumours, acute worsening of renal function or renal transplant evaluations. The mean number of medications prescribed was 9.95 (SD 4.12, range 4 to 19), mainly for hypertension, diabetes mellitus, as immunosuppressive therapy or to correct electrolyte imbalances in dialysis patients.

The mean scores on the MRCI-D in section A (for dosage forms) were 4.65 points (SD 3.05, range 1 to 10); in section B (for dosage frequency) 13.75 points (SD 5.74, range 5 to 22); in section C (about additional instructions) 3.50 points (SD 3.14, range 0 to 12); and 21.90 points (SD 9.58, range 6 to 35.5) in total. The lowest score was achieved with a medication containing four drugs, the highest with a medication containing 19 drugs.

Results of the inter-rater /test-retest reliability are shown in Table 5. While the first version of the tool – especially section C *additional instructions* – revealed an unsatisfying inter-rater correlation, the ratings of the final version MRCI-D showed a high inter-rater correlation (all ICCs above 0.80); test-retest reliability was similarly high.

Table 5 Inter-rater- and test-retest reliability of the German version of the Medication Regimen Complexity Index (MRCI-D)

Section	**inter-rater reliability first version**	**inter-rater reliability final version**	**test-retest reliability (after 3 weeks)**
A *dosage form*	0.671 (0.331; .0856)	0.829 (0.619; 0.929)	0.874 (0.713; 0.948)
B *dosing frequency*	0.897 (0.757; 0.958)	0.984 (0.961; 0.994)	0.993 (0.980; 0.997)
C *additional instructions*	0.159 (-0.096; 0.487) n.s.	0.866 (0.693; 0.945)	0.973 (0.934; 0.989)
A+B+C total	0.784 (-0.010; 0.940) n.s.	0.977 (0.943; 0.991)	0.984 (0.959; 0.994)

Table 5 shows intraclass-correlation coefficients (ICC) with 95% confidence interval. All coefficients are statistically significant ($p<0.05$), except the ones marked with "n.s." (not significant). Interpretation directions according to Cicchetti [113]: <0.40 = low; 0.40 to 0.59 = adequate; 0.60 to 0.74 = high; and 0.75 to 1.00 = very high.

The correlation between the number of medications and the scores in section B *dosage frequency* was high (0.92, $p<0.001$) and intermediately high with section A *dosage forms* (0.61, $p<0.005$) and section C *additional instructions* (0.51, $p<0.023$). The correlation with the end score was 0.91 ($p<0.001$), which suggests an adequate convergent validity of the tool.

An example for the scoring using the MRCI is demonstrated below, given the medication plan (Table 6) and the respective filled out MRCI data sheets (Figure 6)

Table 6 Medication plan (example)

Medication	Morning	Noon	Evening	Night	As needed
Aspirin 100mg		1			
Metoprololsuccinat 95	0,5		0,5		
Enalapril 40mg	0,5		0,25		
Amlodipin 5mg	1		1		
Valsartan 320mg	1				
Aliskiren 150mg	1				
Urapidil 60mg	1		1		
Moxonidin 0,3 mg	1,5		1,5		
Torasemid 10mg	1				
Simvastatin 20mg				1	
Sitagliptin 100mg	1		1		
Novaminsulfon 500mg	1	1	1	1	
Tilidin/Naloxon 50/4mg	1		1		
Paracetamol comp					x
Ximovan 10mg					x

A) Circle the weighting corresponding to each dosage form (ONCE ONLY) present in the regimen.

Dosage Forms		Weighting
ORAL	Capsules/Tablets	(1)
	Gargles/Mouthwashes	2
	Gums/Lozenges	2
	Liquids	2
	Powders/Granules	2
	Sublingual sprays/tabs	2
TOPICAL	Creams/Gels/Ointments	2
	Dressings	3
	Paints/Solutions	2
	Pastes	3
	Patches	2
	Sprays	1
EAR, EYE & NOSE	Ear drops/creams/ointments	3
	Eye drops	3
	Eye gels/ointments	3
	Nasal drops/cream/ointment	3
	Nasal spray	2
INHALATION	Accuhalers	3
	Aerolizers	3
	Metered dose inhalers	4
	Nebuliser	5
	Oxygen/Concentrator	3
	Turbuhalers	3
	Other dry powder inhalers	3
OTHERS	Dialysate	5
	Enemas	2
	Injections: Prefilled Ampoules/Vials	3 4
	Pessaries	3
	Patient controlled analgesia	2
	Suppositories	2
	Vaginal creams	2
	Total for Section A	1

B) For each medication in the regimen tick a box [√] corresponding to the dosing frequency. Then, add the no. of [√] in each category and multiply by the assigned weighting. In cases where there is no exact option, choose the best option.

Dosing Frequency	Medications													Total	Weighting	Weighting × No. of medications
Once daily	√	√	√	√	√	√								5	1	5
Once daily prn															0.5	
Twice daily	√	√	√	√	√	√	√							7	2	14
Twice daily prn															1	
Three times daily															3	
Three times daily prn															1.5	
Four times daily	√													1	4	4
Four times daily prn															2	
q 12h															2.5	
q 12h prn															1.5	
q 8h															3.5	
q 8h prn															2	
q 6h															4.5	
q 6h prn															2.5	
q 4h															6.5	
q 4h prn															3.5	
q 2h															12.5	
q 2h prn															6.5	
prn/sos	√	√												2	0.5	1
On alternate days or less frequently															2	
Oxygen prn															1	
Oxygen <15hrs															2	
Oxygen >15hrs															3	
															Total for Section B	24

C) Tick a box [√] corresponding to the additional directions, if present in the regimen. Then, add the no. of [√] in each category and multiply by the assigned weighting.

Additional Directions	Medications								Total	Weighting	Weighting × No. of medications
Break or crush tablet	✓	✓	✓						3	1	3
Dissolve tablet/powder										1	
Multiple units at one time (e.g. 2 tabs, 2 puffs)	✓								1	1	1
Variable dose (e.g. 1-2 caps, 2-3 puffs)										1	
Take/use at specified time/s (e.g. mane, nocte, 8 AM)										1	
Relation to food (e.g. pc, ac, with food)										1	
Take with specific fluid										1	
Take/use as directed										2	
Tapering/increasing dose										2	
Alternating dose (e.g. one mane & two nocte, one/ two on alternate days)	✓								1	2	2
										Total for Section C	6

Medication Regimen Complexity = Total(A) + Total(B) + Total(C)

= 1 + 24 + 6 = 31

Figure 6 Usage of the MRCI (example)

According to the instructions every section is filled out for each medication and the values are finally summed up to express the Medication Regimen Complexity. In the example the total score for the Medication Regimen Complexity is 31.

4.2 Baseline characteristics

Table 7 Baseline characteristics of C, I and total (T0)

	Control (C)	Intervention (I)	N analyzed	p	Total
N total	108	129			237
Sex (% female)	18 (16.8)	48 (37.5)	235	<0.001	66 (28.1)
Age (yrs., mean (SD))	63.2 (12.0)	64.4 (15.0)	221	0.519	63.8 (13.8)
Family status			182	0.001	
Single	10 (12.0%)	16 (16.2%)			26 (14.3%)
Married	64 (77.1%)	54 (54.5%)			118 (64.8%)
Divorced	6 (7.2%)	5 (5.1%)			11 (6.0%)
Widowed	3 (3.6%)	24 (24.2%)			27 (14.8%)
Highest education			187	0.013	
None or semi-skilled	7 (8.0%)	18 (18.0%)			25 (13.4%)
Professional school	11 (12.6%)	11 (11.0%)			22 (11.8%)
Apprenticeship	44 (50.6%)	59 (59.0%)			103 (55.1%)
College	25 (28.7%)	12 (12.0%)			37 (19.8%)
Number of diagnoses	7.2 (5.2)	8.7 (5.1)	228	0.027	8.0 (5.2)
Hypertension	81 (81%)	121 (93.8%)	229	0.004	202 (88.2%)
Diabetes mellitus	28 (28%)	48 (37.2%)	229	0.159	76 (33.2%)
Hyperlipidemia	12 (12%)	2 (1.6%)	229	0.001	14 (6.1%)
Adipositas	14 (14%)	14 (10.9%)	229	0.544	28 (12.2%)
Renal insufficiency	20 (20.0%)	30 (23.3%)	229	0.630	50 (21.8%)
Malignant tumor	33 (30.8%)	15 (11.6%)	236	<0.001	48 (20.3%)
Ward			225	0.002	
Urology	50 (52.1%)	39 (30.2%)			89 (39.6%)
Nephrology	33 (34.4%)	55 (42.6%)			88 (39.1%)
Endocrinology	13 (13.5%)	35 (27.1%)			48 (21.3%)
Length of stay (days, mean (SD))	6.0 (4.4)	8.3 (5.7)	222	0.001	7.3 (5.3)

N=number of patients; p=level of significance

Table 8 Baseline characteristics of I- and I+ (T0)

	Intervention without detailed letter (I-)	Intervention with detailed letter (I+)	N analyzed	p
N total	64	65		
Sex (% female)	28 (43.8%)	20 (31.3%)	128	0.201
Age (yrs., mean (SD))	64.8 (13.7)	63.9 (13.7)	129	0.720
Family status			99	0.893
Single	8 (17.0%)	8 (15.4%)		
Married	24 (51.1%)	30 (57.7%)		
Divorced	3 (6.4%)	2 (3.8%)		
Widowed	12 (25.5%)	12 (23.1%)		
Highest education			100	0.165
None or semi-skilled	11 (21.6%)	7 (14.3%)		
Professional school	4 (7.8%)	7 (14.3%)		
Apprenticeship	27 (52.9%)	32 (65.3%)		
College	9 (17.6%)	3 (6.1%)		
Number of diagnoses	9.5 (5.0)	7.9 (5.2)	128	0.079
Hypertension	59 (92.2%)	62 (95.4%)	129	0.492
Diabetes mellitus	27 (42.2%)	21 (32.3%)	129	0.277
Hyperlipidemia	2 (3.1%)	0 (0%)	129	0.224
Adipositas	5 (7.8%)	9 (13.8%)	129	0.397
Renal insufficiency	17 (26.6%)	13 (20.0%)	129	0.411
Malignant tumor	6 (9.4%)	9 (13.8%)	129	0.584
Ward			129	0.703
Urology	21 (32.8%)	18 (27.7%)		
Nephrology	25 (39.1%)	30 (46.2%)		
Endocrinology	18 (28.1%)	17 (26.2%)		
Length of stay (days, mean (SD))	8.8 (5.5)	7.8 (5.9)	127	0.327

4.3 Control group at the interfaces between hospital and ambulatory care

A total of 108 patients were assigned to the control group. Loss during follow-up was due to death (n=2) or transfer to wards not included in the study (n=1). Baseline characteristics of the study population are summarised in Table 6. Mean age was 63.1 years (SD 12.0; range 26-84) and 82.4% of the patients were male. The low percentage of female patients partly resulted from the inclusion of a urology ward, where most elective admissions were male. Also, the prevalence of hypertension at the age of 63 years is higher in the male population. At the time of enrolment the patients had a mean of 7.2 diagnoses of chronic diseases (SD 5.3). Their mean length of hospital stay was 6.0 days (SD 4.4).

Adherence rates are shown in Figure 7. The number of patients included in the analysis at T0, T1 and T2 were 88, 85 and 67, respectively. The mean MARS-D score at T0 was 23.57 (SD 2.53), with 60.2% of the patients classified as incompletely adherent (score<25). In hospital (T1), the mean score increased to an average of 24.02 (SD 2.07), with 37.6% of incompletely adherent patients. Six weeks post-discharge (T2), the mean MARS-D score decreased to 23.91 (SD 1.30), with 61.2% of incompletely adherent patients (F=1.74; df=1; p=0.193). Although adherence rates showed a strong tendency to vary substantially across measurement points, they did not reach strict statistical significance (Friedman test; Chi-squared=5.57; df=2; p=0.062).

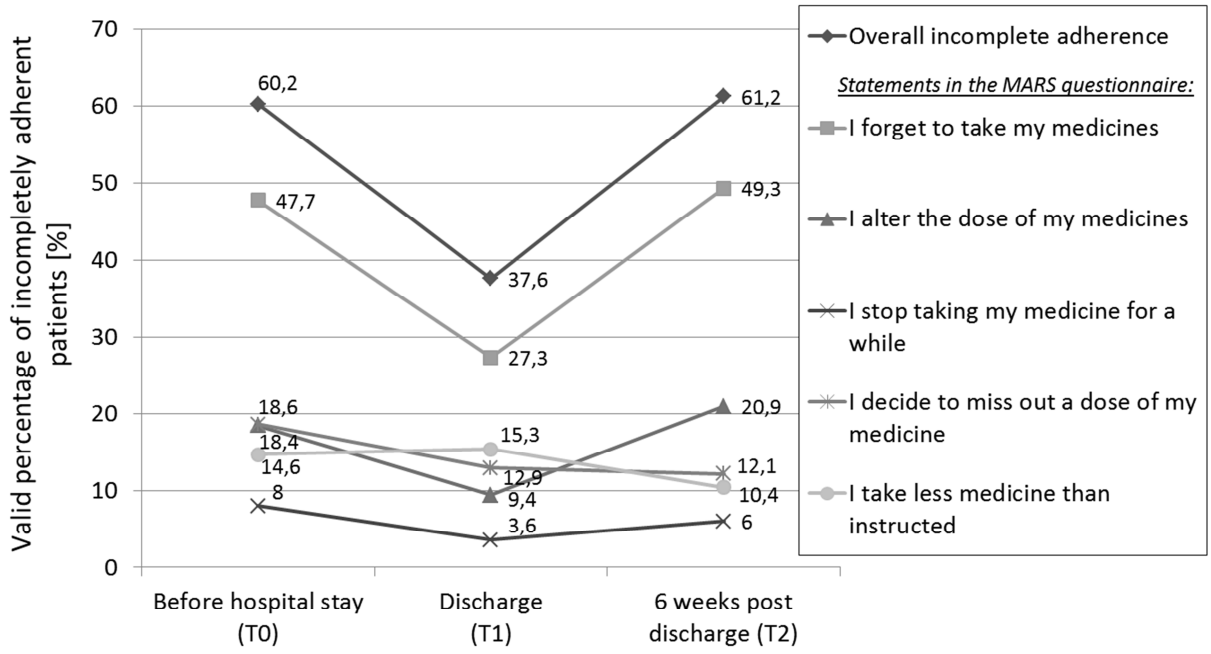

Figure 7 Adherence rates at T0, T1 and T2

The first statement of the MARS-D ("I forget to take my medication") was the item with the highest incomplete adherence rate (47.7%, T0; 49.3%, T2) and the greatest deviation during hospitalization (T1), where this rate decreased significantly to 27.1%. Dosages were altered by fewer patients when they were in hospital than after they were discharged. The number of patients, who consciously decided "I stop taking my medicine for a while", "I decide to miss out a dose of my medicine" or "I take less medicine than instructed" remained at

roughly the same level at all three time points. There were no statistically significant differences in terms of adherence between patients of different age, gender or social status.

For the analysis of regimen complexity, 98 (T0), 85 (T1) and 71 (T2) medication regimens were included in the evaluation. Analysis of the latter time point (T2) was based either on the medication list returned by the GP (n=7) or by the patient (n=40) or both (n=24). Of the 24 doublets, 17 differed from each other. Missing regimens were due to incomplete files on the wards (n=10), absence of medication recommendations in discharge letters (n=20), transfer to wards not included in the study (n=3) or failure to return questionnaires including a medication list (n=37). The average regimen complexity at the three time points is shown in Figure 8.

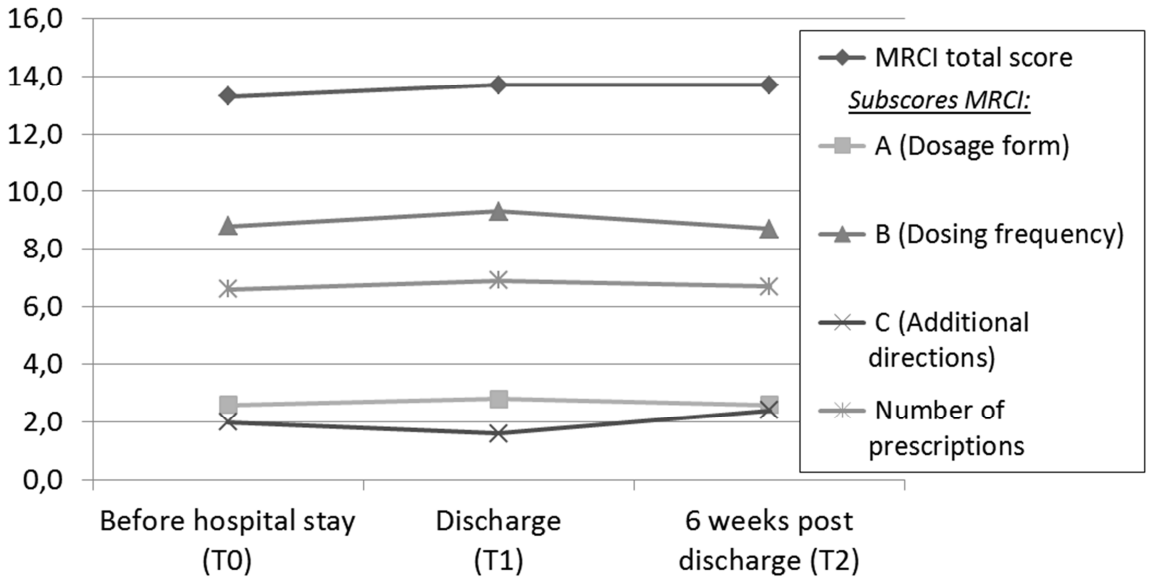

Figure 8 Medication Regimen Complexity at T0, T1 and T2

Complexity of hospital regimens differed little from ambulatory regimens before and after the hospital stay. The overall complexity score was 13.27 (SD 9.18) at T0, 13.72 (SD 8.31) at T1 and 13.73 (SD 9.70) at T2 (F=1.151; df=1; p=0.288). The complexity range was 2-40. The average number of prescriptions (including medications to be taken “as-needed”, excluding OTC (over the counter) medication) was 6.6 (SD 3.93) at T0, 6.9 (SD 3.74) at T1, and 6.7 (SD 3.86) at T2 (F=1.248; df=1; p=0.269), with a range from 1-18. The dosing frequency was slightly elevated in hospital, but this was balanced by fewer additional drug administration directions being given concomitantly (not significant).

As shown in Table 9 scores of the MRCI correlated directly with the diagnosis of Type 2 diabetes mellitus. With the incidence of diabetes the medication regimen gets more complex. A negative correlation is given for the incidence of a tumor.

