ADHERENCE TO POLYPHARMACY – USE OF MULTIDRUG PUNCH CARDS IN PRIMARY CARE

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Prof. Dr. Jörg Schibler
Dekan

To my mother

In memoriam

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List of abbreviations

A	Adherence outcomes
ADA	American Diabetes Association
ADE	Adverse drug event
ADR	Adverse drug reaction
Appl. sci	Applied sciences
BID	Two-times daily intake
BMQ	Believes about Medicines Questionnaire
BSc	Bachelor of Science
C	clinical outcomes
CAM	composite adherence measure
cct	controlled clinical trial
cg	control group
CHF	Swiss francs
CI	Confidence interval
Compl.	completeness
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
d	days
DPPR	daily polypharmacy possession ratio
E	economic outcomes
EASD	European Association for the Study of Diabetes
ECHO	Economic, Clinical and Humanistic Outcomes
EPHPP	Effective Public Health Practice Project
expend.	expenditures
FIP	Fédération Internationale Pharmaceutique
GP	General physician
GPP	Good Pharmacy Practice
GRAMMS	Good Reporting of A Mixed Methods Study
H	humanistic outcomes
h /hrs	hours
HbA_{1C}	Glycosylated hemoglobin
Hc / hcp / hct	Health care / health-care professional / health care team
HIV	Human Immunodeficiency Virus
HMG	Heilmittelgesetz
IC	Informed consent form
ICH	International Conference on Harmonization
ig	intervention group
INR	International normalized ratio
ISMed	Integrated System for Medical Diagnoses
LDL-C	Lipoprotein-cholesterol
LOA	Leistungsorientierte Abgeltung
m	months
MDPC	Multidrug punch card
MEMS®	Medication Event Monitoring System
MeSH	Medical Subject Headings
mi	multiple interventions

min	Minutes
MMAS	Morisky Medication Adherence Scale
MPR	medication possession ratio
MSc	Master of Science
n	Number
n.a.	Not applicable
N.e.	Not evaluated.
n.s.	not significant
NMS	New Medicines Service
no	number
No.	Number
OTC	Over-the-counter
P	Patient
pack.	Packable
PC	Primary care
PDC	Proportion of days covered
POEMS	POlypharmacy Electronic Monitoring System
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QID	Four-times daily intake
QoL	Quality of life
Qual	Qualitative
Quant	Quantitative
RCT	randomized controlled trial
RFID	Radio frequency identification
s/dbp	systolic/diastolic blood pressure
SD	Standard deviation
SF 12 v. 2	Short form 12 v. 2
SOP	Standard Operation Procedure
T	Time
T0	Time point of discharge
T-1	Time period before hospital discharge (index hospitalization)
T12	Time point of follow-up visit at twelve months
T3	Time point of follow-up visit at three months
T6	Time point of follow-up visit at six months
TaA	Taking adherence
TDM	Therapeutic drug monitoring
TiA	Timing adherence
UHBS	University Hospital Basel
UK	United Kingdom of Great Britain
US	United States of America
VAS	Visual analogue scale
Vers.	Version
VKlin	Verordnung über klinische Versuche mit Heilmitteln
vs.	versus
w	weeks
WHO	World Health Organization
xxx	garbled speech, unable to make an educated guess
*	significant change
^{13}C-UBT	^{13}C-urea breath test

Index

Summary

The growing age and multimorbidity of today's society are driving factors for polypharmacy. Polypharmacy is commonly defined as the concurrent use of over five prescribed medications. The prevalence of patients with polypharmacy rises in parallel to the demographic development and occurs in around 20% of the primary and secondary care population in Switzerland. Whereas in secondary care medications are delivered by health-care professionals, the correct and safe medication administration relies on the patient's capabilities in primary care. The patient's capabilities often do not meet the demands of a complex therapy regimen, and especially within the population of older patients with polypharmacy, impaired medication self-management leads to medication errors, non-adherence, and adverse health outcomes.

Adherence is defined as 'the extent to which a person's behavior – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider'. Typical adherence rates to oral medication range from 50-76%. Two types of non-adherent behavior are distinguished: intentional non-adherence is the patient's active decision to alter the treatment plan without feedback to the prescriber, and unintentional non-adherence is the inability of the patient to follow the prescribed treatment plan. Non-adherence has been associated with various adverse health outcomes such as medication resistance, adverse drug events, and impaired quality of life, leading to increased morbidity and mortality. The overall productivity loss, increased healthcare utilization, and increased medication waste result in a huge economic burden for healthcare systems all over the world. Globally, estimations of health related expenditures that could be avoided by improved adherence range from U$172 billion to U$371 billion. This problem also affects European countries including Switzerland. Effective adherence-enhancing interventions were suggested to have a far greater impact on the health of the population than any improvement in specific medical treatment and the costs generated through increased medication use and adherence-enhancing intervention programs are suggested to outweigh the expenses. Manifold interventions have been investigated to enhance adherence, though the evidence remains scarce and the effect on adherence and economic, clinical and humanistic outcomes moderate. Persistent criticism concerns the poor methodological quality, the large heterogeneity of the results, the missing of long-term outcomes, the small size of the study populations and the short study durations of the studies investigating adherence-enhancing interventions. Most promising interventions contained behavioral and repetitive elements and were usually complex. However, complex interventions are doubted to be implementable in daily clinical practice.

Dose-dispensing aids are plastic boxes containing a number of compartments filled with solid, oral medication for specific dosing times, which have been widely distributed to primary care patients to support medication self-management, i.e., the independent correct and safe administration of medication. They can be easily implemented in daily practice and their use is simple and cheap. Various authors have suggested dose-dispensing aids to enhance adherence in unintentionally non-adherent patients with polypharmacy by optimizing medication self-management. Previous reviews attributed a moderate effect of dose-dispensing aids in improving adherence and clinical outcomes, but declared the evidence insufficient to state firm conclusions. Multidrug punch cards constitute a special kind of dose-dispensing aids consisting of disposable frame cards with plastic compartments, sealed with a foil backing and typically providing 28 compartments for all oral solid medications of a patient according to a prescribed dosing regimen. In Switzerland, community pharmacies fill and distribute multidrug punch cards with the support of a specific software. Dose-dispensing service (i.e., the repackaging of solid oral medication by a health-care provider) is reimbursed by the health insurances with CHF 21.60 per week, if the patient has a prescription for over three different medications per week and for a dose-dispensing aid.

Adherence measures encompass subjective methods, such as patient self-report, and objective methods, such as pill count and electronic measurement. Measurement of adherence to polypharmacy has long been difficult due to several limitations. For example, the most commonly used electronic adherence measurement method, the Medication Event Monitoring System (MEMS®), can only package and monitor one single medication. With the availability of POlypharmacy Electronic Monitoring System (POEMS), the situation changed: POEMS is an adhesive polymer film with printed electric circuitries and a RFID chip collecting real time data, which can be flexibly adjusted to fit the back of a multidrug punch card. Affixed like this, POEMS records date, time and location of the medication removal of a whole therapy regimen and thus is able to electronically monitor adherence to polypharmacy.

The goal of this thesis was to investigate the effect of the multidrug punch card use on adherence and patient-relevant outcomes in primary care. We approached this goal through the mapping of the existing evidence on dose-dispensing aids, exploring the status quo of community pharmacy practice and multidrug punch card use by primary care patients, and by developing a randomized controlled trial testing the intervention of electronic multidrug punch card use and feedback on electronic dosing histories.

PROJECT A1 was designated to outline the evidence of dose-dispensing aids in adherence-enhancing interventions and to identify research gaps. For this purpose, we chose the methodology of evidence

mapping, including all prospective controlled trials with an intervention using dose-dispensing aids for patients independently administering medication, and reporting adherence or economic, clinical, or humanistic outcomes. Ten randomized controlled trials, nineteen controlled clinical trials, and one cohort study were included in the analysis. Overall, dose-dispensing aids had a positive but moderate effect, significantly improving adherence in 17 (57%) and clinical outcomes in 10 (33%) studies. The methodological quality was strong in five studies and two studies provided complete information of intervention elements, which limited the evidence and the replicability in clinical practice. Evidence gaps concerned economic and humanistic outcomes, safety issues, long-term, disease-unspecific, and generalizable clinical outcomes, and clinical effects on multimorbid populations with polypharmacy. These results provided a rationale for our research.

In the next step of the thesis, PROJECT B1, we explored the daily practice of community pharmacies in the nature and extent of adherence counseling. One master student in Pharmacy observed patient contacts at 20 community pharmacies and manually recorded counseling on a checklist. At the end of the observation, pharmacists were interviewed on triggers, topics, and barriers of adherence counseling. During the 1'476 observed patient contacts including the dispensing of more than one medications, counseling was provided to 799 (54.1%) patients, predominantly about administration, dose, and effect. Adherence counseling was provided to only 99 (6.7%) patients and mainly by pharmacists. However, all except one of 33 pharmacists stated to approach patients actively for adherence counseling. This discrepancy could be explained by the discordant definition of adherence counseling: while pharmacists mostly named implicit topics (e.g., administration, dose), our definition was more explicit (e.g. direct addressing of adherence, providing adherence support). The pharmacists stated structural (e.g., lack of education, rejection by patients) and procedural (e.g., time constraints, a lack of privacy area) barriers to adherence counseling indicating an implementation problem of research into daily practice.

The following evaluation of the status quo concerned the multidrug punch card production and distribution in the community pharmacy and their use by primary care patients. In PROJECT B2, we mailed a survey to all 51 community pharmacies providing multidrug punch cards of the most common brand in Switzerland. At a response rate of 76%, pharmacies reported to provide 1'869 patients with multidrug punch cards, predominantly nursing home patients (1'402, 75%) and in 14% of the cases primary care patients. Thirty (75%) pharmacies recommended multidrug punch cards actively to primary care patients with a success rate of 31%. Triggers for recommendation encompassed polypharmacy, suspected non-adherence, increased age, inability of medication self-management, and hospital discharge. The dose-dispensing service fitted well in the community pharmacies' daily practice, being cost-covering and acquiring additional value. Pharmacists estimated an adherence rate

of 93% for their primary care patients using the multidrug punch card, and assumed them to be satisfied with the device.

We confirmed this view by a mixed methods study with primary care patients using multidrug punch cards in daily life in PROJECT B3. We combined quantitative and qualitative interviews in an explanatory way to investigate the acceptability, ease of use, preferences, and impact on adherence. Twenty-one community pharmacies in the region of north-western Switzerland recruited primary care patients using multidrug punch cards from a total of 149 patients, of which 22 and 11 patients participated in the quantitative (per telephone) and in the qualitative interviews (face-to-face), respectively. We were able to describe the characteristics of an independent primary care patient accepting to use multidrug punch cards as age over 70 years; low education grade; being retired; living alone; preference for tidiness, rituals, and daily routines; inability or reluctance to leave home; and motivation to lead a healthy life. All 33 patients considered adherence as very important and reported a median score of 10 on a visual analog scale ranging from 0 (= no intake) to 10 (= perfect adherence). Emerging key variables for adherent behavior were personal experience (i.e. either negative clinical experience in case of non-adherence or clinical benefits in case of adherence) and trust in health-care professionals. The absence of package inserts and handling difficulties, reported as risk of dose-dispensing aid use for impaired medication safety, were not perceived as problems by the patients in our study. Rather, our results support the assumption that unintentionally non-adherent patients might substantially benefit from the packaging of their polypharmacy into multidrug punch cards.

Finally, including the experiences and results of the preceding projects, we developed a randomized controlled trial to investigate the effectiveness of electronic multidrug punch cards in connection with feedback on electronic dosing histories to improve adherence and patient-relevant outcomes in a primary care population of various ages and different clinical conditions after hospital discharge. In PROJECT C1, we conducted a pilot study to assess and optimize the feasibility, efficiency, and quality of the study structures and procedures.

At the University Hospital Basel, we screened the patient records of an internal medicine's ward for eligible patients. Recruitment and assessment of baseline parameters were performed at bedside. All patients received medication counseling and an individualized medication plan prior to hospital discharge. Patients randomized to the intervention group received their oral solid medication packaged in an electronic multidrug punch card and regular feedback on their electronic dosing histories by a study pharmacist at the study pharmacy. Patients allocated to the control group received their medication from the community pharmacy of their choice. Follow-up visits were carried out at the study pharmacy at three, six, and twelve months after discharge. Primary outcomes were time to

hospital readmission and major adjustment of drug therapy and adherence calculated from pharmacy claims (medication possession ratio). Secondary outcomes were adherence according to patient self-report and POlypharmacy Electronic Monitoring System data, quality of life, and patient satisfaction. The evaluation of the pilot study was developed according to the 'Planning-Evaluation-Cycle 20' and was based on Donabedian's evaluation model of quality of care.