Table 9 Multicollinearities (pairwise correlations) between analyzed patient characteristics

R	Sex	Age	Empl. Status	Edu.	MRCI	Hypert.	DM II	Hyperl.	Obesity	Tumor
Sex	1	-0.14	0.03	-0.14	0.17	0.003	0.04	0.43*	-0.02	-0.23*
Age	-0.14	1	0.53*	0.07	0.03	-0.02	-0.03	-0.07	-0.13	0.16
Empl. Status	0.03	0.53*	1	-0.08	0.21	-0.07	0.09	-0.01	-0.01	-0.03
Edu.	-0.14	0.07	-0.08	1	0.03	0.05	0.12	0.03	-0.05	-0.12
MRCI	0.17	0.03	0.21	0.03	1	-0.11	0.35*	0.19	-0.16	-0.40*
Hypert.	0.003	-0.02	-0.07	0.05	-0.11	1	0.01	0.18	0.05	0.05
DM II	0.04	-0.03	0.09	0.12	0.35*	0.01	1	0.26*	-0.18	-0.21*
Hyperl.	0.43*	-0.07	-0.01	0.03	0.19	0.18	0.26*	1	-0.06	-0.25*
Obesity	-0.02	-0.13	-0.003	-0.05	-0.16	0.05	-0.18	-0.06	1	0.10
Tumor	-0.23*	0.16	-0.03	-0.12	-0.40*	0.05	-0.21*	-0.25*	0.10	1

r = Pearson product-moment correlation coefficient; *Level of significance < 0.05; Empl. Status = Employment Status; Edu. = Education; MRCI =Medication Regimen Complexity Index; Hypert. = arterial Hypertension; DM II = Diabetes mellitus type 2; Hyperl. = Hyperlipidemia

When asked about their attitudes towards their medication (Figure 9), 68.6% of the patients indicated that they “always” preferred taking as few tablets as possible although most did not regard the number of medications as a burden on their quality of life. Nevertheless, 39.3% were willing to pay an additional charge for a reduction in the number of tablets to take. Of the patients, 5.7% were frequently afraid of forgetting to take their medications or of taking them incorrectly. More than half of the patients valued a distinguished appearance of the tablets to achieve correct administration, and 41.4% regarded varying appearances of the same medication as at least sometimes a potential cause for incorrect administration. Halving tablets was seen as a problem by 33.7% of patients.

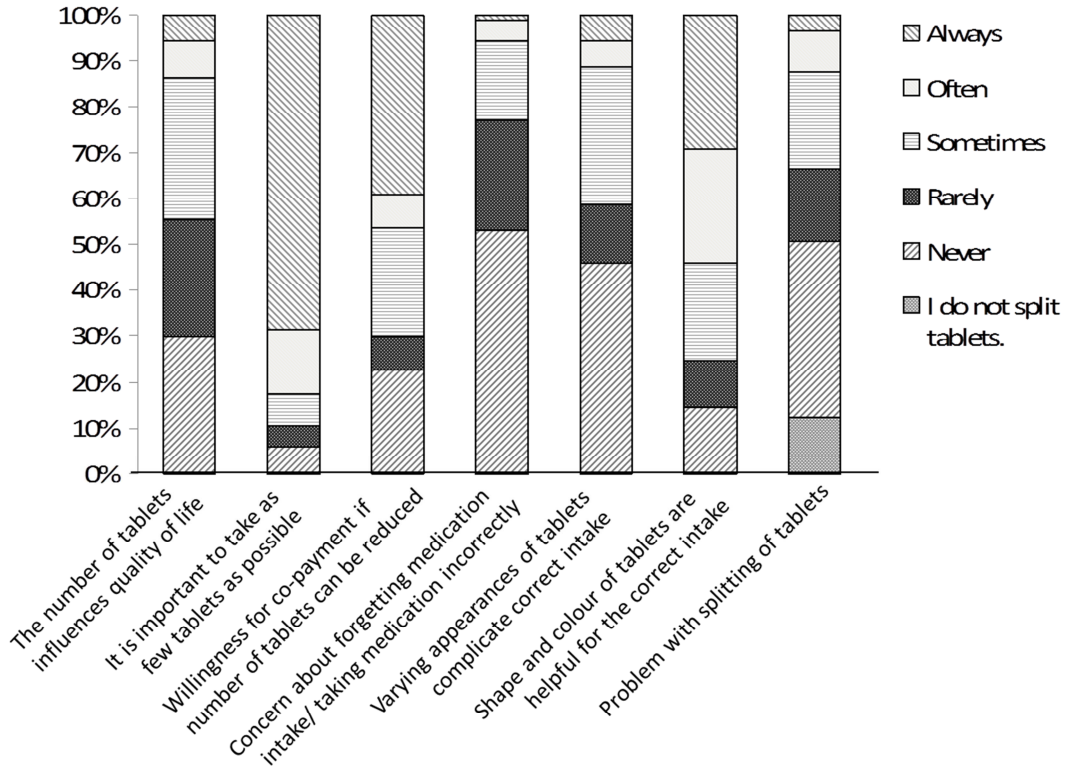

Figure 9 Patients' attitudes towards their medication

In terms of the provision of medication in the hospital, 68.6% of the patients stated that they were aware of the different drugs they received during their hospital stay, and 69.5% of patients stated that a change of these drugs compared to their home medication never or seldom had an influence on their medication intake.

The GPs' responses to the questionnaire about the discharge medication and medication therapy in general are depicted in Figure 10 and Figure 11. Of the 108 patients initially enrolled, 91 GPs were correctly identified and contacted by mail. The questionnaire was returned by 45 GPs, of whom 31 included the therapy plan of the respective patient. Comparing the GPs who answered with the ones who did not return the questionnaire in regards to the patient characteristics did not reveal any differences between the patients except for the age (p=0.009). In the group of GPs that returned the questionnaire the patients were younger (60.89 years (12.83)) than in the other group (65.76 years (14.63)).

Professional medical experience was mainly between 11-20 and 21-30 years (37.2 and 32.6%, respectively), followed by 31-40 years (16.3%) and 1-10 years (14%). Of the GPs who commented on the modifications introduced in hospital, two assessed these much better,

nine as better, seven as inferior and nineteen as equal compared to the treatment before the hospital stay. Nineteen GPs indicated to have modified the discharge medication, while another 19 stated to have continued with the recommended regimen from hospital. The main reasons for a change were unsuccessful therapy or no further defined, followed by patient's request or adverse events. Insufficient information from hospital was only pointed out by one GP. Prime cause for accepting of the discharge medication was a successful therapy and the satisfaction of the patients (Figure 10).

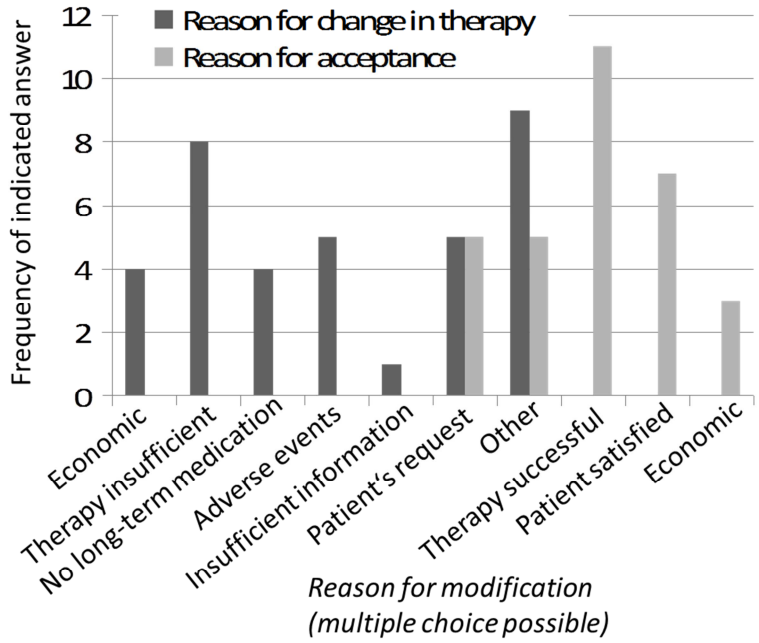

Figure 10 GPs' reasons for modification

Of the 45 GPs who returned the questionnaire, 76.8% indicated that they always or often accepted drug prescriptions from hospital, although many stated to be restricted by their quarterly budgets that limit drug expenses. Willingness to prescribe more expensive drugs if this would result in better therapeutic outcome was dichotomous: one-half expressed such willingness as "always" or "often", the other half only as "sometimes", "seldom" or "never". The conviction that medication regimens should be as simple as possible was expressed by more than 80% of the GPs, and nearly all were aware of the fact that halving tablets can be a problem for some patients.

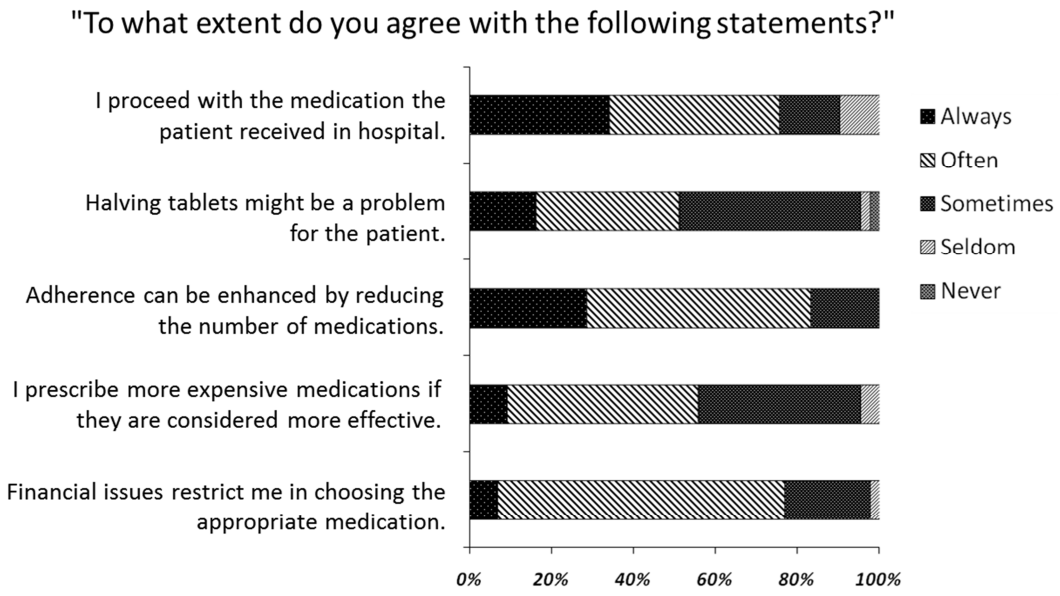

Figure 11 GPs' statements about medication therapy

4.4 Main objectives

Figure 12 shows the inclusion process for the entire study. During the routinely daily visits of the respective wards, the pharmacist screened 1439 admissions with regards to their medication profile and other inclusion criteria. For 930 of these patients no simplification of the medication therapy was recommendable, 26 patients were not able to communicate in German language and 90 patients were cognitively impaired. Another 24 patients refused to participate because of various reasons and 129 patients were repeatedly not available due to other medical appointments in hospital. In the end, a total of 240 patients were enrolled in the study, with 108 patients in the control group (C) and 132 patients in the intervention group (I). Three patients from the intervention group withdrew their consent. The group I was further randomized into two groups (I-, I+) with initially 64 and 65 patients, respectively.

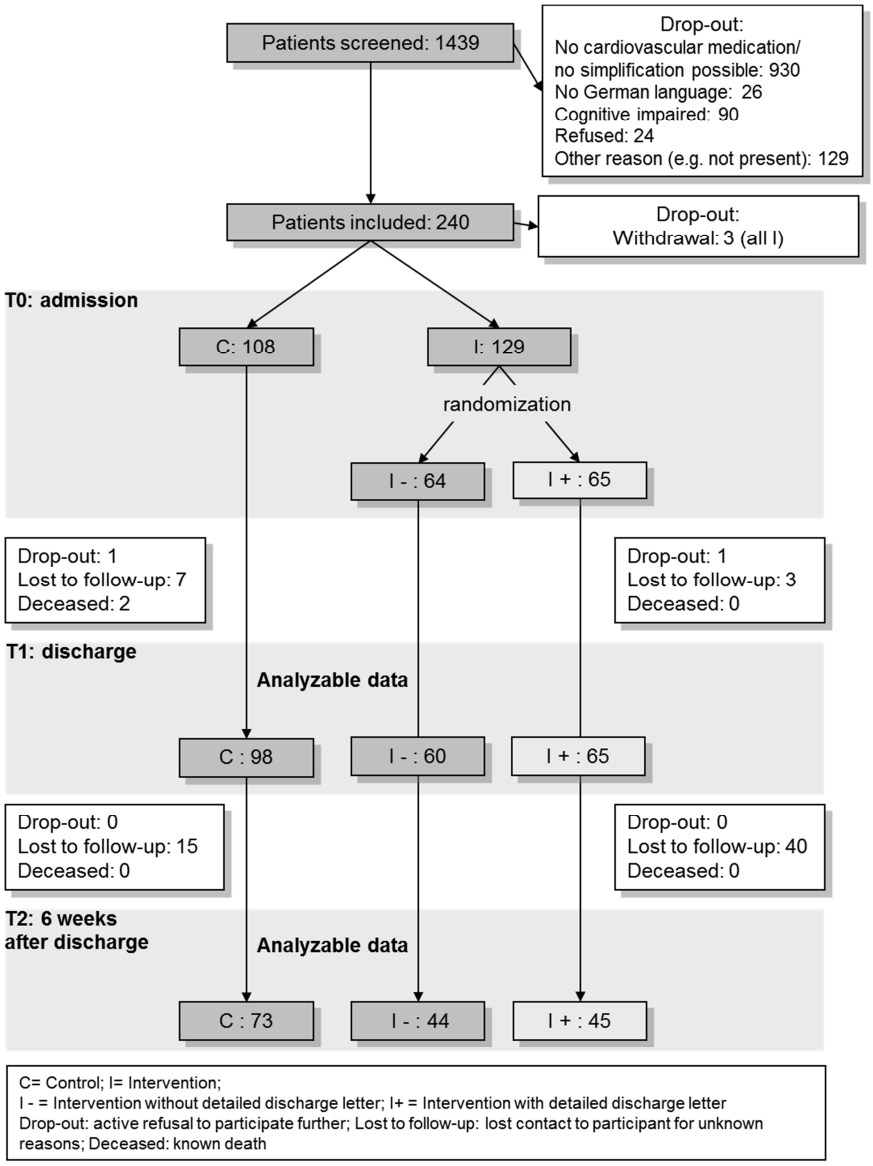

Figure 12 Inclusion process

Detailed baseline characteristics of the study population are summarized in Table 6 Table 8, pp. 43 and 47. Mean age was 63.8 years (SD 13.8; range 19-92) and 28.1% of the patients were female. At time of enrolment, the patients had a mean of 8.0 (SD 5.2) diagnoses of chronic diseases. Hypertension was the most common illness (88.2%), followed by diabetes mellitus (33.2%) and renal insufficiency (21.8%). At admission, the patients were taking a mean of 7 (SD 4.3) medications, with 4 (SD 2.2) study medications. Mean length of hospital stay was 7.3 days (SD 5.3). Significant differences between the control and the intervention group at baseline were e.g. in regards of sex, family status, education, diagnoses and the ward. Patients in the intervention group had more number of diagnoses, were less educated and comprised more widowed and female patients.

Table 10 Medication Complexity, Adherence, QoL and Satisfaction of C, I and total (T0)

	Control (C)	Intervention (I)	N analyzed	p	Total
Completely adherent (MARS)	35 (39.8%)	38 (36.9%)	191	0.398	73 (38.2%)
Medication complexity* (mean (SD))					
MRCI A*	1.0 (1.6)	1.0 (0.3)	218	0.662	1.0 (0.3)
MRCI B*	4.6 (2.8)	6.1 (3.7)	217	0.001	5.4 (3.4)
MRCI C*	1.1 (1.6)	1.2 (1.6)	217	0.838	1.2 (1.6)
MRCI Sum*	6.7 (4.0)	8.3 (5.0)	217	0.001	7.6 (4.6)
Number of medications*	3.6 (2.0)	4.3 (2.2)	218	0.662	4.0 (2.2)
Satisfaction (mean (SD))					
SIMS	10.1 (5.0)	10.2 (4.6)	179	0.881	10.1 (4.8)
SIMS Sub a	6.5 (2.5)	6.7 (2.5)	179	0.551	6.6 (2.5)
SIMS Sub b	3.7 (3.0)	3.5 (2.8)	179	0.732	3.6 (2.9)
Quality of Life (mean (SD))					
QoL somatic	39.6 (11.4)	38.3 (11.3)	176	0.470	38.9 (11.3)
QoL psychic	47.4 (11.0)	45.1 (10.3)	176	0.153	46.2 (10.6)

p=level of significance; MARS= Medication Adherence Report Scale; SIMS = Satisfaction with Information about Medicines Scale; SIMS Sub a: Subscale "Action and usage of medication"; SIMS Sub b = Subscale "Potential problems of medications"; Qol = Quality of life; MRCI = Medication Regimen Complexity Index, MRCI A = Subscale "Dosage form"; MRCI B = Subscale "Dosing frequency"; MRCI C = Subscale "Additional directions"; *only study medications included

Table 11 Medication Complexity, Adherence, QoL and Satisfaction of I- and I+ (T0)

	Intervention without detailed letter (I-)	Intervention with detailed letter (I+)	N analyzed	p
Completely adherent (MARS)	22 (42.3%)	16 (31.4%)	103	0.309
Medication complexity* (mean (SD))				
MRCI A*	1.0 (0.3)	1.0 (0.3)	119	0.734
MRCI B*	6.1 (3.5)	6.0 (4.0)	119	0.911
MRCI C*	1.2 (1.7)	1.1 (1.6)	119	0.816
MRCI Sum*	8.4 (4.8)	8.2 (5.2)	119	0.858
*Number of medications**	4.4 (2.0)	4.2 (2.4)	119	0.670
Satisfaction (mean (SD))				
SIMS	10.1 (4.8)	10.3 (4.5)	93	0.866
SIMS Sub a	6.7 (2.6)	6.7 (2.3)	92	0.877
SIMS Sub b	3.5 (2.9)	3.6 (2.7)	92	0.942
Quality of life (mean (SD))				
QoL somatic	38.1 (11.2)	38.7 (11.5)	92	0.794
QoL psychic	44.9 (10.8)	45.4 (9.7)	92	0.827

p=level of significance; MARS= Medication Adherence Report Scale; SIMS = Satisfaction with Information about Medicines Scale; SIMS Sub a: Subscale "Action and usage of medication"; SIMS Sub b = Subscale "Potential problems of medications"; Qol = Quality of life; MRCI = Medication Regimen Complexity Index, MRCI A = Subscale "Dosage form"; MRCI B = Subscale "Dosing frequency"; MRCI C= Subscale "Additional directions"; *only study medications included

4.4.1 Adherence

Values scored with the MARS questionnaire at admission to hospital (T0) are depicted in Table 10 and Table 11, at times of discharge (T1) and six weeks post-discharge (T2) in Table 12 Table 13. 38.2% of the patients indicated complete adherence to their pre-hospital medication. Propensity adjusted complete adherence rates at discharge (T1) were slightly higher in the intervention group (74.6%) than in the control group (62.4%). However, this difference did not reach statistical significance (odds ratio OR=1.77 [95% CI 0.81 to 3.85]; p=0.151). The value of the odds ratio was obtained by using the logistic regression. The difference in complete adherence rates was statistically not significant between the groups 6 weeks after discharge, either (OR=0.82 [0.27 to 2.52]; p=0.729).