Within nine months of the pilot study, we recruited ten patients and only one patient accepted the use of multidrug punch cards. No patient was readmitted to hospital during the follow-up period. One major adjustment of drug therapy occurred in the intervention patient, but could not be explained with an adherence problem. According to POEMS data and self-reported adherence, he was perfectly adherent. The control patients showed maximal adherence rates as well, by patient self-report and medication possession ratio. Quality of life remained relatively stable at an average value compared to a general population in both treatment groups. In the control group, all patients reported to use a system or strategy to manage their polypharmacy, with which they were very satisfied. However, one younger patient integrated fully in work life and dealing with polypharmacy for the first time after index hospitalization was interested in adopting a multidrug punch card after the completion of the study.

The results of the intervention patient were further explored in PROJECT C2. This was to our knowledge the first case of long-term adherence monitoring of polypharmacy integrated in a pharmaceutical care service. The patient maintained perfect adherence according to all adherence measures and was clinically stable through the whole study period. The stability in quality of life and the gain of confidence with medication self-management might have been the result of successful disease management by the intervention. The patient was very satisfied with the multidrug punch card use, wishing to continue the service after completion of the study. No harms or adverse event could be associated with the intervention.

The evaluation of the pilot study showed that the study design was feasible, but lacked efficiency and quality. The university hospital and the study pharmacy provided excellent infrastructure and working atmosphere. Patient satisfaction with the study procedures was high. Major inadequate points were the high exclusion and rejection rates, the inadequate time management, the vague task assignment within the study team, and the poor communication within the study team. The internal medicines' ward turned out not to accommodate the target population for multidrug punch card service, since recruitment of an adequate number of patients predominantly failed because of the characteristics and preferences of the eligible patients. The poor quality of the study in the hospital phase was basically technical in nature and could be adjusted easily. In the primary care phase, the poor

communication with the community pharmacies, the induction of a potential bias by medication counseling at the follow-up assessments, and technical difficulties with the POEMS diminished the study quality. The evaluation of the pilot study pointed out important barriers for successful study performance and hence proved beneficial.

In conclusion, this thesis showed the following:

- Research gaps and poor methodological and reporting quality precluded a firm conclusion about the evidence of dose-dispensing aids in improving adherence and economic, clinical, and humanistic outcomes, and provided a rationale for future research.
- Structural and procedural barriers (e.g. lack of public acknowledgement of the pharmacists' competences, time mismanagement) hinder pharmacists to adequately deliver explicit adherence counseling.
- Multidrug punch card service is well integrated in daily practice of Swiss community pharmacies, however, its provision for primary care patients is limited.
- A specific group of primary care patients reports to benefit from multidrug punch card use, i.e., patients of the age of over 70 years, low education grade, living alone, appreciation for tidiness and daily routines, trust in health-care professionals, fidelity to pharmacy, and motivation for a healthy lifestyle and medication adherence. Emerging key variables for accepting multidrug punch card use and for perfect medication adherence were trust in health-care professionals and the patient's experiences.
- A pilot study investigating the effectiveness of electronic multidrug punch cards in primary care patients failed in recruitment of an adequate number of patients because of poor efficiency and quality of the study structures and procedures.
- Six patients discharged from the internal medicine's ward without any further intervention than a discharge counseling maintained perfect adherence, stability of clinical condition, and quality of life over one year.
- One patient receiving the intervention of the electronic multidrug punch card combined with recurrent feedback on his adherence behavior showed maintenance of perfect adherence, stability of clinical condition and quality of life, gain in confidence of medication self-management, and satisfaction with the device. No harms could be associated with the use of electronic multidrug punch cards.
- Prototypes of the POlypharmacy Electronic Monitoring System (POEMS) were easy to apply and well accepted by the intervention patient. However, drawbacks in the technology's functionality

and specificity weakened the quality of our results and have to be addressed in future development.

- Our recommendations for practice are:
  - To overcome structural and procedural barriers for patient-centered counseling e.g., by promotion of the pharmacist's role by public information and advertisement, intensification of clinical pharmacy education, and reorganization of pharmacy accommodations and staffing.
  - To actively address medication self-management and non-adherence at patient contacts and to include the patient's experiences, believes, and habits into counseling, respecting the patient's preferences and life-style.
  - To establish trust of the patient to the health-care provider and to promote the patient's active involvement in decision making.
  - To actively recommend multidrug punch cards to primary care patients with polypharmacy with regard to their capabilities, needs, and necessities, emphasizing the advantages of facilitation of medication self-management and increased medication safety.
  - To ensure continuous care by embedding dose-dispensing service in a pharmaceutical care framework.
  - To tailor interventions for non-adherent patients by e.g. *a. screening* of adherence pattern; *b. selection* of an appropriate intervention; and *c. monitoring* of outcomes.
  - To introduce the POEMS technologies to clinical practice for, e.g. diagnosis or pharmaco-vigilance questions.
- Our recommendations for future research encompass:
  - To identify further patient groups who accept multidrug punch cards and benefit from their use.
  - To develop guidelines for the delivery of tailored adherence support.
  - To reconsider the exclusion of adherent patients for clinical trials investigating the effect of an adherence-enhancing intervention.
  - A subsequent randomized controlled study on the effectiveness of multidrug punch cards could be optimized by
    - A well-instructed, adequately sized study team
    - Sufficient communication between all collaborators
    - Integration into clinical practice (e.g. physicians assisting recruitment at the ward and community pharmacies assisting in delivering the intervention)
    - Availability of sufficient, functioning electronic measurement material

- Locations enabling the recruitment of an adequate number of the target population (e.g., a rehabilitation center, community pharmacies).

- To develop studies focusing on adherence-enhancing strategies with larger, multimorbid populations, measuring patient-relevant outcomes, and use of standardized adherence measures to enable comparison and generalization.

General introduction

Polypharmacy and medication self-management

"What constitutes 'too many' drugs is a prescribing dilemma, and choosing the best interventions aimed at ensuring appropriate polypharmacy is a challenge for all prescribers and health care organizations but particularly in general practice." [1]

Polypharmacy constitutes both, a blessing and a curse for the well-being of our society. Accordingly, it can be categorized into *appropriate polypharmacy* and *problematic polypharmacy* [1]. The term *polypharmacy* refers to the 'concurrent use of multiple medication items by one individual' [1] and is defined either by the number of medications prescribed to an individual patient (usually over 5 or over 10 different medications), or by appropriateness of prescribing [1-3].

The beneficial effect of polypharmacy is acknowledged through the evidence of successful treatment of several clinical conditions, e.g., hypertension, diabetes mellitus, and human immunodeficiency virus (HIV) infection. The co-existence of multiple conditions makes it even indispensable. Appropriate polypharmacy occurs, when medication is prescribed according to best evidence and when its use has been optimized. Problematic polypharmacy occurs when the prescription is inappropriate and the benefit is outbalanced by risks. Polypharmacy has been associated with a substantial number of adverse outcomes including prescribing errors, high-risk prescribing, medication errors, adverse drug reactions, drug-drug interactions, non-adherence, increased geriatric syndromes (falls, unhealthy nutrition, urinary incontinence etc.), increased use of health care services, increased hospitalization rates, and increased morbidity and mortality [4-11]. A Dutch study found that among 5.6% of patients experiencing medication related hospitalization, non-adherence and polypharmacy belonged to the major determinants of preventable hospital admissions [12], whereas both factors are known to be strongly interrelated [13,14]. Incorporating the patient's perspective reveals the *pill burden*, which strongly affects their quality of life, by interfering with daily activities and social life [15-17].

Today, we find ourselves in a society of increasing age and multimorbidity, which are driving factors for polypharmacy. In Switzerland, the proportion of the over 65 year-old population increased from 5.8% in 1900 to 17.4% in 2012 (**Figure 1**) [18] and the overall proportion of multimorbid patients was 14.5% in 2012. The prevalence of multimorbidity rises with age (CH: 60-69 years: 25.8%, 70-79 years: 33.6; 80-89 years: 37.7%) [19] and occurs in most patients with a long-term condition [20]. However, the absolute number of multimorbid patients appears to be substantially higher in younger patients under 65 years old [20], reflecting a highly multimorbid society.

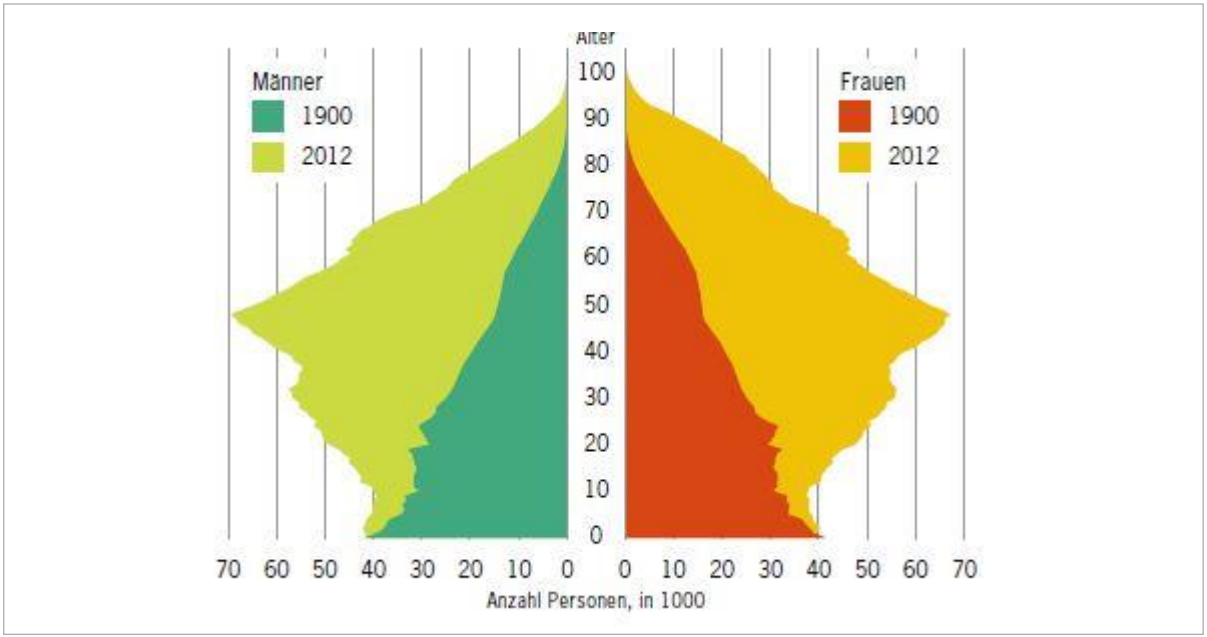

Figure 1. Demographic change from 1900 to 2012 in Switzerland according to the federal office for statistics (men: left; women: right) [18].

Due to these demographic changes, polypharmacy affects a vast proportion of the population in many countries, and is common in primary and secondary care [1,21-23]. The proportion of the Swiss primary care population over 18 years with zero, one to four, and over five different medications filled in a quarter year were 52.2%, 31.1%, and 16.7%, respectively [24]. In the age group of over 65 years, this distribution altered considerably with 21.5% filling zero, 37.4% filling one to four, and 41.2% filling over five medications [24]. Twenty-one percent of these medications were determined inappropriate according to the PRISCUS list [25] and the Beers criteria [26]. In a European comparison of the prevalence of polypharmacy in secondary care, Switzerland scored highest with a proportion of 21% elderly patients taking ten or more prescribed medications at hospital admission [23]. Further, the number of medications usually again increases from hospital admission to discharge [27,28] with the consequences of confusion and non-adherence in discharged patients [29].

Society more and more depends on the autonomous living of old and multimorbid patients and health policy increasingly encourages a development towards early hospital discharges in many countries, including Switzerland [1,30]. This corresponds to the preferences of elderly patients with polypharmacy to maintain control and independency [31,32]. Therefore, the primary care sector is especially charged, relying on the appropriate medication self-management of the patients. In this thesis, *medication self-management* refers to the cognitive and physical ability of the patient to self-administrate medication according to a prescribed regimen [31,33]. Studies showed that medication self-management was

remarkably impaired in older patients, leading to medication errors and thereby constituting problematic polypharmacy [34,35].

Medicines optimization is an approach to ensure appropriate polypharmacy, setting medication use into a broad field from medication selection until the actual use [1]. Evidence-based decision-making, active patient engagement, and professional collaboration are central elements of this approach and coincide with the concept of patient-centered care. Under these aspects, strategies for optimizing polypharmacy can be delivered by the community pharmacy and may comprise the assessment of the patient's expectations and resources, the careful review of medications for appropriateness, the reduction of the number of inappropriately prescribed medication, as well as the support of the patient's medication self-management [36]. A comprehensive World Health Organization (WHO) report on adherence to long-term therapies asserts that there is ' […] strong evidence that suggests that self-management programs offered to patients with chronic diseases improve health status and reduce utilization and costs' [37].

This thesis aimed at the optimization of medication use to reach appropriate polypharmacy through effective support of the patient's medication self-management by pharmaceutical care services.