With regard to the second research question, patients of the intervention group treated by GPs who received a detailed discharge letter from the hospital (I+) showed higher complete adherence rates 6 weeks after discharge (56.2%) than the control (I-) group (34.4%). Although this effect was comparably large (OR=2.45 [0.69 to 8.67]), it did not reach statistical significance (p=0.164) as variance was also large in the two groups.

Table 12 Outcomes of C, I and total (T1, T2)

T1: discharge	**Control (C)** est. proportions/ means (95% CI)	**Intervention (I total)** est. proportions/ means (95% CI)	**N**	**p**
Completely adherent (MARS)[a] in %	62.4 (52.1-72.7)	74.6 (66.1-83.1)	186	0.151
MRCI A*	not estimable (no variance in outcome)			
MRCI B*	5.59 (5.06-6.12)	3.97 (3.52-4.42)	199	<0.001
MRCI C*	0.94 (0.59-1.29)	0.43 (0.14-0.73)	199	0.031
MRCI* Sum	7.55 (6.82-8.28)	5.47 (4.84-6.09)	199	<0.001
Number of medications*	4.10 (3.75-4.45)	3.60 (3.30-3.90)	200	0.036

T2: 6 weeks after discharge	**Control (C)** est. proportions/ means (95% CI)	**Intervention (I-)** est. proportions/ means (95% CI)		
Completely adherent (MARS) [a] in %	38.8 (26.7-49.9)	34.4 (17.7-51.1)	98	0.729
SIMS	7.14 (5.49-8.80)	9.44 (7.00-11.88)	93	0.126
SIMS Sub a	4.52 (3.58-5.47)	5.95 (4.55-7.35)	84	0.097
SIMS Sub b	2.67 (1.78-3.56)	3.62 (2.30-4.93)	84	0.242
QoL somatic	39.36 (36.48-42.23)	40.04 (35.75-44.33)	83	0.793
QoL psychic	47.82 (44.39-51.25)	48.12 (42.98-53.23)	83	0.926
MRCI A*	1.02 (0.95-1.09)	1.00 (0.91-1.09)	109	0.740
MRCI B*	4.77 (4.13-5.41)	4.59 (3.84-5.33)	108	0.710
MRCI C*	1.45 (1.02-1.88)	1.05 (0.55-1.55)	108	0.235
MRCI* Sum	7.28 (6.38-8.17)	6.65 (5.61-7.69)	108	0.368
Number of medications*	3.60 (3.12-4.07)	3.85 (3.30-4.40)	107	0.495

estimates are propensity adjusted; N=number of patients; p=level of significance; est. means=estimated means (averages) adjusted for respective baseline score; est. proportions= estimated proportions for percentage; CI=Confidence Interval; MARS= Medication Adherence Report Scale; a = no estimated means calculable for stratified data; SIMS = Satisfaction with Information about Medicines Scale; SIMS Sub a: Subscale "Action and usage of medication"; SIMS Sub b=Subscale "Potential problems of medications"; QoL = Quality of life; MRCI = Medication Regimen Complexity Index; MRCI A= Subscale "Dosage form"; MRCI B= Subscale "Dosing frequency"; MRCI C= Subscale "Additional directions"; *only study medications included

Table 13 Outcomes of I- and I+ (T1, T2)

	RCT: Evaluation of detailed discharge letter			
T2: 6 weeks after discharge	**Intervention (I-)** est. proportions/ means (95% CI)	**Intervention (I+)** est. proportions/ means (95% CI)	**N**	**p**
Completely adherent (MARS) [a] in %	34.4 (17.7-51.1)	56.2 (38.1-74.3)	54	0.164
SIMS	9.34 (7.53-11.15)	7.92 (5.96-9.87)	52	0.290
SIMS Sub a	5.81 (4.79-6.83)	5.30 (4.20-6.41)	52	0.502
SIMS Sub b	3.51 (2.53-4.49)	2.69 (1.63-3.75)	52	0.259
QoL somatic	39.11 (36.20-42.03)	37.35 (34.06-40.64)	50	0.424
QoL psychic	48.01 (44.28-51.73)	47.82 (43.61-52.02)	50	0.946
MRCI A*	1.00 (0.97-1.03)	0.98 (0.94-1.01)	84	0.321
MRCI B*	5.53 (4.92-6.14)	4.30 (3.69-4.91)	84	0.006
MRCI C*	1.27 (0.87-1.67)	0.92 (0.53-1.32)	84	0.231
MRCI* Sum	7.81 (6.96-8.66)	6.19 (5.34-7.04)	84	0.009
Number of medications*	4.36 (3.89-4.84)	3.58 (3.10-4.06)	83	0.024

RCT=randomized controlled trial (estimates unadjusted); N=number of patients; p=level of significance; est. means=estimated means adjusted for respective baseline score; CI=Confidence Interval; MARS= Medication Adherence Report Scale; a = no estimated means calculable for stratified data; SIMS = Satisfaction with Information about Medicines Scale; SIMS Sub a: Subscale "Action and usage of medication"; SIMS Sub b=Subscale "Potential problems of medications"; QoL = Quality of life; MRCI = Medication Regimen Complexity Index; MRCI A= Subscale "Dosage form"; MRCI B= Subscale "Dosing frequency"; MRCI C= Subscale "Additional directions"; *only study medications included

4.4.2 Medication Regimen Complexity

Table 10 – Table 13 show the medication regimen complexities of the study medications for each group (T0, T1 and T2). At admission to hospital the overall complexity of the medication regimens as well as the dosing frequencies were significantly higher in the intervention group. At discharge, the MRCI score was significantly lower in the intervention than in the control group: 5.47 (4.84-6.09) vs. 7.55 (6.82-8.28); $p<0.05$ (Figure 13). At the same time, the number of medications was reduced from 4.10 (3.75-4.45 in C to 3.60 (3.30-3.90) in I (Figure 14).

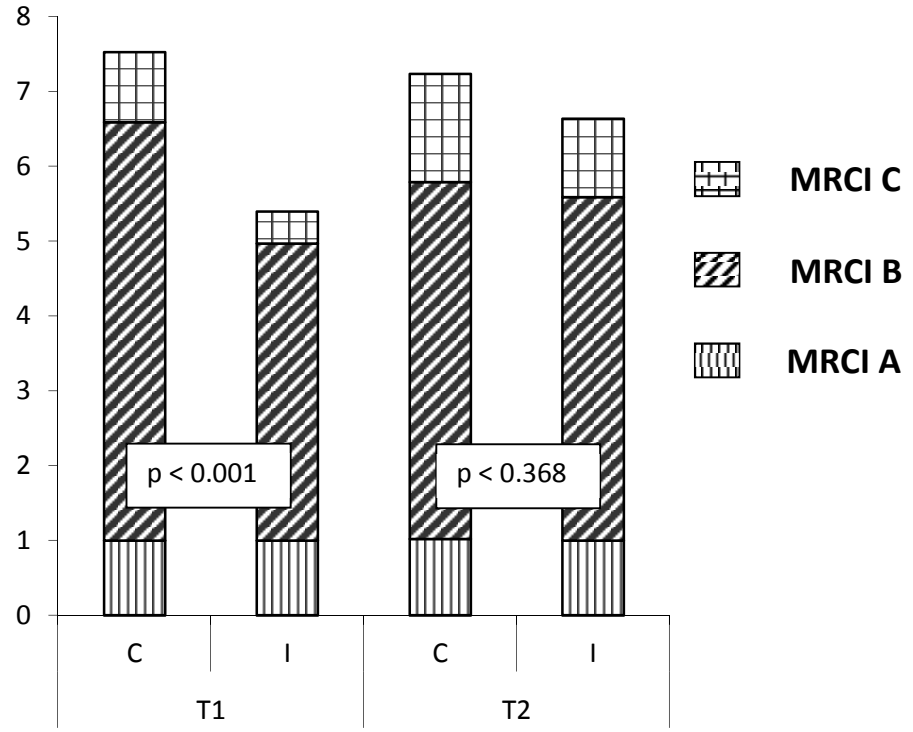

Figure 13 Medication Regimen Complexity, I vs. C

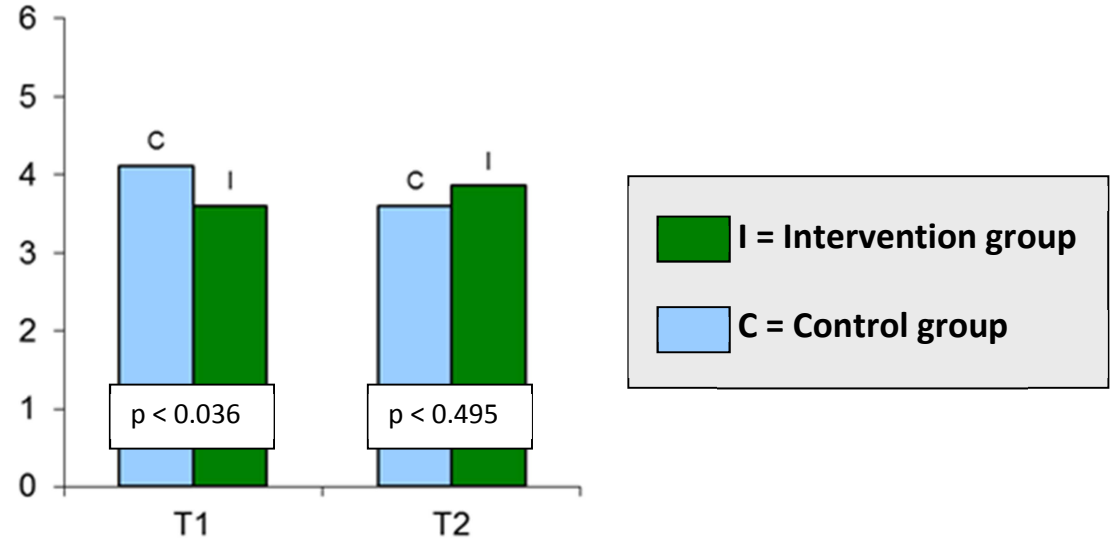

Figure 14 Number of medications, I vs. C

Comparing the complexity six weeks after discharge, patients in I still tended to have less complex medication regimens than patients in C: 6.65 (5.61-7-69) vs. 7.28 (6.38-8.17). However this difference was not statistically significant (p = 0.368). The number of

medications was slightly higher in the intervention group, though without statistical significance (p=0.495).

Evaluating the effect of additional information for the GP in the discharge letter of patients in I+, the complexity at T2 was significantly lower for I+ (6.19 (5.34-7.04)) than for I- (7.81 (6.96-8.66); p<0.05, Figure 15). Especially the score of subscale B, which is the dosing frequency, was reduced from 5.53 (4.92-6.14) to 4.30 (3.69-4.91); p< 0.05, as was the total number of medications in I+ (3.58 vs. 4.36 in I-; p< 0.05, Figure 16).

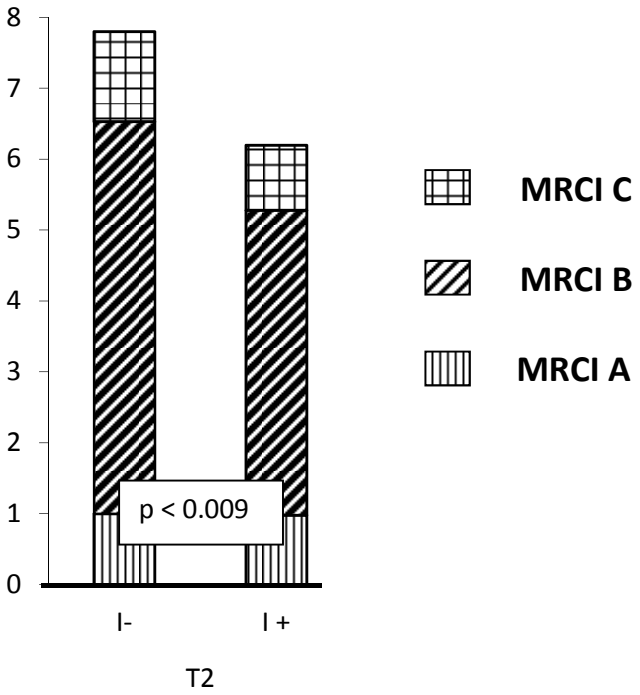

Figure 15 Medication Regimen Complexity at T2, I+ vs I-

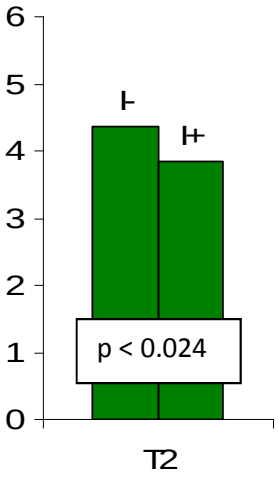

Figure 16 Number of medications, I+ vs I-

4.4.3 Quality of Life

Table 10 – Table 13 show the quality of life throughout the study. At baseline, the somatic QoL had an average score of 38.9 (11.3), the psychic QoL a score of 46.2 (10.6). Similar were the values for I- and I+ at baseline, with no significant difference in between the two randomised groups ($p>0.05$). At T2 the differences between the groups C and I did not reach statistical significance ($p>0.05$). The somatic QoL in the control group was 39.36 (36.48-42.23) and 40.04 (35.75-44.33) in the intervention group. The psychic QoL was 47.82 (44.39-51.25) and 48.12 (42.98-53.23), respectively. Differences between I- and I+ were not significant ($p>0.05$), either. Compared to T0 the values for both scales were slightly higher at T2. Also the somatic QoL was higher than the psychic QoL in all groups for all time-points.

4.4.4 Satisfaction with Information

The satisfaction with information about medicines at T2 is shown in Tables
Table 12 and Table 13. In the intervention group satisfaction was slightly higher with 9.44 (7.00-11.88) vs. 7.14 (5.49-8.80), but without reaching significance ($p=0.126$). Sub score a (SIMS Sub a = information about action and usage of medication) showed a statistical tendency to be higher in the intervention group ($p<0.10$). No differences were found between groups I- and I+. Compared to the average baseline value (10.1 (4.89)), satisfaction was slightly lower at T2. At all points of time the satisfaction with information about action and usage of the medications (SIMS Sub a) was greater than the satisfaction with the information about potential problems (SIMS Sub b). At baseline the average scores were 6.6 (2.5) and 3.6 (2.9), respectively.

4.4.5 Further analyses

- **Drop-out-analysis: All patients having at least one evaluable outcome at T2 vs. all patients not having evaluable outcomes at T2**

  Differences regarding following variables:

  - Ward
  - Tumor
  - Number of diagnoses
  - MRCI A (tendency)

- MRCI B
- Number of medications
- QoL physical

Analyzing the patients lost to follow up revealed that they were more frequently from the nephrology ward than patients form the urology ward. Also patients without tumor, but with more diagnoses in total were more likely to have no evaluable outcomes at T2. Concerning their medication therapy patients with a higher number of medications, a higher dosing frequency (MRCI B) and with more complex dosage forms (MRCI A, tendency) were more likely to drop out. Also, a low physical QoL had a negative impact on study continuity.

No differences regarding following variables:

- Phase
- Additional information
- Sex
- Family status
- Highest education completed
- Hypertension
- Diabetes
- Hyperlipidemia
- Adipositas
- Renal insufficiency
- MARS
- MRCI total
- MRCI C
- SIMS total, subscale a and b
- QoL psychic sum scale

- **Baseline differences between control and intervention group after stratification:**

After stratification most of the differences between the control and intervention group were equalized. Differences remained regarding following variables:

- Family status in Strata 3 & 4
- Ward in Strata 2 (Tendency) und Strata 3
- Age (Tendency)

No differences regarding following variables:

- Sex
- Highest education completed
- Hypertension
- Diabetes
- Hyperlipidämie
- Adipositas
- Renal insufficiency
- Tumor
- MARS
- Number of diagnoses
- Length of stay
- Number of medications
- MRCI total, A, B, C
- SIMS total, sub scale a and b
- QoL physical and psychic sum scale

5 Discussion

5.1 Evaluation of the MRCI-D

The MRCI-D quantifies the complexity of medication regimens as an open index since neither the number of medications to be taken nor the instructions given by the prescriber are limited. Thus every additional written instruction from the physician augments the score.

The MRCI-D showed a good correlation between the number of medications to be taken and the complexity. It was able to discriminate between regimens with the same number of medications but different complexity as it has also been shown for the English version [114]. The authors of the translated version agreed with the authors of the original version on the importance of raters defining scoring rules in order to achieve a uniform interpretation of the classifications and to obtain consistent results. However, the smaller the need for individual scoring rules in different studies, the better their comparability. Some of the problems in the interpretation and classification of items within a medication plan via the MRCI were already discussed by other research groups, i.e. the definition of “use at specific times” and the use of insulin, considered as multiple units at the same time [113]. Therefore, it was decided to incorporate minor modifications in the German version: point 9 in the instructions and the word “effervescent tablets” as a dosage form were added and examples for “take at specific times” that were considered as more appropriate in German “prescriber language” were included.

The accuracy of the calculated score is dependent on the quality of the source of the medication regimen that underlies the scoring. It is highly desirable for routine clinical use to have a medication data registry as complete and standardized as possible. As stated in the instructions on the first page, the medication regimen complexity index is to be calculated exclusively on the basis of information given on the label or the drug chart. In other words, collection of additional information (e.g. about specific administration instructions) is not permissible. The rater might be tempted to do this when scoring an obviously incomplete medication plan. However, if the patient does not know about the special instructions, these

do not contribute to his perception of medication regimen complexity and do not influence adherence. Therefore, it is justifiable to exclude such additional information when estimating complexity with the intention of correlating it with patients' attitudes or behaviour. For a better comparability of results with the MRCI this instruction should also be considered for the use in other settings.

The MRCI-D is not confined to a specific indication and can be used for medicines other than cardiovascular ones. However, further testing apart from the present setting will be necessary. In South Africa, the MRCI has been used to retrospectively analyse the complexities of 200 patient scripts from the outpatient dispensary of a public hospital in KwaZulu-Natal. The correlation between medication complexity and the parameters of age, gender, underlying disorder and the number of medications were determined. The results showed that in this undefined, randomly assigned population, age and number of medications were significant parameters impacting medication complexity – the latter aspect is supported by our results [115].

Besides the potential to study the relation of patient adherence and the medication complexity, the index may be used in clinical practice to identify patients where a high complexity may compromise adherence and, in consequence, therapeutic outcome. The predicted effect of changing the MRCI score on the number of hospitalizations experienced by home patients has already been investigated by the Visiting Nursing Center in New York: modest reduction in medication complexity (-10%) has the potential to lower the number of hospitalizations (-2%) experienced by that population [114]. However, further screenings and interventions to reduce the regimen complexities need to be put into practice and analysed. Patients who have difficulties taking the medication correctly and who have very complex therapy regimen may be identified directly at hospital discharge in order to provide ambulatory support, e.g. by a nursing service in the community. Research with regard to the definition of a cut-off point between tolerable and unacceptable complexity for a specific group of patients, e.g. the elderly, is desirable.

5.2 The interfaces between hospital and ambulatory care

The analyses of the control group focused on the complexity as well as the adherence to medication regimens in a wide range of patients with chronic diseases in outpatient care *before* admission to hospital care, during hospitalisation and in outpatient care six weeks *after* hospitalization. It was shown that overall medication complexity did not change significantly over this period of time. The definition of complexity included more facets of medication complexity than most other studies, which focused on only one detail of complexity (for example the number of medications to take or the number of daily doses), using the MRCI-D as a tool [116, 117].

The complexity score of approximately 13 in this analysis was of low level. It is representative of a population of mainly hypertensive patients with little comorbidity. Compared to a sample of mainly diabetic patients [46], the average complexity was slightly higher in that cohort, with a score of 15. This may be due to the fact that the addition of insulin to a medication regimen is associated with a distinct increase in complexity. A similar trend was seen in a study of patients with end-stage renal disease and the need for dialysis; the MRCI score was 22 - 28, depending on the dialysis procedure and the medications taken [118]. The rise of complexity with an increasing number of medications in the regimen has been verified by Oosthuizen et al.: In patients receiving between 1 and 5 different types of medication, the complexity score was 13.89 ± 5.593, while in patients taking between 6 to 10 different types of medication concurrently, the complexity score was nearly doubled to 26.93 ± 6.061 ($p<0.0001$) [115]. The median number of medications at the time of admission to hospital (6.6 at T0) in the present study population is in agreement with earlier findings [119, 120].

It has been reported that during a hospital stay the number of medications increases [97]. Thus, one might have expected a rise of medication complexity as well. However, neither the complexity nor the number of medications in this investigation did significantly change at the three points of time. One reason for this may be the inclusion of long-term medications only. OTC products, which may complicate the therapy in the ambulatory sector, and temporary medications added to the therapeutic regimen in hospital, such as antibiotics or analgesics, were not considered. Hence, the complexity scores found in this analysis might underestimate the actual complexity.

At T0 the complexity calculations were performed on the basis of the pre-admission medication history as reported by the patients or documented in the medical files. In the past, this method has frequently been reported to yield incomplete and discrepant information in medication reconciliation studies [121], leading to further underestimation of complexity. Nevertheless, when assessing complexity with the aim of estimating its influence on adherence, it seems justified to rely on the medication details as perceived by the patient.

The percentage of incompletely adherent patients in outpatient care identified in this investigation (60.2%) was higher than reported in other studies [122, 123]. Though, it is still in line with the incomplete adherence values of 26-59% reported by Van Eijken et al. [124]. Yet, the percentage has to be regarded with caution. It depends strongly on the way of measuring adherence and its definition. Moreover, adherence certainly varies between populations with different clinical characteristics and individual patients. This has to be kept in mind when scaling the adherence of different individuals using average adherence scores and comparing the results with other patient groups. These findings are applicable to inpatients with one or more chronic conditions requiring antihypertensive medication. This is a clinically heterogeneous population in terms of diagnoses and demographic characteristics. But with regard to the received treatment and setting, it is a homogeneous group and is representative of everyday routine care.

The method of measuring adherence was by self-report even though the validity of self-reports has been criticised in the past [101, 104]. Nevertheless, compared to the direct measurement of adherence, it is an inexpensive and pragmatic tool for the use in clinical practice. Similar to other studies using self-report [125], patients tended to overestimate their adherence and had very high scores in the validation process of the MARS-D [28]. A further validation study of the MARS-D suggested a high cut-off value in order to ameliorate sensitivity and specificity of the questionnaire [106].

To avoid a skewed response distribution and to increase sensitivity in recognizing non-adherent patients, this recommendation was followed for the present study and a high cut-off of 25 was chosen. The high cut-off and the resulting increase in sensitivity also explain the high incomplete adherence rates (with a rate of 60.2%). In a sample of mainly chronic obstructive pulmonary disease patients, incomplete adherence defined with the same cut-off was even higher (63%). When interpreting the results it has to be kept in mind that even

the occasional failure to take the medication as advised is classified by this definition. Hence, the term “incomplete adherence” was chosen rather than absolute “non-adherence”. Nonetheless this surrogate parameter was used, knowing that it seems impossible to define the precise extent of adherence that is necessary to ensure a given therapeutic benefit.

Corresponding to the answers on the MARS-D, incomplete adherence was mainly due to forgetfulness concerning the medication intake. Adherence increased during hospital stay, where the supply of medications was more controlled, the intake supervised and the day scheduled with pre-determined meal times. Still, it did not reach 100% in hospital. This is in line with a recent investigation, where a non-adherence of 23.3% at any time during hospitalization was reported [126]. Being in hospital does not necessarily mean that the patients take all the medications they are supplied with. Reasons may be patient-related (e.g. no belief in medication, not feeling well) as well as circumstance-related (being absent in examinations). To ensure complete adherence in hospital, patients are sometimes requested to take their medication under supervision.

The number of patients concerned about the varying appearances of their drugs was far lower than expected. This might be due to a general ”nonchalance” towards treatment, as deduced from the fact that less than 10% are afraid of forgetting their medication or taking it incorrectly. Another explanation is the current healthcare regulation in Germany, which enable insurance companies to negotiate contracts with drug manufacturers on a quarterly basis. This leads to frequent switches in the brand of medications taken by the patients, who apparently become accustomed to the differently named and looking drugs. Latter aspect is specific to Germany and differs from other countries with different healthcare systems and medication supply processes. Nevertheless, the fact that the majority of patients valued the appearance of their medications as being helpful for correct drug use is not obligatorily population specific. The preference for simple drug therapies as mentioned by the patients in this study suggests that adherence may benefit from simplifications. 39.3% of the patients were even willed to pay an additional charge for a reduction of the total number of tablets to take. It demonstrates that co-payments for medications do not necessarily have a negative effect on adherence. This is also underlined by a meta-analysis about adherence to drugs in the prevention of cardiovascular diseases, showing that decreasing adherence was unrelated to patients’ payments for the medications [127]. The proportion of patients that never had to split tablets (12.4%) seemed to be very low in this

population. Presumably some patients misunderstood the answering and chose “never” as response even though “I do not have to split tablets” would have been correct.

According to the GPs’ statements, the most frequent reason for accepting or modifying the discharge medication from hospital was either a successful or an ineffective therapy. This was an expectable answer as the treatment of hypertension requires the continuous adjustment of therapy – according to the reached blood pressure reduction. The second most important reasons for GPs’ therapy decision were patients’ requests and satisfaction. This is also reasonable as inclusion into the decision-making process is known to improve adherence [128]. The influence of economic issues mentioned by the GPs as reason for modifications of the discharge medication (Figure 10, page 52) might again be specific to Germany. This has to be taken into account when comparing the results with other countries.

Still, the statements from the GPs have to be regarded with caution as the number of responses was low and the results may underlie a sampling bias: GPs who disagreed with hospital-induced modifications of medication therapy, may have been less likely to participate in the study and return the completed questionnaire. In addition to that, it is possible that both, GPs as well as patients, answered in a social desirable way in order to keep in with the doctors from hospital or the researcher. To minimize these bias, incorrect answers and social pressure on patients to “conform”, questionnaires were anonymous and no reminders were made if questionnaires were not returned spontaneously as previously recommended in another study [129].

Neither the MRCI nor the MARS have shown a strong correlation between gender and the total scores in the past [28, 34]. Also, the present statistical analyses did not reveal any influences of these aspects. Thus, the results are probably not biased due to the unbalanced gender distribution in the control group. In general, published data on associations between adherence and sociodemographic parameters are inconsistent [106]. In line with the present findings, Breuil et al. did not find a correlation [130]; neither did van de Steeg et al. [104]. Slightly higher adherence among older patients was noted in a population of chronically ill patients [28]. A more organized behavior with higher age might explain these findings [106]. Important to notice is the fact that patients living alone are probable to be less adherent – conceivably because a spouse or family member helping to manage the medication regimen is lacking [28].

5.3 Main objectives

Comparing the control and intervention group of the study, the results demonstrate that the complexity of medication regimens can be reduced by pharmaceutical counseling of the hospital doctors. While it has been shown before that medication therapies often get more complicated in hospital [97], this study gives insight to what extent therapies can be simplified in this setting. Very recently, investigations from Australia have been published, analyzing the theoretical potential for simplifications of medication regimens in a hospital setting or the feasibility and barriers of such an intervention [131, 132]. Reviewing 40 discharge medication regimens, 90 simplifications to long-term medications were proposed retrospectively, and 84 (93%) were rated by the clinical pharmacologist as feasible with the same or similar therapeutic outcomes as the complex regimens. These changes, if implemented, could have reduced medication regimen complexity at discharge by an average of 14% [131]. In the second intervention pharmacists reviewed medication regimen complexity for 173 inpatients and identified 149 potential changes to reduce regimen complexity for 79/173 (45.7%) reviewed patients. Ninety-four (63.1%) changes were successfully implemented. Still, no study has combined the quantitative assessment of the reduction of medication complexity in hospital (by using the validated Medication Regimen Complexity Index) with its follow-up in the ambulatory sector and the correlation to patient adherence yet.

In the present work it was possible to decrease the overall number of antihypertensive/anti-diabetic/lipid-lowering medications (study medications) and particularly the dosing frequency. This goes in line with Elliott et al., identifying the dosing frequency as simplification with the highest potential (48/ 173 reviewed regimen), followed by the number of dose units (43/173) and the dosing time (33/173) [132].

Nevertheless, reducing the complexity of the discharge medication in this study did not significantly influence the long-term adherence of the included patients. This may have various reasons and contradicts earlier findings that showed a correlation between medication complexity and adherence [47]. One explanation is the heterogeneous way of defining and assessing complexity and/or adherence: While the MRCI-D the MARS-D were used for the present work, Claxton et al. defined complexity simply as dosing frequency and adherence was estimated by electronic monitoring systems [47]. Another reason for such

discrepancies may be that some studies compared the adherence to a single versus a two pill regimen [39, 133]. However, in this setting the patients took a mean of 7.2 medications at time of admission, with 4.0 medications only for the treatment of their hypertension, diabetes and/or dyslipidaemia. The amount of additional medications prescribed in hospital and thereafter might have had a levelling effect on adherence.

Simplifications focused exclusively on the "study medications" and did not include the entire medication regimen of the patient nor the evaluation if medications were really necessary. However, studies have shown that especially elderly people often receive unnecessary drugs; Hajjar et al. found that forty-four percent of patients had at least one unnecessary drug [134, 135]. Including unnecessary drugs into the intervention could have increased the magnitude of simplifications.

Therapeutic adherence is multidimensional. Several factors contribute to it, including patient-, physician- and therapy-related factors [27]. Still, the importance and/or effect size of each component for adherence is unknown and variable. In this study only one therapy-related factor (complexity of therapeutic regimens) and one physician-related factor (counseling the prescribers in hospital) were regarded. However, as the analysis of the control group showed, incomplete adherence was mainly due to forgetfulness of the patients. Interventions that encompass more factors, especially patient-related factors that are relevant for adherence, may result in a stronger increase of patient adherence [8].

Reducing complexity means a modification in the medication regimen. A postulated increase in adherence due to the simpler regimen may be outweighed by a decrease in adherence due to the differently named and looking drugs of the new regimen. In line with this, some studies described that changes in drug regimens were significantly associated with non-adherence [136, 137]. On the other hand, Mansur et al. did not find a correlation between the overall adherence and regimen changes when investigating potential relationships one month after hospital discharge [93].

Discharge from hospital holds a rare chance to simplify complex medication regimens. However, according to the experience gained from this study, several factors limit its potential benefit:

- Financial reimbursement of hospital care in the DRG-(diagnosis-related groups) system in Germany minimises the length of stay. Hence, final dose titration and determination of the availability of suitable combination or extended-release drugs is frequently left to the GPs.
- Simplification of drug therapy has so far had a low priority in hospital. Controlling clinical parameters seems to be more in the focus of the majority of the medical staff.
- Medical staff rotates frequently, at least in large hospitals, requiring constant reminders from the clinical pharmacist (also in this study) to prescribe drugs providing simplification.
- Simplifications discussed and agreed with the ward staff are not always adopted in the discharge letter, owing to spontaneous discharges (at the weekend) by medical staff not knowing about the background of the suggested modifications or oblivion in a hectic clinic routine.
- Hospital staff may be apprehensive to offend GPs by modifying prescriptions originating from before admission. This might result in hesitant changes of the medication regimens.
- Hospital pharmacies usually tend to provide drugs with single active ingredients rather than combination drugs in order to minimize storage costs. The willingness-to-pay for extra costs arising from a “medication simplification policy” needs to be established.
- Due to formulary restrictions of the hospital pharmacy other simplifications might be impeded as well, for example by having stocked only one dosage strength or the lack of sustained release medications.
- Lack of acceptance by patients may occur when they are used to their medications for a long time and fear to get confused by changing their well-established routine of medication intake.
- GPs decide about long-term (dis-)continuation of discharge medications, and their decisions obey different economical regulations in Germany rather than treatment decisions from hospital staff.

These findings partly correspond with experiences gathered in a major metropolitan public hospital in Australia [132]. An additional aspect discussed in that work as the most common barrier to implement simplifications, was the lack of time of the pharmacist. This may be well explained by the “real-life”- setting of the study since pharmacists were asked to

minimize regimen complexity during routine medication regimen reviews. The significant amount of time needed is allegeable by the fact that changes first need to be discussed with the prescriber and the patient, followed by a required patient education about the changes that have been done. As working time of the pharmacist is needed for this relatively time-consuming intervention, costs for the hospital are generated. Patient education was omitted in the present work, but would have surely complemented the intervention.

The results of this study show that the reduction of complexity achieved in hospital was mostly reversed in subsequent ambulatory care. Combined with the factors mentioned above it might be suggested that simplifications are better conducted in the ambulatory setting than in hospital. Nevertheless, leaving aside that aspect, the results underline the necessity to involve GPs in treatment decisions if sustainability and continuity of care are desired. Previous analyses have shown GPs' partial dissatisfaction with discharge information from hospital, and the current study demonstrates that complexity of medication regimens remained significantly lower post-discharge if the GP received additional information in the discharge letter about the background of medication changes [89]. As mentioned before, economic issues play another role in the decision of GPs about continuing therapies from hospital or not (Figure 10) and may therefore explain reversed simplifications post-discharge as well. As some of the new combination drugs are more expensive than available generics, critics fear the use of combination strategies as a technique for "evergreening" an expiring patent to extend the life of a drug brand [53]. Podolsky et al summarise this query as following: "No one knows how the improvement in adherence resulting from a single expensive pill stacks up against the known adherence benefits of a more affordable regimen of generic medications. This type of comparative effectiveness data would be far more useful in separating hope from hype when it comes to the new combination drugs." [53] However, it was no objective of this study to further investigate economic issues of the costs for the respective medication therapy or incomplete adherence with all its clinical consequences. So further research will be needed for it is a highly complex issue with very diverging views.

In former studies correlations between medication complexity and health related quality of life have been discussed controversially. While Cardone et al. did not find a significant relationship between the medication regimen complexity and the SF-36 in the setting of nocturnal home dialysis patients [118], a higher pill burden was associated with lower

quality of life for patients with traditional in-center haemo-dialysis [138]. In the present work, quality of life was measured at times of admission to hospital and six weeks post-discharge. As medication complexity before admission and six weeks post-discharge were similar, it was impossible to judge a correlation between medication regimen complexity and quality of life. It is not surprising that this intervention failed to improve quality of life.

Similar are the results in terms of satisfaction with information about medicines. There was a tendency that patients in the intervention group were more likely to be satisfied with the information they received from their doctor, however, without reaching significance. A change in therapy and a reduction of regimen complexity might have contributed to a better understanding of the medication for the patient, which is underlined by the fact that especially the section “understanding and usage” was ameliorated.

Concerning the study design, some limitations need to be discussed. Not all of the patients were assigned to their group by randomization though this is the preferred design for a clinical trial. The advantage of randomization is that confounder are reduced by equalising factors (independent variables) that have not been accounted for in the experimental design. However, for the present work a semi-randomized study was designed in order to avoid a knowledge bias of the medical staff in hospital (see 3.1.5), with the control group chronologically antedated. This resulted in two not equally distributed groups (control and intervention) in terms of various sociodemographic characteristics. Statistical analysis comparing C and I were therefore conducted using the propensity score stratification, a well-established method that is often used in observational (non-randomized) studies – attempting to provide unbiased estimations of treatment-effects. The diverging proportion of urology and internal medicine patients in the two groups might explain the baseline differences. In the control group 52.1% of the patients were enrolled from the urology ward, in the intervention group only 30.2%. A possible explanation – and limitation of the study design – is the discontinuation of one urology ward as participating unit during phase 2 due to a hospital internal ward restructuring.

As another limitation, the calculated sample size of 300 patients was not fully reached in the designated study period. This was due to a slower inclusion process than expected, time limitations of the responsible pharmacist and disease-related closure of the internal medicine wards over a period of several weeks. However, the calculated minimum of 300 patients resulted from the second research question (evaluation of the effect of an

additional information for the GP) and the detection of moderate effect sizes between I+ and I-. As this was not the main objective, a smaller study population was tolerated.

Strength of the study design was the randomisation of the intervention group in phase 2 as it is the most adequate way of allocating patients to a respective group in order to obtain well-balanced cohorts and meets the requirements of clinical studies. Moreover, the performance of the intervention by only one pharmacist enabled a comparable transaction for all participants. Finally, the extensive data collection across the interfaces between ambulatory and hospital care together with a comparably high response rate at T2 of both, the patients and the GPs, allow comprehensive statements about the cross sectional patient care in Germany with regard to the medication therapy.