Pharmaceutical care

Medication management services are understood as the multidisciplinary support of the patient's medication use by in ensuring its appropriateness, effectiveness, safety, and the ability and willingness of the patient to execute the medication plan as intended [38]. Pharmaceutical care constitutes the professional practice of the pharmacist delivering patient-centered medication management services and thereby assuming responsibility for clinical decision-making. The current definition published by the Pharmaceutical Care Network Europe is:

"Pharmaceutical care is the pharmacist's contribution to the care of individuals in order to optimize medicines use and improve health outcomes." [39]

The activities of pharmaceutical care involve the detection, resolution, and monitoring of actual and potential drug-related problems (**Figure 2**). A *drug related problem* is 'an event or circumstance involving drug treatment that actually or potentially interferes with the patient's experiencing an optimum outcome of medical care' [40]. This includes non-adherence, which can be evaluated at the community pharmacy during medication review, out of the refill history, in direct conversation with the patient or by monitoring of clinical outcome parameters, e.g., blood pressure, LDL-cholesterol. Part of the goal of pharmaceutical care is an optimal medication adherence, and the intervention to support it falls into the professional responsibility of the pharmacist.

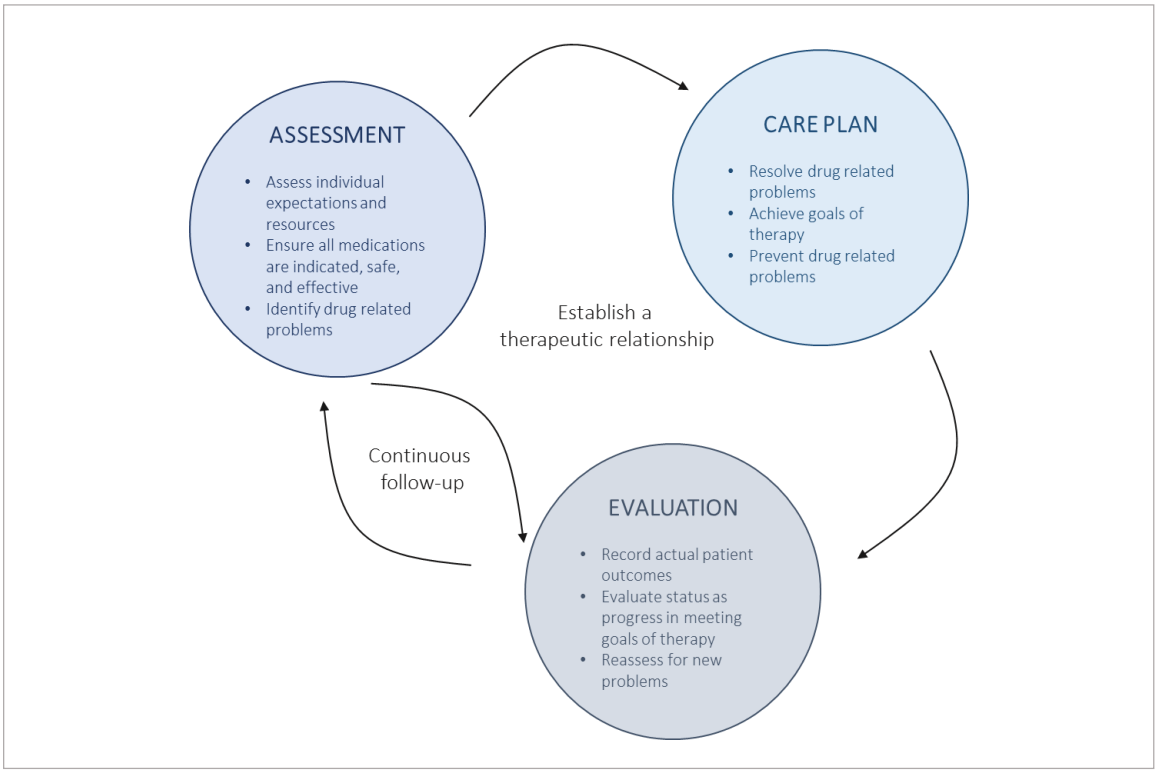

Figure 2. The pharmaceutical care process adapted from Cipolle et al. [38] and Hersberger et al. [41].

In 2011, the WHO and the Fédération Internationale Pharmaceutique (FIP) updated a joint publication on guidelines for Good Pharmaceutical Practice (GPP) specifically requiring the pharmacist to take an active role in patient-centered care and defining the core of GPP as 'to help patients to make the best use of their medicines' [42]. The FIP further highlighted the important role of the pharmacist in assessing, addressing and improving medication adherence [43]. Pharmaceutical care services delivered by community pharmacies were shown to significantly improve adherence [44-50]. Recent Cochrane reviews even confirmed the pharmacists' cognitive services to contribute beneficially to safe an effective medication use [51,52].

Medication adherence

The rational use of medication includes appropriate prescribing AND full adherence to prescriptions [37]. Various models have tried to describe the patients' behavior of medication taking, e.g., the Health Belief Model [53] , the Theory of Planned Behavior [54], and the Transtheoretical Model of behavior change [55]. The WHO defines adherence as follows:

Adherence is "the extent to which a person's behavior – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider." [37]

This definition embraces the whole process of therapeutic actions, from the seeking of medical advice to the actual intake of medication. An important point within this definition is the term *agreed* because it highlights the active participation of the patient in the prescribing process. The concept of *adherence* awards the patient's own will and capability to initiate and implement a prescribed medication plan. In fact, it is now widely acknowledged that a therapeutic intervention will only be successful if the patient is involved in the clinical decision making [37].

This definition also coincides with optimization of medicine taking and the model of patient-centered care discussed above, where a partnership between the patient and the health care professional draws on the capabilities of both to assess barriers, find solutions and plan follow-up on adherence. Despite adherence being the subject of a vast number of publications, this patient behavior is still poorly understood. The focus of this thesis lies in adding a contribution to the knowledge of medication adherence of primary care patients to polypharmacy.

Factors and models of adherence

"Despite evidence to the contrary, there continues to be a tendency to focus on patient-related factors as the causes of problems with adherence, to the relative neglect of provider and health system-related determinants." [37]

Adherence is a complex behavior requiring many of the patient's resources, i.e. physical and cognitive ability, organizational skills, mobility etc., but also is dependent on four further dimensions. These dimensions group social/economic, health system / healthcare team, condition related, and therapy related factors (**Figure 3**). Frequently the patient related factors are made responsible for non-adherent behavior, which accounts only insufficiently for the overall problem. A comprehensive review of reviews compiled 771 factors and grouped them according to their effect on adherence, i.e. beneficial, deteriorative, and neutral [13]. Interplay of all sets of factors again lead to multiple interactions and makes adherence an even more complex multidimensional phenomenon. We can assume that the factors negatively affecting adherence represent targets for adherence-enhancing interventions. For example, if a patient is non-adherent because she/he forgets the medication intake, a memory support may be provided. Due to the many factors that can be influenced it seems obvious that adherence is a challenge for every patient and therefore merits special attention in consultations and during dispensing of medication at the community pharmacy.