6 Conclusions

With the translation of the Medication Regimen Complexity Index (the MRCI-D), a new German tool to assess medication complexity is now available. Its adequate psychometric quality (reliability and validity) to measure and compare the complexity of drug therapies of patients has been shown. It can therefore serve as a useful tool in clinical practice and research concerning the influence of medication complexity on other aspects related to medicines like adherence – as in this study – or further treatment outcomes.

The complexity of medical regimens does not necessarily change at the outpatient-inpatient interface in German healthcare of patients with chronic conditions. The rather low outpatient adherence to medication is mostly attributable to forgetfulness and increases substantially in inpatient care, just to return to its original level after discharge. Obviously, external control of the medication process increases adherence.

By counseling the prescribers in hospital about the availability of combination and extended-release drugs and the once-daily dosing, the complexity of cardiovascular hospital medications can be reduced. However, the effect is largely reversed in the subsequent ambulatory care, reducing the potential of this intervention to ameliorate medication adherence in the long run, unless the GPs receive an explanation justifying the modifications. Moreover, this pharmaceutical intervention needs to be continuous rather than transient. Further research is needed to define potential clinical benefits of an intervention comprising more aspects that influence adherence than just complexity of therapeutic regimens.

Ideally, the medication complexity should be reduced, the patient sufficiently informed about the new medication, the GP (if started in hospital) well integrated into the modification process and patient adherence as well as therapy success (i.e. blood pressure) assessed.

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Zusammenfassung

„Medicine won't work if you don't take them"- zu diesem Schluss ist auch die WHO in ihrem 2003 herausgegebenen Bericht gekommen, der sich ausführlich mit dem Thema Nicht-Adhärenz auseinander setzt. Fast 50 % der chronisch Kranken nehmen ihre Medikamente nach einem Jahr deutlich seltener oder gar nicht mehr ein, obwohl dies für einen Therapieerfolg ausschlaggebend ist. Für das Gesundheitswesen bedeutet das unter anderem eine große ökonomische Last.

In der vorliegenden Arbeit wurde eine prospektive, kontrollierte Studie mit chronisch kranken Patienten, die Medikamente zur Behandlung von Bluthochdrucks, Diabetes oder Dyslipidämie einnehmen, durchgeführt. Untersucht wurde ob die Adhärenz indirekt durch eine Verringerung der Komplexität der Medikation gesteigert werden kann, indem (1) die Ärzte im Krankenhaus pharmazeutisch hinsichtlich Vereinfachungsmöglichkeiten beraten werden und (2) der Hausarzt zusätzlich eine Information über die veränderte Medikation im Entlassungsbrief erhält. Außerdem wurde analysiert ob dadurch die Lebensqualität der Patienten sowie ihre Zufriedenheit beeinflusst werden.

Vor Beginn der Studie wurde der englische Medication Regimen Complexity Index gemäß international anerkannten Richtlinien ins Deutsche übersetzt und evaluiert, um ein auch im deutschen Sprachgebrauch validiertes Instrument zur Erfassung der Komplexität zu haben.

In die Studie wurden insgesamt 240 Patienten eingeschlossen. Primärer Endpunkt war die Adhärenz (MARS-D), sekundäre Endpunkte stellten Komplexität der Medikation (MRCI-D), Lebensqualität (SF-12) sowie die Zufriedenheit mit der Information über die Medikamente (SIMS-D) dar. Die Adhärenz und Komplexität des Medikationsregimes wurden bei Aufnahme ins Krankenhaus (T0), bei Entlassung (T1) und 6 Wochen nach der Entlassung (T2) erfasst. In der Interventionsgruppe wurden die Ärzte im Krankenhaus hinsichtlich möglicher Vereinfachungen der kardiovaskulären Medikation beraten. In einer Subgruppe der Interventionsgruppe erhielt der weiterbehandelnde ambulante Arzt ein zusätzliches Informationsschreiben im Entlassungsbrief, das die Hintergründe der Veränderungen erklärte, mit der Bitte die Medikation wenn möglich so fortzuführen.

Die Komplexität der Medikationsregime konnte bei T1 signifikant in der Interventionsgruppe gesenkt werden. Dieser Effekt war bei T2 zum Teil aufgehoben, so dass die Unterschiede statistisch nicht mehr signifikant waren. Propensity adjustierte vollständige Adhärenz bei T1 und T2 nach der Entlassung war in der Interventionsgruppe geringfügig höher, allerdings ohne statistische Signifikanz zu erreichen.

Die Komplexität bei T2 war signifikant niedriger wenn der ambulant weiterbehandelnde Arzt zusätzliche Informationen im Entlassungsbrief erhielt. Besonders die Einnahmehäufigkeit und die Gesamtanzahl an Medikamenten waren reduziert. Der Anteil vollständig adhärenter Patienten war nicht-signifikant höher in dieser Subgruppe.

Die Studie zeigt, dass die Komplexität kardiovaskulärer Medikation im Krankenhaus durch die pharmazeutische Beratung der Ärzte im Krankenhaus reduziert werden kann. Allerdings wird der Effekt zum großen Teil wieder im ambulanten Sektor nivelliert, wenn die niedergelassenen Ärzte nicht ausreichend über die Änderungen im Krankenhaus werden. Patientenadhärenz wurde von der Intervention nicht signifikant verbessert. Da Adhärenz von unterschiedlichsten Faktoren abhängt, ist vermutlich eine Intervention, die multifaktorielle Strategien zur Adhärenzverbesserung kombiniert, nötig, um einen signifikanten klinischen Nutzen zu erzielen.

Appendices

Appendix A Patient Information

Universitätsklinikum Hamburg-Eppendorf

Zentrale Dienste

Apotheke
Dorit Stange

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o Ansprechpartner
Frau Stange

„Vereinfachung komplexer Therapieregime zur Verbesserung der Adhärenz von Patienten“

- PATIENTENINFORMATION -

Liebe Patientin, lieber Patient,

Sie wurden gefragt, ob Sie an dieser wissenschaftlichen Studie teilnehmen möchten. Bitte lesen Sie hierzu die Aufklärung sorgfältig und vollständig durch, und überdenken Sie Ihre Entscheidung ausreichend, bevor Sie sich für eine Teilnahme entscheiden. Sie können sich vollkommen frei entscheiden, ob Sie an der Studie teilnehmen möchten oder nicht, und Sie können Ihre Teilnahme jederzeit beenden. Wenn Sie sich gegen eine Teilnahme entscheiden, hat dies keinerlei Einfluss auf Ihre weitere medizinische Versorgung. Sie wollen vielleicht auch erst mit einem Familienangehörigen/ Freund sprechen, bevor Sie sich zu einer Teilnahme entschließen. Bitten Sie Ihren Studienansprechpartner, Ihnen alles, was Sie nicht verstehen, zu erklären. Die zuständige Ethikkommission hat die Durchführung dieser wissenschaftlichen Studie positiv bewertet.

1. ZIELSETZUNG/ ZWECK DER STUDIE

Durch den Studienleiter oder die verantwortliche Apothekerin Dorit Stange werden Sie im Folgenden unterrichtet:

In dieser Studie soll untersucht werden, inwieweit sich komplexe Therapiepläne im Krankenhaus infolge pharmazeutischer Beratung der Stationsärzte im Klinikalltag vereinfachen lassen, ob die Therapien an den Schnittstellen ambulant-stationär-ambulant fortgeführt werden und ob die Adhärenz der Patienten dadurch gefördert werden kann. Unter Adhärenz (aus dem Englischen von *Festhalten, Befolgen* abgeleitet) versteht man in der Medizin die Einhaltung der gemeinsam von Patient und Arzt gesetzten Therapieziele, wie zum Beispiel die regelmäßige Tabletteneinnahme.

2. STUDIENABLAUF

Sind Sie für eine Studienteilnahme geeignet?
Eingeschlossen werden Patienten des Universitätsklinikums Eppendorf, die über 18 Jahre sind und Medikamente zur Behandlung von Herz- und Stoffwechselerkrankungen bekommen. Ausschlusskriterien sind unzureichende Kenntnisse der deutschen Sprache, sowie erheblich kognitive Einschränkung des Patienten.

Studientyp
Es handelt sich um eine wissenschaftliche Studie, bei der die ersten 200 eingeschlossenen Patienten automatisch der „Kontrollgruppe“ (I) angehören; die Zuteilung zur jeweiligen „Interventionsgruppe“ (IIa, IIb) erfolgt randomisiert, also per Zufall. Bei der Kontrollgruppe werden lediglich Daten erfasst, wohingegen bei der Interventionsgruppe der Arzt durch einen Apotheker dahingehend beraten wird, ein möglichst einfaches Therapieregime bei der Medikamentenwahl zu berücksichtigen. Die niedergelassenen Ärzte der Interventionsgruppe IIb erhalten zusätzlich zum gewöhnlichen Entlassungsbrief ein Informationsschreiben, das ihn über die Hintergründe der Studie aufklärt und um eine Weiterführung der Verordnungen bittet, soweit aus therapeutischer Sicht keine weiteren Veränderungen nötig sind.

Ablauf der Studie
Bei Ihrem ersten Besuch wird Ihnen ein Verantwortlicher die Studie erklären, und Ihnen werden diese Patienteninformation und Einwilligungserklärung, ausgehändigt. Nachdem Sie alle offenen Fragen zu Ihrer Zufriedenheit geklärt haben und falls Sie sich zur Teilnahme an der Studie entschlossen haben werden Sie gebeten, die Einwilligungserklärung mit Datum zu unterzeichnen. Hiermit bestätigen Sie Ihre Teilnahme an dieser Studie. Eine vom Aufklärenden unterschriebene Kopie der Einwilligungserklärung erhalten Sie für Ihre Unterlagen.

An der Studie nehmen insgesamt 400 männliche oder weibliche Patienten freiwillig teil, die im Universitätsklinikum Eppendorf behandelt werden.

Dauer der Studie
Die Dauer der Studie umfasst insgesamt ca. 12 Monate, wobei für Sie persönlich lediglich ein geringer Zeitaufwand besteht: Wir bitten Sie zu Beginn und am Ende Ihres Krankenhausaufenthalts zusammen mit dem Apotheker einen Fragebogen auszufüllen. Im Verlauf der Studie wird Ihnen ca. 2 Monate nach Ihrer Entlassung ein weiterer Fragebogen zugeschickt, mit der Bitte ihn ausgefüllt in einem vorfrankierten Umschlag wieder zurück zu senden.

Diese Studie ist von einer unabhängigen Ethikkommission hinsichtlich ihrer medizinischen, rechtlichen und ethischen Vertretbarkeit beraten und zustimmend bewertet worden. Die Verantwortung für die Durchführung verbleibt jedoch beim Studienleiter.

Nebenwirkungen
Es werden keine Nebenwirkungen erwartet, da es sich um eine Beobachtungsstudie handelt.

3. FREIWILLIGKEIT/ STUDIENABBRUCH

Ihre Teilnahme an dieser Studie ist freiwillig. Auch der Auftraggeber kann die Entscheidung treffen, die gesamte wissenschaftliche Prüfung abzubrechen oder lediglich Ihre Teilnahme vorzeitig zu beenden.

Sie haben das Recht, jederzeit Fragen zu stellen. Nutzen Sie dies bitte ausführlich (auch während der Studie) bis Sie sich völlig ausreichend informiert fühlen.

Sie haben das Recht, jederzeit und ohne Angabe von Gründen Ihre Teilnahme an der Studie zu beenden. Außerdem kann Sie der Prüfarzt jederzeit aus der Studie herausnehmen, wenn er den Eindruck hat, dass dies im Interesse Ihrer Sicherheit ist.

4. DATENSCHUTZ

Aufklärung zum Datenschutz

Die im Rahmen der Studie nach Einverständniserklärung erhobenen persönlichen Daten insbesondere Befunde unterliegen der Schweigepflicht und den datenschutz-gesetzlichen Bestimmungen. Sie werden in Papierform und auf Datenträger in der Apotheke des Universitätsklinikums Hamburg-Eppendorf aufgezeichnet bzw. pseudonymisiert (verschlüsselt) [1] gespeichert.

Die Nutzung der Daten erfolgt in pseudonymisierter Form.

Eine Weitergabe der erhobenen Daten im Rahmen des Forschungszwecks erfolgt nur in pseudonymisierter Form. Gleiches gilt für die Veröffentlichung der Studienergebnisse.

Sie haben das Recht, über die von Ihnen gesammelten personenbezogenen Daten Auskunft zu verlangen, und über möglicherweise anfallende personenbezogene Ergebnisse der Studie gegebenenfalls informiert oder nicht informiert zu werden. Gegebenfalls wird der Leiter der Studie Ihre Entscheidung darüber einholen.

Die Aufzeichnung bzw. Speicherung erfolgt für die Dauer von 3 Jahren.

Im Falle des Widerrufs des Einverständnisses werden die bereits erhobenen Daten entweder gelöscht oder anonymisiert[2] und in dieser Form weiter genutzt.

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[1] Pseudonymisieren ist das Ersetzen des Namens und anderer Identifikationsmerkmale durch ein Kennzeichen zu dem Zweck, die Bestimmung des Betroffenen auszuschließen oder wesentlich zu erschweren (§3 Abs. 6a BDSG).

[2] Anonymisieren ist das Verändern personenbezogener Daten derart, dass die Einzelangaben über persönliche oder sachliche Verhältnisse nicht mehr oder nur mit einem unverhältnismäßig großen Aufwand an Zeit, Kosten und Arbeitskraft einer bestimmten oder bestimmbaren natürlichen Person zugeordnet werden können (§3 Abs. 6a BDSG).

5. SONSTIGE HINWEISE

Um die Studie so aussagekräftig wie möglich zu machen, müssen wir dafür sorgen, dass für alle Teilnehmer ähnliche Bedingungen herrschen. Aus diesem Grund möchten wir Sie bitten, die folgenden Einschränkungen zu akzeptieren:

- Es ist unbedingt erforderlich, dass Sie die Studienärzte vor Beginn der Studie über bisherige Erkrankungen und von Ihnen eingenommene Medikamente informieren. Geben Sie auch an, ob und wogegen Sie allergisch oder besonders empfindlich sind.
- Wenn Sie während der Studie irgendwelche Veränderungen Ihres Wohlbefindens bemerken - auch solche, die Sie nicht auf die Medikamenteneinnahme zurückführen - melden Sie dies bitte umgehend Ihrem Prüfarzt.
- Während der gesamten Studie ist jederzeit ein Verantwortlicher für Sie erreichbar. Die entsprechenden Informationen mit den Telefonnummern finden Sie am Ende dieser Aufklärungsschrift und auf dem Seitenkopf.
- Zur Gewährleistung Ihrer Sicherheit ist es wichtig, dass Sie sämtliche der Ihnen gegebenen Anweisungen einhalten, wahrheitsgemäße Antworten auf alle an Sie gestellte Fragen geben und eine Pflegekraft oder den Arzt über jegliche Änderungen Ihres Gesundheitszustands informieren.

6. ANFALLENDE KOSTEN

Dem Studienteilnehmer entstehen keine Unkosten, falls er aus der Studie ausscheidet oder ausgeschlossen wird, und alle Untersuchungen oder Maßnahmen, die Teil dieser Studie sind, werden für Sie kostenlos durchgeführt.

7. ALLGEMEINES

Kontaktperson

Wenn Sie noch weitere Fragen im Zusammenhang mit der Studie haben wenden Sie sich bitte an:

Frau Dorit Stange
Apotheke im UKE
Martinistr.52

20246 Hamburg

Tel.Nr.: 040/ 74105- 8517
- 2086
Fax: 040/ 74105- 4593
e-mail: d.stange@uke.de

Wir bitten Sie, die Prüfbedingungen zu befolgen, da nur bei einer korrekt durchgeführten wissenschaftlichen Studie verwertbare, aussagekräftige Ergebnisse zu erzielen sind.

Wir danken für Ihre Bereitschaft an dieser Untersuchung teilzunehmen!

Appendix B Written consent

Universitätsklinikum Hamburg-Eppendorf

Zentrale Dienste

Apotheke
Dorit Stange

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o Ansprechpartner
Frau Stange

Einwilligungserklärung

Studiennummer: 2009 DS 01

Vom Zentrumspersonal auszufüllen!

Name: _____

Nummer: _____

Leiter der wissenschaftlichen Studie:

Herr Dr. Michael Baehr,
Apotheke im UKE,
Martinistr.52, 20246 Hamburg

Ethikvotum: 03.12.2009

Schriftliche Einwilligungserklärung des Patienten zur Teilnahme an der Studie

„Vereinfachung komplexer Therapieregime zur Verbesserung der Adhärenz von Patienten“

Durch den verantwortlichen Leiter oder einer seiner Stellvertreter bin ich über Wesen, Bedeutung und Tragweite dieser wissenschaftlichen Studie sowie über meine Rechte und Pflichten als Studienteilnehmer mündlich und schriftlich aufgeklärt worden. Ich hatte ausreichend Zeit Fragen zu stellen bevor ich meine Entscheidung zur Teilnahme an dieser Studie getroffen habe.

Mir ist bewusst, dass ich durch die Teilnahme an dieser Studie keine direkten medizinischen Vorteile haben werde. Meine Teilnahme ist freiwillig. Ich kann jederzeit ohne Angabe von Gründen und ohne Nachteile aus der Prüfung ausscheiden.

Es ist mir klar, dass es außerordentlich wichtig ist, alle Anweisungen, die mir vom Studienpersonal gegeben werden, genauestens zu befolgen.

Ich bestätige, dass meine Angaben zur Anamnese (Krankengeschichte) vollständig und richtig sind. Ferner bestätige ich, dass ich in den letzten 30 Tagen an keiner klinischen Studie teilgenommen habe und bis zum Ende dieser Studie an keiner anderen Studie

teilnehmen werde. Ich versichere, dass mir keine Überempfindlichkeit gegen Medikamente oder sonstige Stoffe bekannt sind und über Medikamente, die ich in den letzten 3 Monaten regelmäßig eingenommen habe, vollständig berichtet habe.

Falls sich bei klinischen Untersuchungen herausstellt, dass ich falsche Angaben zu den oben erwähnten Punkten und zu meiner Krankengeschichte gemacht habe bzw. wichtige Informationen verschwiegen habe, ist mir bewusst, dass ich sofort von der Studie ausgeschlossen werde.

Mir ist bewusst, dass der Bundes- und Landesdatenschutz in vollem Umfang beachtet wird. Ich bin über die Verwendung meiner personenbezogenen Daten aufgeklärt worden und habe hierzu eine Datenschutzerklärung unterschrieben.