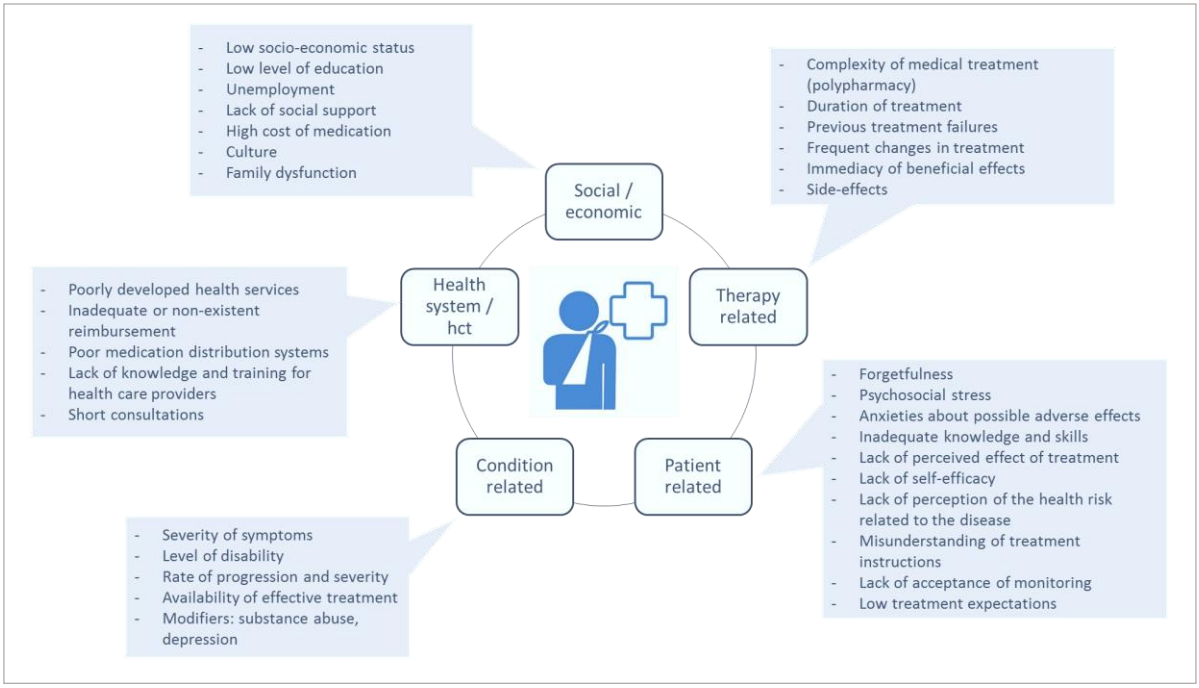

Figure 3. The five dimensions influencing adherence according to the World Health Organization report [37] and examples of factors negatively associated with adherence. Hct, healthcare team.

Based on these factors, various models were developed to describe the patients' behavior of medication taking. In the Health Belief Model [53], the patient weighs her/his believes about necessity against concerns, resulting in a skeptical, ambivalent, indifferent, or accepting attitude towards medication taking. The Theory of Planned Behavior [54] proposes behavior to be guided by attitude, subjective norms, perceived behavioral control, and behavioral intention, were the latter is the immediate precursor of the actual behavior. In the model of Interpersonal Behavior [56], apart from cognitive, social, and personal factors, habits take a dominant role in affecting behavior change. In fact, habit has been described as a major determinant influencing adherence [57,58]. The Transtheoretical Model of behavior change [55] describes the different stages that a patient has to pass through to reach effective behavior change, namely precontemplation, contemplation, preparation, action, and maintenance. Lately, Marcum et al. proposed a conceptual model of the effect of polypharmacy on adherence [14]. In this model, polypharmacy can directly affect adherence, by the greater number of medications that can be missed on a daily basis and the close relation to regimen complexity, which has been associated with poor adherence. The effect of polypharmacy can also be mediated by various patient, health-system, or provider factors to lead to non-adherence [14].

Despite of efforts made to group patients into 'adherent' and 'non-adherent', such prototype patients do not exist. There are rather several patterns of non-adherence, which might make sense (e.g., reducing the dose at experience of toxicity) or not. Types of non-adherent behaviors include, e.g.,

stockpiling, drug holiday, white coat adherence, taking the wrong medication, overdosing, underdosing, erratic dosing, wrong dosing frequency, and wrong duration of treatment. These timely patterns can be revealed by electronic adherence monitoring [59].

Adherence taxonomy

"[A transparent taxonomy] should provide researchers and clinicians with a common language for describing different experimental investigations." [60]

Compliance – Adherence –Concordance. *Compliance* describes the passive following of the physician's order. It indicates that the patient did not actively take part in the decision process about the treatment. In contrary, the term *adherence* implies the patient's active participation in and agreement with the treatment. However, adherence and compliance are frequently used interchangeably, also in this thesis [61]. *Concordance* describes the agreement of the patient and physician on the clinical condition, the therapy goals and the choice of therapy [62].

Intentional non-adherence – unintentional non-adherence. These terms describe the behavior of the patient and relate to the reason of non-adherence. *Intentional non-adherence* applies when the patient willingly alternates the prescribed treatment without feedback to the physician. This is an active decision, occurring when patients, e.g., do not trust health-care professionals, fear adverse reactions or feel stigmatized by medication taking. In contrary, *unintentional non-adherence* is characterized through the patient's prevention of medication intake against his/her actual intent, typically because of physical or cognitive barriers to medication self-management, but also because of language barriers, inability to pay for the treatment or not recalling treatment instructions. It is a passive process and the patient's ability to memorize and polypharmacy are related to it. To distinguish these two behaviors at the assessment of non-adherence might be crucial for picking the right intervention for a patient. For example, unintentionally non-adherent patient may benefit from dose-dispensing aids, whereas intentionally non-adherent patients will persist with this kind of adherence support [33,62,63].

Primary non-adherence – secondary non-adherence. These terms distinguish the behavior of medication filling and the actual intake, where *primary non-adherence* constitutes the lack of filling a first prescription and *secondary non-adherence* represents the non-execution of the treatment plan after filling the prescription [64].

Initiation – Implementation – Discontinuation – Persistence. In order to describe the secondary adherence process, the Ascertaining Barriers to Compliance (ABC) project team defined adherence to medication as a process containing several steps: *initiation* is the intake of the first dose of a prescribed treatment; *implementation* is the extent of the patient's dosing corresponding to the prescribed

treatment; *discontinuation* is the stop of intake. The time period between initiation and discontinuation is defined as *persistence*. Whereas adherence relates to the intensity of medication intake, persistence describes the duration of intake. Persistence and implementation are continuous variables, while initiations and discontinuation are two discontinuous actions (**Figure 4**) [60].