Im Falle von Veröffentlichungen der Studienergebnisse bleibt die Vertraulichkeit meiner persönlichen Daten gewährleistet.

Diese Einwilligungserklärung kann ich jederzeit widerrufen.

Ich habe die mir ausgehändigte Patienteninformation zu dieser Studie sorgfältig gelesen und verstanden und akzeptiere die Studienbedingungen. Alle meine Fragen sind zu meiner Zufriedenheit beantwortet worden.

Mit meiner Unterschrift erkläre ich mich einverstanden, an dieser Studie teilzunehmen. Mir ist bewusst, dass dieses Schriftstück keine Vertragsgrundlage darstellt.

Des Weiteren bin ich damit einverstanden, dass mein Hausarzt oder ein mich weiterbehandelnder niedergelassener Arzt im Rahmen dieser Studie von seiner Schweigepflicht befreit wird und er in einem Fragebogen Daten über die aktuell verordneten Medikamente an die Verantwortlichen der Studie weitergeben darf.

Hamburg, den

Datum	Nachnahme des Patienten (in Druckschrift)
	Unterschrift des Patienten

Bezeugung durch den Studienleiter/ die verantwortliche Apothekerin:

Mit meiner Unterschrift bezeuge ich, dass der Patient die Einwilligungserklärung eigenhändig in der Gegenwart meiner Person unterzeichnet hat.

Hamburg, den

Datum	Nachnahme des Studienleiters/ der verantwortlichen Apothekerin (in Druckschrift)
Uhrzeit	Unterschrift des Studienleiters/ der verantwortlichen Apothekerin

Appendix C Ethical review committee approval

ETHIK-KOMMISSION DER
ÄRZTEKAMMER
HAMBURG
Körperschaft des öffentlichen Rechts

Ärztekammer Hamburg · Postfach 76 01 09 · 22051 Hamburg

Herrn Dr. Michael Baehr
Apotheke
Universitätsklinikum Hamburg-Eppendorf
Martinistr. 52
20246 Hamburg

03.12.2009

Bearb.-Nr.: **PV3366 (Bitte stets angeben!)**
Studie: Vereinfachung komplexer Medikationsregime zur Verbesserung der Adhärenz von Patienten mit kardiovaskulären und Stoffwechselerkrankungen
Prüfplancode: 2009-DS-01

Sehr geehrter Herr Dr. Baehr,

über Ihr oben bezeichnetes, zur Primärberatung vorgelegtes Projekt hat die Ethik-Kommission ausführlich beraten.

Das Vorhaben entspricht den berufsrechtlichen bzw. gesetzlichen Anforderungen. Die Ethik-Kommission stimmt dem Vorhaben zu.

Die Kommission weist darauf hin, dass die Verantwortung des Versuchsleiters für das Forschungsvorhaben und seine Durchführung durch das obige Votum der Kommission nicht berührt wird.

Sie werden gebeten, die Ethik-Kommission über alle schwerwiegenden oder unerwarteten Ereignisse, die während der Studie auftreten und die die Sicherheit der Studienteilnehmer gefährden, in Verbindung mit Ihrer Stellungnahme zu unterrichten.
Die Kommission geht davon aus, dass die personenbezogenen Daten der Probanden/ Patienten den datenschutzrechtlichen Vorschriften entsprechend behandelt werden.

Die Ethik-Kommission erwartet, dass ihr nach Abschluss des Projektes unaufgefordert ein Abschluss-Bericht übersandt wird (unter Angabe der Bearb.-Nr.), aus dem der Erfolg/Misserfolg der Studie sowie Angaben darüber, ob die Studie abgebrochen oder geändert bzw. ob Regressansprüche geltend gemacht wurden, ersichtlich sind.

Mit verbindlicher Empfehlung
Im Auftrage der Kommission:

Prof. Dr. med. Th. Weber
- Vorsitzender -

P.S. Die Ethik-Kommission arbeitet auf der Grundlage deutschen Rechts und Berufsrechts sowie in Anlehnung an die ICH-GCP

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Appendix D MRCI (Original)

MEDICATION REGIMEN COMPLEXITY INDEX

Patient ID: ----------

Total no. of medications (including prn/sos medications): ----------

Instructions

1. MRCI applies only to prescribed medications. All entries are to be made only based on information on the label or drug chart (at the time of dispensing or discharge). No assumptions are to be made based on clinical judgement.
2. There are three sections in the scale. Complete each section before proceeding to the next. At the end, add the scores for the three sections to give the MRCI.
3. If the same medication (same brand and same dosage form) is present more than once in different strengths in a regimen (e.g. warfarin 5mg, 3mg and 1mg mdu), it is still considered as one medication.
4. In cases where the dosage is optional, choose the dosing instruction with the smallest dose/frequency. (e.g. albuterol MDI 1-2 puffs, 2-3 times daily will get weightings for 'metered dose inhalers', 'variable dose' and 'twice daily'; but not for 'multiple units at one time')
5. In certain cases the dosing frequency needs to be calculated (e.g. ranitidine 1mane and 1nocte is 1twice daily)
6. It is possible that with certain 'use as directed' instructions, the regimen will not get a score under dosing frequency (e.g. prednisolone 5mg mdu)
7. If there is more than one dosing frequency direction, they should be scored for all the dosing frequency directions (e.g. albuterol MDI 2 puffs bd and prn, will get scores for 'metered dose inhalers', 'multiple units at one time', 'twice daily' as well as 'prn')
8. Instances where two or more medications are mutually exclusive, they need to be scored twice or more as prn with the recommended dosing frequency (e.g. albuterol MDI or albuterol nebuliser twice daily will get scores for both 'metered dose inhalers' and 'nebuliser' under dosage forms, but needs to be scored two times for 'twice daily prn')
9. In cases where there is no matching option, choose the closest option (e.g. six times daily could be considered as 'q4h')

A) Circle the weighting corresponding to each dosage form (ONCE ONLY) present in the regimen.

Dosage Forms		Weighting
ORAL	Capsules/Tablets	1
	Gargles/Mouthwashes	2
	Gums/Lozenges	2
	Liquids	2
	Powders/Granules	2
	Sublingual sprays/tabs	2
TOPICAL	Creams/Gels/Ointments	2
	Dressings	3
	Paints/Solutions	2
	Pastes	3
	Patches	2
	Sprays	1
EAR, EYE & NOSE	Ear drops/creams/ointments	3
	Eye drops	3
	Eye gels/ointments	3
	Nasal drops/cream/ointment	3
	Nasal spray	2
INHALATION	Accuhalers	3
	Aerolizers	3
	Metered dose inhalers	4
	Nebuliser	5
	Oxygen/Concentrator	3
	Turbuhalers	3
	Other dry powder inhalers	3
OTHERS	Dialysate	5
	Enemas	2
	Injections: Prefilled	3
	Ampoules/Vials	4
	Pessaries	3
	Patient controlled analgesia	2
	Suppositories	2
	Vaginal creams	2
	Total for Section A	

B) For each medication in the regimen tick a box [√] corresponding to the dosing frequency. Then, add the no. of [√] in each category and multiply by the assigned weighting. In cases where there is no exact option, choose the best option.

Dosing Frequency	Medications	Total	Weighting	Weighting × No. of medications
Once daily			1	
Once daily prn			0.5	
Twice daily			2	
Twice daily prn			1	
Three times daily			3	
Three times daily prn			1.5	
Four times daily			4	
Four times daily prn			2	
q 12h			2.5	
q 12h prn			1.5	
q 8h			3.5	
q 8h prn			2	
q 6h			4.5	
q 6h prn			2.5	
q 4h			6.5	
q 4h prn			3.5	
q 2h			12.5	
q 2h prn			6.5	
prn/sos			0.5	
On alternate days or less frequently			2	
Oxygen prn			1	
Oxygen <15hrs			2	
Oxygen >15hrs			3	
		Total for Section B		

C) Tick a box [√] corresponding to the additional directions, if present in the regimen. Then, add the no. of [√] in each category and multiply by the assigned weighting.

Additional Directions	Medications	Total	Weighting	Weighting × No. of medications
Break or crush tablet			1	
Dissolve tablet/powder			1	
Multiple units at one time (e.g. 2 tabs, 2 puffs)			1	
Variable dose (e.g. 1-2 caps, 2-3 puffs)			1	
Take/use at specified time/s (e.g. mane, nocte, 8 AM)			1	
Relation to food (e.g. pc, ac, with food)			1	
Take with specific fluid			1	
Take/use as directed			2	
Tapering/increasing dose			2	
Alternating dose (e.g. one mane & two nocte, one/ two on alternate days)			2	
		Total for Section C		

Medication Regimen Complexity = Total (A) + Total (B) + Total (C)=

Page 2 of 2

Appendix E MRCI-D

Medication Regimen Complexity Index – D (MRCI – D)

Patienten-ID:_____

Gesamtzahl an Arzneimitteln (inkl. Bedarfsmedikation): _____

Anweisungen:

1. Der MRCI – D ist nur für verordnete Arzneimittel anwendbar. Alle Eingaben sind ausschließlich auf Basis der Information auf der Arzneimittelverpackung oder der Patientenakte (zur Zeit der Abgabe oder Entlassung) vorzunehmen. Es dürfen keine Annahmen aufgrund der klinischen Beurteilung erfolgen.
2. Die Skala besteht aus drei Abschnitten. Vervollständigen Sie jeden Abschnitt bevor Sie zum Nächsten übergehen. Addieren Sie am Ende die Punktzahlen der drei Abschnitte, um den MRCI – D zu erhalten.
3. Wenn dasselbe Arzneimittel (gleiche Marke und gleiche Darreichungsform) mehr als einmal in unterschiedlichen Wirkstärken in einem Therapieschema enthalten ist (z.B. Phenprocoumon 5mg, 3mg und 1mg je nach Bedarf) wird es als ein einziges Arzneimittel betrachtet.
4. Falls die Dosierung optional ist, wählen Sie die Dosierungsangabe mit der geringsten Dosis/ Frequenz (z.B. erhält „Salbutamol DA 1-2 Hübe, 2-3x täglich" Punkte für ‚Dosieraerosol', ‚variable Dosierung' und ‚2x täglich'; nicht aber für ‚mehrere Einheiten zur selben Zeit').
5. In bestimmten Fällen muss die Anwendungshäufigkeit ermittelt werden (z.B. ergibt Ranitidin 1 mal morgens und 1 mal abends ‚zweimal täglich').
6. Es ist möglich, dass bei bestimmten Hinweisen wie „nach Anweisung einzunehmen" ein Schema keine Punkte für die Anwendungshäufigkeit erhält (z.B. Marcumar nach INR, Prednisolon 5mg nach Anweisung, Insulin nach BZ).
7. Falls es mehr als eine Anweisung zur Einnahmehäufigkeit gibt, sollten Punkte für jede Anweisung gegeben werden (z.B. erhält ‚Salbutamol DA 2 Hübe 2x täglich und bei Bedarf' Punkte für ‚Dosieraerosol', ‚mehrere Einheiten zur selben Zeit', ‚zweimal täglich' und ‚bei Bedarf').
8. Wenn zwei oder mehr Arzneimittel alternativ angewandt werden, müssen sie zwei- oder mehrmals als Bedarfsmedikation mit der empfohlenen Anwendungshäufigkeit gewertet werden (z.B. erhält ‚Salbutamol Dosieraerosol oder Salbutamol Vernebler zweimal täglich' Punkte für ‚Dosieraerosol' und ‚Vernebler ' als Applikationsform und zweimal Punkte für ‚zweimal täglich bei Bedarf'.
9. In bestimmten Fällen, in denen die Dosiseinheit aus mL, Tropfen oder I.E. besteht, werden keine Punkte für ‚mehrere Einheiten zur selben Zeit' gegeben (z.B. Insulin 20 - 0 - 23, Tramaltropfen 20°- 20°- 20°, Lactulose 15mL 1x täglich).
10. In Fällen, in denen es keine passende Option gibt, wählen Sie die der Anweisung am nächsten kommende Option (z.B. kann ‚sechsmal täglich' als ‚alle 4 h' gewertet werden).

DA= Dosieraerosol

A) Kreisen Sie die Wertung für jede Applikationsform (JEWEILS NUR EINMAL) ein, die im Therapieschema vorhanden ist.

Applikationsform		Wertung
Oral	Kapseln / Tabletten	1
	Gurgel- / Mundspüllösungen	2
	Kaugummis / Lutschpastillen / -bonbons	2
	Flüssigkeiten	2
	Pulver, Granulate, Brausetabletten	2
	Sublingualsprays / -tabletten	2
Topisch	Cremes / Gele / Salben	2
	Verbände	3
	Pinsel-/ Lösungen	2
	Pasten	3
	Pflaster	2
	Sprays	1
Ohr, Auge, Nase	Ohrentropfen / -cremes / -salben	3
	Augentropfen	3
	Augengele / -salben	3
	Nasentropfen / -cremes / -salben	3
	Nasensprays	2
Inhalation	Diskus	3
	Aerolizer	3
	Dosieraerosole	4
	Vernebler	5
	Sauerstoff/-konzentrator	3
	Turbohaler	3
	Andere Pulverinhalatoren	3
Andere	Dialysate	5
	Klistiere	2
	Injektionen:	
	Fertigspritzen	3
	Ampullen/ Vials	4
	Pessare	3
	Patienten-kontrollierte Analgesie	2
	Suppositorien	2
	Vaginalcremes	2
	Summe für Abschnitt A	

B) Setzen Sie für jedes im Therapieschema enthaltene Arzneimittel einen Haken [✓] in das Kästchen für die dazugehörige Anwendungshäufigkeit. Addieren Sie dann die Zahl der Haken in jeder Kategorie und multiplizieren Sie diese Summe mit der dazugehörigen Wertung. Falls es keine exakt passende Option gibt, wählen Sie die am besten Passende.

Anwendungshäufigkeit	Arzneimittel	Summe	Wertung	Wertung x Zahl der Arzneimittel
Einmal täglich			1	
Einmal täglich b. Bedarf			0,5	
Zweimal täglich			2	
Zweimal täglich b. Bedarf			1	
Dreimal täglich			3	
Dreimal täglich b. Bedarf			1,5	
Viermal täglich			4	
Viermal täglich b. Bedarf			2	
Alle 12h			2,5	
Alle 12h b. Bedarf			1,5	
Alle 8h			3,5	
Alle 8h b. Bedarf			2	
Alle 6h			4,5	
Alle 6h b. Bedarf			2,5	
Alle 4h			6,5	
Alle 4h b. Bedarf			3,5	
Alle 2h			12,5	
Alle 2h b. Bedarf			6,5	
B. Bedarf			0,5	
An alternierenden Tagen oder seltener			2	
Sauerstoff b. Bedarf			1	
Sauerstoff < 15h			2	
Sauerstoff > 15h			3	
		Summe für Abschnitt B		

C) Setzen Sie einen Haken [✓] für zusätzliche Anweisungen, die im Therapieschema vorhanden sind. Addieren Sie dann die Zahl der Haken in jeder Kategorie und multiplizieren Sie diese Summe mit der zugehörigen Wertung.

Zusätzliche Anweisungen	Arzneimittel	Summe	Wertung	Wertung x Zahl der Arzneimittel
Tablette teilen oder mörsern			1	
Tablette/ Pulver auflösen			1	
Mehrere Einheiten zur selben Zeit (z.B. 2 Tbl., 2 Hübe)			1	
Variable Dosis (z.B. 1-2 Kps., 2-3 Hübe)			1	
Anwendung/ Einnahme zu festgelegten Zeitpunkten (z.B. vor dem Schlafen, 8:00)			1	
Abhängig von Mahlzeiten (z.B. nach dem Essen, vor dem Essen, zum Essen)			1	
Einnahme mit bestimmter Flüssigkeit			1	
Einnahme nach Anweisung			2	
Dosis erhöhen/ ausschleichen			2	
Alternierende Dosis (z.B. eine morgens & zwei abends; eine/ zwei an alternierenden Tagen)			2	
		Summe für Abschnitt C		

Komplexität des Medikationsregimes = Summe(A) + Summe(B) + Summe(C) =

Appendix F Morisky Questionnaire

Morisky Scale

1 Do you ever forget to take your medicine?

2 Are you careless at times about taking your medicine?

3 When you feel better, do you sometimes stop taking your medicine?

4 Sometimes if you feel worse when you take the medicine, do you stop taking it?

Score is 'yes' or 'no'. Every 'no' is one point, every 'yes' 0 points.

Adherence Scale 0–4.

High = 4, Medium = 2–3, Low = 0–1.

Appendix G MARS-D

MARS – D

Medication Adherence Report Scale - D

Viele Leute nehmen ihre Medikamente so ein, wie sie am besten damit zu Recht kommen. Dies weicht vielleicht von dem ab, was der Arzt ihnen gesagt hat oder von dem, was im Beipackzettel steht. Wir möchten gerne von Ihnen erfahren, wie Sie selbst Ihre Medikamente einnehmen.
Hier finden Sie Aussagen anderer Leute zur Medikamenteneinnahme.
Bitte kreuzen Sie zu jeder Aussage das Kästchen an, das bei Ihnen am ehesten zutrifft.

Ihre eigene Art, Medikamente einzunehmen	**immer**	**oft**	**manch-mal**	**selten**	**nie**
1. Ich vergesse sie einzunehmen	☐	☐	☐	☐	☐
2. Ich verändere die Dosis	☐	☐	☐	☐	☐
3. Ich setze sie eine Weile lang aus	☐	☐	☐	☐	☐
4. Ich lasse bewusst eine Dosis aus	☐	☐	☐	☐	☐
5. Ich nehme weniger als verord-net ein	☐	☐	☐	☐	☐

Appendix H SIMS-D

Hinweise zum Ausfüllen des Fragebogens:

- Verwenden Sie bitte nur Kugelschreiber (keinen Bleistift).
- Geben Sie Freitextangaben in Druckbuchstaben an.
- Kreuzen Sie die Kästchen deutlich an: ☒. Bei versehentlicher Falschauswahl füllen Sie bitte das entsprechende Kästchen ganz aus ■ und kreuzen Ihre Auswahl erneut an: ☐.

Fragen zur Medikamenteninformation

Bitte beurteilen Sie zu den einzelnen Punkten die **Information,** die Sie von Ihrem Hausarzt erhalten haben. Falls Sie mehr als ein Medikament einnehmen, geben Sie bitte Ihren Gesamteindruck von den erhaltenen Informationen zu allen Ihren Medikamenten an.

Wie bewerten Sie die von Ihrem Hausarzt erhaltenen Informationen zu folgenden Punkten:	**Zu viel**	**Etwa richtig**	**Zu wenig**	**keine Information dazu erhalten**	**keine Information dazu *notwendig***
1. Wie Ihr Medikament heißt	☐	☐	☐	☐	☐
2. Wofür das Medikament Ihnen hilft	☐	☐	☐	☐	☐
3. Was es bewirkt	☐	☐	☐	☐	☐
4. Wie es wirkt	☐	☐	☐	☐	☐
5. Wie lange es dauert, bis es wirkt	☐	☐	☐	☐	☐
6. Woran Sie erkennen, ob es wirkt	☐	☐	☐	☐	☐

Wie bewerten Sie die von Ihrem Hausarzt erhaltenen Informationen zu folgenden Punkten:	**Zu viel**	**Etwa richtig**	**Zu wenig**	**keine Information dazu erhalten**	**keine Information dazu *notwendig***
7. Wie lange Sie das Medikament benötigen werden	☐	☐	☐	☐	☐
8. Wie Sie das Medikament anwenden sollen	☐	☐	☐	☐	☐
9. Wie Sie das Medikament wieder beschaffen können	☐	☐	☐	☐	☐
10. Ob das Medikament Nebenwirkungen (unerwünschte Wirkungen) hat	☐	☐	☐	☐	☐
11. Mit welcher Wahrscheinlichkeit Sie Nebenwirkungen bekommen werden	☐	☐	☐	☐	☐
12. Was Sie tun sollen, wenn bei Ihnen Nebenwirkungen auftreten	☐	☐	☐	☐	☐
13. Ob Sie Alkohol trinken können, solange Sie das Medikament nehmen	☐	☐	☐	☐	☐
14. Ob Wechselwirkungen mit anderen Medikamenten bestehen	☐	☐	☐	☐	☐
15. Ob die Medikation Sie schläfrig machen wird	☐	☐	☐	☐	☐
16. Ob die Medikation Ihr Sexualleben beeinträchtigen wird	☐	☐	☐	☐	☐
17. Was Sie tun sollten, falls Sie die Einnahme mal vergessen	☐	☐	☐	☐	☐

Appendix I Patient Questionnaire N°1

Patienten-Nr.:

Universitätsklinikum Hamburg-Eppendorf

FRAGEBOGEN 1

ADHÄRENZ, LEBENSQUALITÄT UND PATIENTENZUFRIEDENHEIT

Klinische Pharmazie und Versorgungsforschung
Universitätsklinikum Hamburg-Eppendorf

Dr. Michael Baehr
Dorit Stange

Sollten Sie Fragen zur Studie oder zum Ausfüllen des Fragebogens haben, erreichen Sie uns unter folgender Adresse:

Dorit Stange
Universitätsklinikum Eppendorf
Apotheke
Tel.: 040/7410-58517 Fax.: 040/7410-54592
Martinistr. 52, 20246 Hamburg
E-Mail: d.stange@uke.uni-hamburg.de

Liebe Patientin, lieber Patient,

Bitte lesen Sie die Instruktionen und beantworten Sie möglichst alle Fragen. Meistens können Sie Ihre Angaben einfach durch Ankreuzen einer Antwortalternative machen, andere Angaben tragen Sie bitte direkt in die dafür vorgesehenen freien Felder ein. Falls manche Fragen nicht genau auf Sie zutreffen, oder Sie Schwierigkeiten haben sich für eine Antwort zu entscheiden, kreuzen Sie bitte die Antwort an, die Ihnen am ehesten geeignet erscheint.

Angaben zu Ihrer Person

Wir **möchten Sie zunächst bitten, uns einige Informationen zu Ihrer Person zu geben.**

1.1	**Muttersprache**	☐ deutsch	☐ andere: _____ (bitte angeben)
1.2	**Familienstatus**	☐ ledig	☐ geschieden
		☐ verheiratet	☐ verwitwet
1.3	**Höchste Berufsausbildung**		
	☐ keine bzw. angelernt		☐ abgeschlossene berufliche Ausbildung
	☐ Fach-/Meisterschule		☐ Fachhochschule/ Universität
1.4	**Aktueller beruflicher Status**		
	☐ erwerbstätig (angestellt)		☐ Rentner/in
	☐ erwerbstätig (selbständig)		☐ Schüler/Student/Azubi
	☐ erwerbslos		☐ Wehrdienst/Ersatzdienst
	☐ Hausfrau/Hausmann		☐ sonstiges _____ (bitte angeben)

Ihr Gesundheitszustand

Bei den folgenden Fragen geht es um die Beurteilung Ihres aktuellen Gesundheitszustandes. Bitte beantworten Sie jede der Fragen, indem Sie die Antwortmöglichkeit ankreuzen, die am besten auf Sie zutrifft.

		ausge-zeichnet	sehr gut	gut	weniger gut	schlecht
2.	Wie würden Sie Ihren Gesundheitszustand im Allgemeinen beschreiben?	☐	☐	☐	☐	☐

Im Folgenden sind einige Tätigkeiten beschrieben, die Sie vielleicht an einem normalen Tag ausüben. Sind Sie durch Ihren derzeitigen Gesundheitszustand bei diesen Tätigkeiten eingeschränkt? Wenn ja, wie stark?

		ja, sehr stark eingeschränkt	ja, etwas eingeschränkt	nein, überhaupt nicht eingeschränkt
3.	mittelschwere Tätigkeiten, z.B. einen Tisch verschieben, staubsaugen, kegeln, Rasen mähen	☐	☐	☐
4.	mehrere Treppenabsätze steigen	☐	☐	☐

Hatten Sie in den vergangenen 4 Wochen aufgrund Ihrer körperlichen Gesundheit irgendwelche Schwierigkeiten bei der Arbeit oder anderen alltäglichen Tätigkeiten im Beruf bzw. zu Hause?

		ja	nein
5.	Ich habe weniger geschafft, als ich wollte	☐	☐
6.	Ich konnte nur bestimmte Dinge tun	☐	☐

Hatten Sie in den vergangenen 4 Wochen aufgrund seelischer Probleme irgendwelche Schwierigkeiten bei der Arbeit oder anderen alltäglichen Tätigkeiten im Beruf bzw. zu Hause (z.B. weil Sie sich niedergeschlagen oder ängstlich fühlten)?

		ja	nein
7.	Ich habe weniger geschafft, als ich wollte	☐	☐
8.	Ich konnte nicht so sorgfältig wie üblich arbeiten	☐	☐

9. **Inwieweit haben Schmerzen Sie in den vergangenen 4 Wochen bei der Ausübung Ihrer Alltagstätigkeiten zu Hause und im Beruf behindert?**

überhaupt nicht	ein bisschen	mäßig	ziemlich	sehr
☐	☐	☐	☐	☐

Bei den nächsten Fragen geht es darum, wie Sie sich fühlen und wie es Ihnen in den vergangenen 4 Wochen ergangen ist. Wie oft waren Sie in den vergangenen 4 Wochen…

		immer	meistens	ziemlich oft	manchmal	selten	nie
10.	ruhig und gelassen?	☐	☐	☐	☐	☐	☐
11.	voller Energie?	☐	☐	☐	☐	☐	☐
12.	entmutigt und traurig?	☐	☐	☐	☐	☐	☐

13. **Wie häufig haben Ihre körperliche Gesundheit oder seelischen Probleme in den vergangenen 4 Wochen Ihre Kontakte zu anderen Menschen (Besuche bei Freunden, Verwandten usw.) beeinträchtigt?**

immer	meistens	manchmal	selten	nie
☐	☐	☐	☐	☐

Fragen zur Medikamenteneinnahme

Viele Leute nehmen ihre Medikamente so ein, wie sie am besten damit zu Recht kommen. Dies weicht vielleicht von dem ab, was der Arzt ihnen gesagt hat oder von dem, was im Beipackzettel steht. Wir möchten gerne von Ihnen erfahren, wie Sie selbst Ihre Medikamente einnehmen. Hier finden Sie Aussagen anderer Leute zur Medikamenteneinnahme. Bitte kreuzen Sie zu jeder Aussage das Kästchen an, das bei Ihnen am ehesten zutrifft.

		nie	selten	manchmal	oft	immer
14.	Ich vergesse sie einzunehmen	☐	☐	☐	☐	☐
15.	Ich verändere die Dosis	☐	☐	☐	☐	☐
16.	Ich setze sie eine Weile ab	☐	☐	☐	☐	☐
17.	Ich lasse bewusst eine Dosis aus	☐	☐	☐	☐	☐
18.	Ich nehme weniger als verordnet	☐	☐	☐	☐	☐

Fragen zur Medikamenteninformation

Bitte beurteilen Sie zu den einzelnen Punkten die Information, die Sie von Ihrem Hausarzt erhalten haben. Falls Sie mehr als ein Medikament einnehmen, geben Sie bitte Ihren Gesamteindruck von den erhaltenen Informationen zu allen Ihren Medikamenten an.

	Wie bewerten Sie die von Ihrem Hausarzt erhaltenen Informationen zu folgenden Punkten:	zu viel	etwa richtig	zu wenig	keine Info dazu erhalten	keine Info dazu notwendig
19.	Wie Ihr Medikament heißt	☐	☐	☐	☐	☐
20.	Wofür Ihr Medikament Ihnen hilft	☐	☐	☐	☐	☐
21.	Was es bewirkt	☐	☐	☐	☐	☐
22.	Wie es wirkt	☐	☐	☐	☐	☐
23.	Wie lange es dauert, bis es wirkt	☐	☐	☐	☐	☐
24.	Woran Sie erkennen, ob es wirkt	☐	☐	☐	☐	☐
25.	Wie lange Sie das Medikament benötigen werden	☐	☐	☐	☐	☐
26.	Wie Sie das Medikament anwenden sollen	☐	☐	☐	☐	☐
27.	Wie Sie das Medikament wieder beschaffen können	☐	☐	☐	☐	☐
28.	Ob das Medikament Nebenwirkungen (unerwünschte Wirkungen) hat	☐	☐	☐	☐	☐
29.	Mit welcher Wahrscheinlichkeit Sie Nebenwirkungen bekommen werden	☐	☐	☐	☐	☐
30.	Was Sie tun sollen, wenn bei Ihnen Nebenwirkungen auftreten	☐	☐	☐	☐	☐
31.	Ob Sie Alkohol trinken können, solange Sie das Medikament nehmen	☐	☐	☐	☐	☐

	Wie bewerten Sie die von Ihrem Hausarzt erhaltenen Informationen zu folgenden Punkten:	zu viel	etwa richtig	zu wenig	keine Info dazu erhalten	keine Info dazu notwendig
32.	Ob Wechselwirkungen mit anderen Medikamenten bestehen	☐	☐	☐	☐	☐
33.	Ob die Medikation Sie schläfrig machen wird	☐	☐	☐	☐	☐
34.	Ob die Medikation Ihr Sexualleben beeinträchtigen wird	☐	☐	☐	☐	☐
35.	Was Sie tun sollten, falls Sie die Einnahme mal vergessen	☐	☐	☐	☐	☐

Allgemeine Fragen zur Medikation

		immer	oft	manch-mal	selten	nie
36.	Beeinträchtigt die Anzahl an einzunehmenden Tabletten Ihre Lebensqualität?	☐	☐	☐	☐	☐
37.	Ist es Ihnen wichtig, möglichst wenige Tabletten einzunehmen?	☐	☐	☐	☐	☐
38.	Wären Sie bereit eine Zuzahlung für die Medikamente zu leisten, wenn sich dadurch die Tablettenzahl reduziert?	☐	☐	☐	☐	☐
39.	Haben Sie Angst, versehentlich Tabletten zu vergessen oder falsch einzunehmen?	☐	☐	☐	☐	☐
40.	Erschwert Ihnen ein Wechsel des Aussehens die richtige Einnahme?	☐	☐	☐	☐	☐
41.	Hilft Ihnen die Form oder Farbe von Tabletten zur Orientierung?	☐	☐	☐	☐	☐

		immer	oft	manch-mal	selten	nie	Ich nehme keine geteilten Tabletten ein.
42.	Bereitet Ihnen das Teilen von Tabletten Schwierigkeiten?	☐	☐	☐	☐	☐	☐

Vielen Dank für das Ausfüllen des Fragebogens.
Sie haben uns damit sehr geholfen!

Appendix J Patient Questionnaire N°2

Patienten-Nr.:

Universitätsklinikum Hamburg-Eppendorf

FRAGEBOGEN 2

MEDIKAMENTENEINNAHME IM KRANKENHAUS

Klinische Pharmazie und Versorgungsforschung
Universitätsklinikum Eppendorf

Dr. Michael Baehr
Dorit Stange

Bitte Rückseite beachten!

Bei Fragen zur Studie oder zum Ausfüllen des Fragebogens, erreichen Sie uns unter folgender Telefonnummer:

Dorit Stange, Apotheke
Tel.: 040/7410-58517

Liebe Patientin, lieber Patient,

Bitte lesen Sie die Instruktionen und beantworten Sie möglichst alle Fragen. Meistens können Sie Ihre Angaben einfach durch Ankreuzen einer Antwortalternative machen, andere Angaben tragen Sie bitte direkt in die dafür vorgesehenen freien Felder ein. Falls manche Fragen nicht genau auf Sie zutreffen, oder Sie Schwierigkeiten haben sich für eine Antwort zu entscheiden, kreuzen Sie bitte die Antwort an, die Ihnen am ehesten geeignet erscheint.

Fragen zur Medikamentengabe im Krankenhaus

		immer	oft	manch-mal	selten	nie
1.1	Achten Sie auf die einzelnen Medikamente, die Sie im Krankenhaus bekommen?	☐	☐	☐	☐	☐

		immer	oft	manch-mal	selten	nie	kein Wechsel
1.2	Beeinflusst ein Präparatewechsel Ihrer Medikamente im Krankenhaus Sie dort in Ihrem Einnahmeverhalten?	☐	☐	☐	☐	☐	☐

Fragen zur Medikamenteneinnahme

Viele Leute nehmen ihre Medikamente so ein, wie sie am besten damit zu Recht kommen. Dies weicht vielleicht von dem ab, was der Arzt ihnen gesagt hat oder von dem, was im Beipackzettel steht. Wir möchten gerne von Ihnen erfahren, wie Sie selbst Ihre Medikamente während des Krankenhausaufenthalts eingenommen haben. Hier finden Sie Aussagen anderer Leute zur Medikamenteneinnahme. Bitte kreuzen Sie zu jeder Aussage das Kästchen an, das bei Ihnen am ehesten zutrifft.

		nie	selten	manchmal	oft	immer
2.	Ich vergesse sie einzunehmen	☐	☐	☐	☐	☐
3.	Ich verändere die Dosis	☐	☐	☐	☐	☐
4.	Ich setze sie eine Weile ab	☐	☐	☐	☐	☐
5.	Ich lasse bewusst eine Dosis aus	☐	☐	☐	☐	☐
6.	Ich nehme weniger als verordnet	☐	☐	☐	☐	☐

Vielen Dank für das Ausfüllen des Fragebogens.
Sie haben uns damit sehr geholfen!

Appendix K Patient Questionnaire N°3

Patienten-Nr.:

Universitätsklinikum
Hamburg-Eppendorf

FRAGEBOGEN 3

ADHÄRENZ, LEBENSQUALITÄT UND PATIENTENZUFRIEDENHEIT

Klinische Pharmazie und Versorgungsforschung
Universitätsklinikum Eppendorf

Dr. Michael Baehr
Dorit Stange

Liebe Patientin, lieber Patient,

Zur Vervollständigung der Daten, die wir für die Studie *„Vereinfachung komplexer Medikationsregime zur Verbesserung der Adhärenz von Patienten mit kardiovaskulären und Stoffwechselerkrankungen“* noch benötigen, schicken wir Ihnen hiermit einen weiteren Fragebogen, den Sie bitte ausgefüllt in den beigefügten Freiumschlag stecken und zurückschicken!

Im Folgenden werden Fragen zu Ihrer *Gesundheit*, zu Ihrer *Lebensqualität* und *Zufriedenheit mit der Versorgung* sowie zu Ihrer *aktuellen Medikation* gestellt.

Bitte lesen Sie die Instruktionen und beantworten Sie möglichst alle Fragen. Meistens können Sie Ihre Angaben einfach durch Ankreuzen einer Antwortalternative machen, andere Angaben tragen Sie bitte direkt in die dafür vorgesehenen freien Felder ein. Manche Fragen werden vielleicht nicht genau auf Sie zutreffen, oder Sie werden Schwierigkeiten haben sich für eine Antwort zu entscheiden. Bitte kreuzen Sie in diesen Fällen die Antwort an, die Ihnen am ehesten geeignet erscheint.

Alle Angaben sind vertraulich und werden nicht von Ihrem Arzt/Ärztin eingesehen. Die Auswertung führen wir anonymisiert am Universitätsklinikum Eppendorf durch. Es werden nur gruppenbezogene Auswertungen durchgeführt.

Wir freuen uns sehr über Ihre Kooperation. Bereits an dieser Stelle danken wir Ihnen ganz herzlich für Ihre Unterstützung!

Dr. Michael Baehr — Dorit Stange

(Universitätsklinikum Eppendorf)

Sollten Sie Fragen zur Studie haben, erreichen Sie uns unter folgender Adresse:

Dorit Stange
Universitätsklinikum Eppendorf
Apotheke
Tel.: 040/74105-8517 Fax.: 040/74105-4592
Martinistr. 52, 20246 Hamburg
E-Mail: d.stange@uke.uni-hamburg.de

Ihre aktuelle Medikation

Bitte tragen Sie in die folgende Tabelle alle Medikamente mit Einnahmehinweisen ein, die Ihr Arzt Ihnen zurzeit verschrieben hat! Bitte achten Sie auch besonders auf die Angabe der Dosis der entsprechenden Präparate!

1.	**Name des Medikaments** (z.B. Delix; Meto/HCT 100/12,5)	**Dosis** (z.B. 5 mg)	**Einnahmeanweisung** (z.B. morgens und abends je 1 Tablette; 1-0-1)
a.			
b.			
c.			
d.			
e.			
f.			
g.			
h.			
i.			
j.			