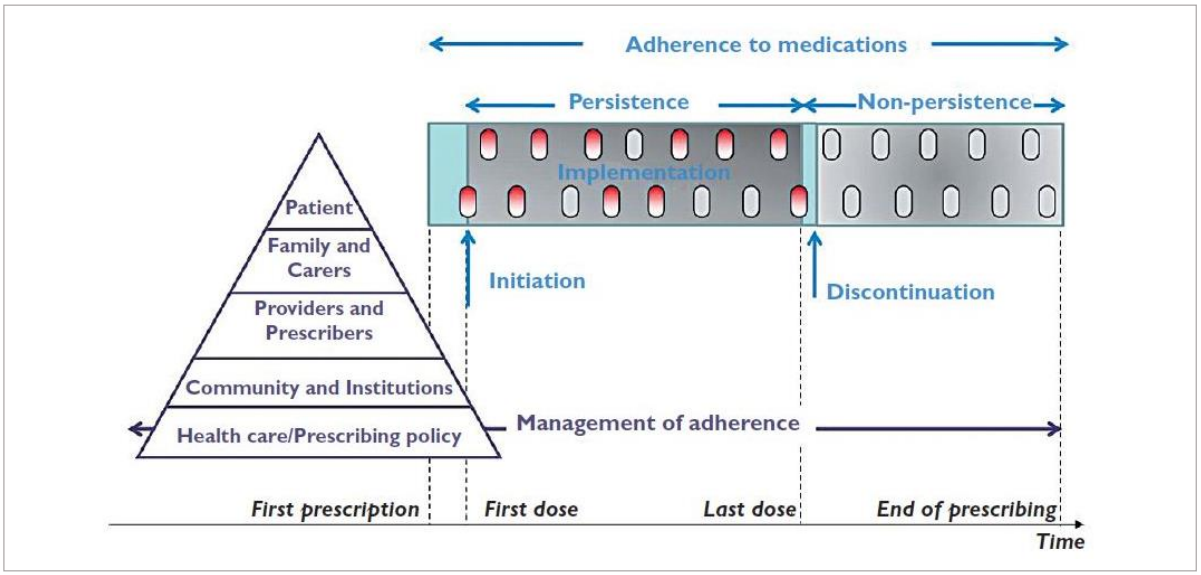

Figure 4. Illustration of terminology of the single steps of the adherence process according to the Ascertaining Barriers to Compliance (ABC) project team [60]. Light blue: process of adherence to medication; dark blue: process of management of adherence.

Taking adherence – timing adherence. To further characterize the patients intake behavior, these terms express the proportion of the medication taken as prescribed per day and the proportion of medication taken at the right time, i.e. prescribed time per day [65].

In order to understand, report, and describe adherence, the terms defined above enable to convert the abstract health related behavior 'medication adherence' into a measureable entity. Several measurement methods have been developed to quantify this complex behavior.

Adherence Measurement

"In order to compare and reproduce medication adherence results, researchers and healthcare providers have to consider, firstly, using an internationally accepted operational, standardized definition of medication adherence; secondly, accurately describing medication adherence methods used; and thirdly ensuring the quality, validity and reliability of the methods and data analysis employed." [66]

Adherence measurement methods

Direct and indirect methods constitute two groups of adherence measurement methods (**Table 1**). Thereon, they can further be divided into subjective and objective methods. Whereas objective measurement methods are usually deemed more reliable, subjective methods allow deeper insight in the patients' behavior with the possibility to ascertain the reasons for it.

Table 1. Direct and indirect methods of adherence measurement, adapted from Osterberg et al. [65].

Indirect	**Direct**
Self-report	Directly observed therapy
Clinical response / physical marker	Therapeutic drug monitoring
Medication refill frequency	Biomarker monitoring
Pill count	
Electronic medication monitoring	

Patient self-report is a subjective measurement method and is applied by interviews, questionnaires, and diaries. Many different instruments exist for different clinical conditions, with different scales, and for different patient populations. Valid instruments are, e.g., the Morisky Medication Adherence Scale 8 [67], the Believes about Medicines Questionnaire [53], and the Adherence Estimator [68]. The advantages of the self-report measurement methods, namely their practicability, flexibility in use, low cost, low time expenditure, have made them a common tool used in clinical and research settings. They can assess social, situational and behavioral aspects and allow the differentiation between intentional and unintentional adherence. Patient self-report, however, has been criticized to overestimate adherence [66].

Objective adherence measurement methods can be viewed as a camera capturing momentous pictures with different zoom levels. For example, pharmacy refill and prescription claims data would represent a wide-angle lens, capturing large community samples, thereby representing the community. Their use is non-invasive, of strong statistical power, economic and show the real-world picture apart from clinical trials. Data are comparable to electronically measured adherence. However, pharmacy refill and prescription claims are afflicted with a certain level of blur, because

implementation and discontinuation cannot be observed. Factors limiting the validity are patients receiving medication samples from the physician, stock-piling their medication at home without using them, collecting their medication at different pharmacies, or claims registered at different health insurance databases [66].

If we zoom further in, pill count gives information on *if* and *how much* the patients took from medication they (re-)filled at the pharmacy. Pill count is easy to perform in any setting, inexpensive and therefore a globally used measurement method. The opponents argue that it provides no information on the actual taking, that the patients have to bring back the pill containers at each visit, that there is a risk of the patients discarding the medication before a visit, and that does not represent an accurate measure for detecting poor adherers, i.e., patient persisting but not implementing correctly the treatment plan [66].

The highest resolution to date is provided by electronic monitoring. Electronic monitoring was first reported in 1984 [69] and records *when* the medication was taken additionally to the amount of taken medication. A continual real time monitoring is feasible, recording treatment initiation, implementation, taking adherence, timing adherence, discontinuation, and persistence. Through this method, adherence patters like drug holidays and white coat adherence can be uncovered, and conclusions can be drawn about the clinical outcomes of the treatment [59]. Nevertheless, electronic medication monitoring has its limits. The high cost of the devices precludes their widespread use. Further, despite capturing intake patterns, it still does not capture the actual swallowing of the pill. The patients might take a pill out of the device at the right time and then discard it or take pocket doses and so produce false-negative registrations. Not all patients are comfortable with electronic monitoring devices and it does not suit all galenic formulations [66]. Electronic monitoring and pill count were concluded to complement each other [70,71].