Ihr Gesundheitszustand

Bei den folgenden Fragen geht es um die Beurteilung Ihres aktuellen Gesundheitszustandes. Bitte beantworten Sie jede der Fragen, indem Sie die Antwortmöglichkeit ankreuzen, die am besten auf Sie zutrifft.

		ausge-zeichnet	sehr gut	gut	weniger gut	schlecht
2.	Wie würden Sie Ihren Gesundheitszustand im Allgemeinen beschreiben?	☐	☐	☐	☐	☐

Im Folgenden sind einige Tätigkeiten beschrieben, die Sie vielleicht an einem normalen Tag ausüben. Sind Sie durch Ihren derzeitigen Gesundheitszustand bei diesen Tätigkeiten eingeschränkt? Wenn ja, wie stark?

		ja, sehr stark eingeschränkt	ja, etwas eingeschränkt	nein, überhaupt nicht eingeschränkt
3.	mittelschwere Tätigkeiten, z.B. Tisch ver-schieben, staubsaugen, kegeln, Rasen mähen	☐	☐	☐
4.	mehrere Treppenabsätze steigen	☐	☐	☐

Hatten Sie in den vergangenen 4 Wochen aufgrund Ihrer körperlichen Gesundheit irgendwelche Schwierigkeiten bei der Arbeit oder anderen alltäglichen Tätigkeiten im Beruf bzw. zu Hause?

		ja	nein
5.	Ich habe weniger geschafft, als ich wollte	☐	☐
6.	Ich konnte nur bestimmte Dinge tun	☐	☐

Hatten Sie in den vergangenen 4 Wochen aufgrund seelischer Probleme irgendwelche Schwierigkeiten bei der Arbeit oder anderen alltäglichen Tätigkeiten im Beruf bzw. zu Hause (z.B. weil Sie sich niedergeschlagen oder ängstlich fühlten)?

		ja	nein
7.	Ich habe weniger geschafft, als ich wollte	☐	☐
8.	Ich konnte nicht so sorgfältig wie üblich arbeiten	☐	☐

9. **Inwieweit haben Schmerzen Sie in den vergangenen 4 Wochen bei der Ausübung Ihrer Alltagstätigkeiten zu Hause und im Beruf behindert?**

überhaupt nicht	ein bisschen	mäßig	ziemlich	sehr
☐	☐	☐	☐	☐

Bei den nächsten Fragen geht es darum, wie Sie sich fühlen und wie es Ihnen in den vergangenen 4 Wochen ergangen ist. Wie oft waren Sie in den vergangenen 4 Wochen…

		immer	meistens	ziemlich oft	manchmal	selten	nie
10.	ruhig und gelassen?	☐	☐	☐	☐	☐	☐
11.	voller Energie?	☐	☐	☐	☐	☐	☐
12.	entmutigt und traurig?	☐	☐	☐	☐	☐	☐

13. **Wie häufig haben Ihre körperliche Gesundheit oder seelischen Probleme in den vergangenen 4 Wochen Ihre Kontakte zu anderen Menschen (Besuche bei Freunden, Verwandten usw.) beeinträchtigt?**

immer	meistens	manchmal	selten	nie
☐	☐	☐	☐	☐

Fragen zur Medikamenteneinnahme

Viele Leute nehmen ihre Medikamente so ein, wie sie am besten damit zu Recht kommen. Dies weicht vielleicht von dem ab, was der Arzt ihnen gesagt hat oder von dem, was im Beipackzettel steht. Wir möchten gerne von Ihnen erfahren, wie Sie selbst Ihre Medikamente einnehmen. Hier finden Sie Aussagen anderer Leute zur Medikamenteneinnahme. Bitte kreuzen Sie zu jeder Aussage das Kästchen an, das bei Ihnen am ehesten zutrifft.

		nie	selten	manchmal	oft	immer
14.	Ich vergesse sie einzunehmen	☐	☐	☐	☐	☐
15.	Ich verändere die Dosis	☐	☐	☐	☐	☐
16.	Ich setze sie eine Weile ab	☐	☐	☐	☐	☐
17.	Ich lasse bewusst eine Dosis aus	☐	☐	☐	☐	☐
18.	Ich nehme weniger als verordnet	☐	☐	☐	☐	☐

Fragen zur Medikamenteninformation

Bitte beurteilen Sie zu den einzelnen Punkten die Information, die Sie von Ihrem Hausarzt erhalten haben. Falls Sie mehr als ein Medikament einnehmen, geben Sie bitte Ihren Gesamteindruck von den erhaltenen Informationen zu allen Ihren Medikamenten an.

	Wie bewerten Sie die von Ihrem Hausarzt erhaltenen Informationen zu folgenden Punkten:	zu viel	etwa richtig	zu wenig	keine Info dazu erhalten	keine Info dazu notwendig
19.	Wie Ihr Medikament heißt	☐	☐	☐	☐	☐
20.	Wofür Ihr Medikament Ihnen hilft	☐	☐	☐	☐	☐
21.	Was es bewirkt	☐	☐	☐	☐	☐
22.	Wie es wirkt	☐	☐	☐	☐	☐
23.	Wie lange es dauert, bis es wirkt	☐	☐	☐	☐	☐
24.	Woran Sie erkennen, ob es wirkt	☐	☐	☐	☐	☐
25.	Wie lange Sie das Medikament benötigen werden	☐	☐	☐	☐	☐
26.	Wie Sie das Medikament anwenden sollen	☐	☐	☐	☐	☐
27.	Wie Sie das Medikament wieder beschaffen können	☐	☐	☐	☐	☐
28.	Ob das Medikament Nebenwirkungen (unerwünschte Wirkungen) hat	☐	☐	☐	☐	☐
29.	Mit welcher Wahrscheinlichkeit Sie Nebenwirkungen bekommen werden	☐	☐	☐	☐	☐
30.	Was Sie tun sollen, wenn bei Ihnen Nebenwirkungen auftreten	☐	☐	☐	☐	☐
31.	Ob Sie Alkohol trinken können, solange Sie das Medikament nehmen	☐	☐	☐	☐	☐
32.	Ob Wechselwirkungen mit anderen Medikamenten bestehen	☐	☐	☐	☐	☐
33.	Ob die Medikation Sie schläfrig machen wird	☐	☐	☐	☐	☐
34.	Ob die Medikation Ihr Sexualleben beeinträchtigen wird	☐	☐	☐	☐	☐
35.	Was Sie tun sollten, falls Sie die Einnahme mal vergessen	☐	☐	☐	☐	☐

Vielen Dank für das Ausfüllen des Fragebogens.
Sie haben uns damit sehr geholfen!

Appendix L GP Questionnaire

Patienten-Nr.:
Arzt-Nr.:

Universitätsklinikum
Hamburg-Eppendorf

FRAGEBOGEN

PATIENTENVERSORGUNG

Klinische Pharmazie und Versorgungsforschung
Universitätsklinikum Hamburg-Eppendorf
APOTHEKE

Dr. Michael Baehr
Dorit Stange

Sehr geehrte Kollegin, sehr geehrter Kollege,

Die Apotheke des Universitätsklinikums Hamburg-Eppendorf führt derzeit in Kooperation mit verschiedenen Kliniken eine wissenschaftliche Untersuchung zum Thema „Patientenadhärenz - Vereinfachung komplexer Therapieregime“ durch. Mit dieser Befragung soll die medizinische Behandlung von chronisch kranken Patienten weiter verbessert werden. Im Folgenden stellen wir daher Fragen zu *der aktuellen Medikation Ihres Patienten*, Ihren *Erfahrungen bei therapeutischen Entscheidungen* sowie zu Ihrer *Zufriedenheit mit der Versorgung*.

Bitte beantworten Sie möglichst alle Fragen. Wenn Sie den Fragebogen ausgefüllt haben, stecken Sie ihn bitte samt eines **aktuellen Therapieplans** Ihres Patienten in den beigefügten Freiumschlag. Alle Angaben sind vertraulich; die Auswertung erfolgt pseudonymisiert.

Wir würden uns sehr über Ihre Kooperation freuen. Bereits an dieser Stelle danken wir Ihnen ganz herzlich für Ihre Unterstützung.

Dr. Michael Baehr Dorit Stange

(Universitätsklinikum Eppendorf)

Sollten Sie Fragen zur Studie haben, erreichen Sie uns unter folgender Adresse:

Dorit Stange
Universitätsklinikum Eppendorf
Apotheke
Tel.: 040/74105-8517 Fax.: 040/74105-4593
Martinistr. 52, 20246 Hamburg
E-Mail: d.stange@uke.uni-hamburg.de

Teil I Fragen zur aktuellen Medikation Ihres Patienten

Bitte hängen Sie einen AKTUELLEN THERAPIEPLAN Ihres Patienten an und kreuzen Sie im Folgenden die Antwort an, die Ihnen am ehesten geeignet erscheint.

1. **Wie beurteilen Sie die im Krankenhaus angesetzte Therapie im Vergleich zur vorherigen Hausmedikation?** (siehe beigefügten Entlassbrief)

	deutlich besser	besser	schlechter	deutlich schlechter	keine Veränderung zur vorherigen Hausmedikation
	☐	☐	☐	☐	☐

2.	Haben Sie **Veränderungen** vorgenommen?	ja	nein
		☐	☐

2.1	Wenn **JA**, Gründe für Veränderungen (mehrere Antworten sind möglich)		
	a	ökonomisch	☐
	b	keine ausreichende Einstellung des Patienten	☐
	c	fehlende persönliche Erfahrung	☐
	d	keine Dauermedikation	☐
	e	Wunsch des Patienten	☐
	f	Nebenwirkungen	☐
	g	unzureichende Infos aus dem Krankenhaus	☐
	h	andere	☐ _____

2.2	Wenn **NEIN**, Gründe für Übernahme (mehrere Antworten sind möglich)		
	i	guter Therapieerfolg	☐
	j	Patientenzufriedenheit	☐
	k	guter Entlassbrief	☐
	l	Wunsch des Patienten	☐
	m	andere	☐ _____

Teil II Allgemeine Angaben zur Arzneimittelverordnung

Der folgende Abschnitt ist zu Ihrer Zeitersparnis nur auszufüllen, wenn Sie den Fragebogen erstmalig erhalten.

3. Fachrichtung: _____

4.	Dauer der Berufstätigkeit (in Jahren)	1-10	11-20	21-30	31-40	>40
		☐	☐	☐	☐	☐
5.	Bereitschaft zur Übernahme einer Krankenhaus-Verordnung	immer	oft	manchmal	selten	nie
		☐	☐	☐	☐	☐

Für wie wichtig halten Sie…

6.	…eine möglichst geringe Anzahl an Tabletten für den Patienten	sehr wichtig	wichtig	weniger wichtig	unwichtig	weiß nicht
		☐	☐	☐	☐	☐

Ziehen Sie bei der Therapieauswahl in Betracht,

dass	**…**	immer	oft	manch-mal	selten	nie	weiß nicht
7.	…Tablettenteilen oftmals ein Problem für den Patienten darstellt?	☐	☐	☐	☐	☐	☐
8.	…die Adhärenz durch eine geringere Anzahl an Tabletten erhöht werden kann?	☐	☐	☐	☐	☐	☐
9.	Wären Sie bereit, teurere Medikamente zu verordnen, wenn dadurch bessere Therapieerfolge erzielt werden könnten?	☐	☐	☐	☐	☐	☐
10.	Sehen Sie sich durch gesetzliche Vorschriften hinsichtlich Ihres Arzneimittelbudgets in Ihrer Therapiewahl eingeschränkt?	☐	☐	☐	☐	☐	☐

Weitere Anmerkungen:

_____

_____

_____

Vielen Dank für das Ausfüllen des Fragebogens.
Sie haben uns damit sehr geholfen!

Appendix M Additional information for the GP

Universitätsklinikum Hamburg-Eppendorf

Zentrale Dienste

Apotheke
Dorit Stange

Martinistraße 52
20246 Hamburg
Telefon: (040) 74105-8517
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d.stange@uke.uni-hamburg.de
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einrichtungen/apotheke

Betreff: Studie Versorungsforschung

Sehr geehrte Kollegin, sehr geehrter Kollege,

Adhärenz ist eine entscheidende Voraussetzung für den Therapieerfolg unserer Patienten. Studien belegen allerdings, dass **max. 60 %** der Patienten regelmäßig ihre Medikamente einnehmen. Je komplexer das Therapieregime ist, desto geringer ist die Adhärenz. Gerade bei Erkrankungen wie Hypertonie und Diabetes, die eine langjährige Therapie voraussetzen, ist die Patientenmitarbeit jedoch essentiell.

Aus diesem Grund haben wir uns am UKE das Ziel gesetzt, bei Therapieentscheidungen vermehrt auf ein einfaches Therapieregime zu achten, zum Beispiel durch den Einsatz von Kombinationspräparaten, langwirksamen Medikamenten, die eine tägliche Einmalgabe ermöglichen, sowie der Vermeidung geteilter Tabletten. **Wir bitten Sie daher, die Medikation aus dem Krankenhaus wenn möglich so zu übernehmen oder bei notwendigen Änderungen ein einfaches Arzneiregime zu berücksichtigen.** Selbstverständlich sind Sie weiterhin vollkommen uneingeschränkt in Ihrer weiteren Therapie.

Der Effekt einer solchen Therapievereinfachung wird in Kooperation verschiedener Kliniken und der Medizinischen Psychologie im Rahmen einer wissenschaftlichen Untersuchung betrachtet. Dafür benötigen wir die Daten über den weiteren Verlauf der Arzneimitteltherapie. Ihr Patient hat eingewilligt, an der Untersuchung teilzunehmen und seine patientenbezogenen Daten hinsichtlich der Therapie zur Verfügung zu stellen.

In **ca. 6 Wochen** werde ich Sie daher erneut kontaktieren, um mich in Form eines **Fragebogens** nach der aktuellen Medikation Ihres Patienten zu erkundigen. Dieses Schreiben gilt nur als Vorabinformation für Sie!

Vielen Dank für Ihre Kooperation!
Ihre

Dorit Stange
Apothekerin

Dr. Michael Baehr
Apothekenleiter

Appendix N Data sheet for data from patient medical file

	Daten aus Patientenakte							
1)Patienten-ID:								
2)Behandlungsgruppe:								
3)KH_Patienten-ID:				4)Fall-Nr				
5)Aufnahmdatum in KH:				6)Entlassdatum				
7)Station im KH:								
8)Fachrichtung:								
9)Studieneintrittsdatum:								
10)Aufnahme ins KH	**O**	1=als Notfall	**O**	2=elektiv				
11)Versicherungsstatus :	**O**	1=gar nicht	**O**	2=gesetzlich	**O**	3=gesetzlich,	**O**	4=privat
						mit Zusatz		
12)Geb.Dat.:								
13)Alter								
14)Geschlecht:	**O**	1=männlich	**O**	2=weiblich				
15)Gewicht in KG:								
16)Körpergröße in cm:								
Arzt für Hausmedis:								
17)Diagnose:								
18)Dauerdiagnose_								
Phase 2:								
19) Anzahl an Vereinfachungsmöglichkeiten:								
20) Art der Vereinf.	**O**	1=Kombi	**O**	2=v. 2x auf 1x	**O**	3=ungeteilt	**O**	4=langwirks.
	O	5=andere:						
21) initiiert durch	**O**	1=Apo	**O**	2=Arzt				
22) Umgesetzt	**O**	1=ja	**O**	2=nein	**O**	3=zum Teil		

Appendix O Hazardous materials

In the present work no hazardous materials were used. It was exclusively a counseling intervention.

Curriculum vitae

Personal Information

Dorit Stange

*14/08/1984 in Minden/ Westf., GER

Employment

since 01/2009 *Hospital Pharmacy*

University Medical Center Hamburg-Eppendorf, Hamburg, GER

since 12/2008 *Pharmacy*

Part time pharmacist, privilig. Adler-Apotheke Wandsbek, GER

03/2005 – 05/2006 *Department for Production of Cytostatica and Parenteral nutrition*

Study accompanied, Oster-Apotheke, Hamburg, GER

Internships

07/2003 *Pharmaceutical traineeship*

Pharmacie Du Lion in Forbach, France

09/2004 *Pharmaceutical traineeship*

Bahnhof-Apotheke, Lörrach, GER

03/2005 *Pharmaceutical traineeship*

Mühlen-Apotheke, Bünde, GER

09/2006 *Elective practical course*

Department of pharmaceutical technology, University Franche-Comté, France

Final Year Electives

11/2007 – 05/2008 Farmacia Puerta del Sur, Madrid, Spain

05/2008 – 11/2008 privilig. Adler-Apotheke, Wandsbek, Hamburg, GER

Academic Studies

10/2003 – 03/2004 *Undergraduate Studies*
Pharmaceutical studies, Halle/ Wittenberg, GER

04/2004 – 10/2007 *Undergraduate Studies*/ *Graduate Studies*
Pharmaceutical studies, University of Hamburg, GER

01/2009 – 09/2012 *Doctoral Program*
Department of Clinical Pharmacy, University of Hamburg, GER

Education

08/1994 – 06/2003 *Advanced Education*
Freiherr-vom-Stein-Gymnasium, College Preparatory High School
Bünde, GER

09/2000 – 07/2001 *High School Exchange Year*
Bishop's College Boarding School, Québec, Canada

04/1994 – 07/1994 *Basic Education*
Elementary school, Bünde, GER

08/1990 – 03/1994 *Basic Education*
Elementary school, Hahlen, GER

Degrees and Qualifcations

12/2008 Pharmacist Licensure

12/2008 Third Pharmaceutical State Exam

09/2007 Second Pharmaceutical State Exam

09/2005 First Pharmaceutical State Exam

06/2003 German High School Diploma

Publication list

First author –

peer reviewed

Stange D, Kriston L, Langebrake C, Cameron LK, Wollacott JD, Baehr M, et al. *Development and psychometric evaluation of the German version of the Medication Regimen Complexity Index (MRCI-D).* J Eval Clin Pract 2011 Feb 14. doi: 10.1111/j.1365-2753.2011.01636.x.

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others

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Co-Author –

peer reviewed

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Hüther J., von Wolff A, **Stange D**, Kriston L, Baehr M, Dartsch D.C., Härter M. *Incomplete Medication Adherence and its Predictors in Chronically Ill Patients in German Primary Care.* BMJ. Accepted.

others

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Conference contributions – *Abstracts/ Poster*

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Stange, D., Kriston, L., von Wolff, A., Baehr, M., Dartsch, D.C.: *Simplification of medication regimens – a novel aspect of pharmaceutical care in hospital.* EAHP, März 2012, Mailand

Dehmel C, Dörre L, Fenske A., Fritsch A., Griewel E., Marquardt G., Nehrdich D., Schonn I., **Stange D.,** Dartsch D.C., *Zur Klinischen Pharmazie gehören immer zwei: das Arzneimittel und der Patient,* Tag der Pharmazie, Universität Hamburg, September 2011

Dartsch, D.C., Nehrdich, D., **Stange, D**., Langebrake, C., Baehr, M.: *Evaluation of two medication safety-related interventions for cardiovascular inpatients in a German teaching hospital: standardized discharge education and simplification of complex therapies.* ACCP Mai 2012, online Symposium

oral presentations

Arab health forum 2009, Hamburg - patient safety

LAUD Doktorandentreffen Erlangen 2011

Declaration on oath

I hereby declare, on oath, that I have written the present dissertation by my own and without the aid of unfair or unauthorized resources. Indications of sources are given whenever content was taken directly or indirectly from other sources.

I also declare that the dissertation has neither been accepted nor graded 'failed' in a previous doctoral procedure.

Hamburg, 03.08.2012