Direct adherence measurement methods are usually costly, invasive and obtrusive and are not used routinely in clinical practice or research. They are not relevant for this thesis.

In summary, every method has its strengths and limits and there has not been agreement on a 'gold standard'. Despite the progress in the field of adherence measurement, the patient's action after removal of the medication from the container remains hidden and the number is only a surrogate for the patient's actual behavior. Whenever adherence is to be measured, the setting, resources, goals of the measurement and the accuracy requirement have to be considered for the choice of the appropriate method. The current state-of-art of adherence measurement is concordantly considered as the combining two or more methods, to benefit from all their strengths [37,65,66].

Electronic measurement devices

The Medication Event Monitoring System (MEMS®; AARDEX Group Ltd., Sion, Switzerland) is the most commonly used electronic measurement device for oral solid dosage forms (**Figure 5**). The medication is placed in a pill bottle with a microprocessor chip embedded in its cap. At every opening of the bottle, the chip records time and duration of the 'medication taking event'. The major drawback of MEMS® is its limitation to the monitoring of one lead drug, and thus it is not suitable to monitor polypharmacy. Further, it remains unknown if and how many pills are removed with each opening. The high costs of these containers do not allow their use in routine clinical practice.

The POlypharmacy Electronic Monitoring System (POEMS; Confrérie Clinique S.A., Lausanne, Switzerland) consists of an adhesive polymer film with printed electric circuitries. It can be fixed on the back of a regular blister pack to record date, time and location of medication removal. Transmission to an electronic database yields numeric and visual data (**Figure 6**). Acceptance and internal validity were reported to be similar and data quality to be higher compared to MEMS® [72]. The advantage of POEMS is the flexible adjustment to multidrug punch cards (i.e. cards with several plastic compartments to pack oral solid medication according to dosing times) (**Figure 5**). This allows the electronic measurement of adherence to a whole medication regimen and thereby restores the allocation of single dose-units to a specific signal. Knowing the adherence pattern of the entire medication regimen provides the possibility to explain unreached clinical outcome, drug–drug interactions, and drug resistance.

Figure 5. Medication Event Monitoring System (MEMS®, left) [73]; multidrug punch card, front (middle); multidrug punch card, back with affixed POlypharmacy Electronic Monitoring System (POEMS, right).

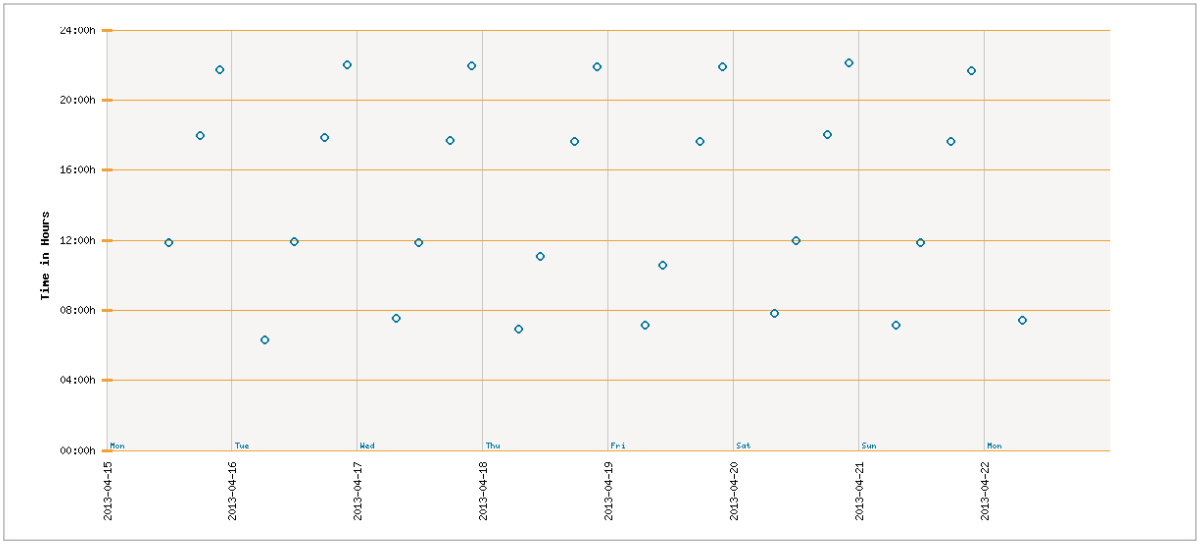

Figure 6. Example of output graph of the POlypharmacy Electronic Monitoring System (POEMS) measuring adherence to a four-times daily regimen over one week.

POEMS was used so far in a study on primary care patients with polypharmacy over one week to rule out adherence as a determinant for drug resistance to aspirin and clopidogrel [74]. The technology could demonstrate that a smaller intake time variability of the lipid lowering drug was significantly associated with better levels of LDL-cholesterol [75]. In a case study, it discovered a distorted adherence pattern which allowed the conduction and monitoring of a personalized intervention [76].

Several other electronic measurement devices exist, most of them are connected with automatic dose dispensing, they come with or without acoustic alarm, and apply to different dosage forms e.g., DO-Pill SecuR™, Electronic Medication Management Assistant (EMMA®), Medido® Pill Pouch Dispenser, Wisepill™, Neb Nebulizer™, eye-drop monitor, IDAS®, and Helping Hand® [66,77].

Adherence measures

Several measures have been proposed to calculate and present adherence out of measured data. The two most commonly used measures are the *medication possession ratio* (MPR) and the *proportion of days covered* (PDC). The MPR describes the proportion of supply to fulfil a treatment plan over a distinct period of time and is calculated as the total days' supply of medication dispensed divided by duration of prescribed therapy in the period of interest. The PDC describes the proportion of days on which the medication is available for the patient divided by the total days of the analysis period. Both measures are usually ranging between 0 and 1, with 1 signifying perfect adherence. Although thresholds separating *good adherers* from *bad adherers* have been widely used, their validity is controversially discussed. Thresholds of 0.8-0.9 have been associated with fewer hospitalizations in schizophrenia, hypertension, diabetes mellitus and hyperlipidemia [78,79]. For HIV, adherence rates between 50-80% were associated with increased drug resistance, whereas a threshold of > 95% was

considered evident for successful viral suppression [80]. However, these values are not above doubt, and for many clinical conditions the question of how much adherence is necessary remains unanswered. An approach to this question was proposed by the concept of *forgiveness*, which sets the medication's duration of beneficial action in relation to its prescribed dosing frequency and hence describes how long the therapeutic effect will prevail in case of non-adherence [59,81].

Whereas MPR and PDC suffice the requirements of monotherapy regimens, a new method for calculating adherence to polypharmacy was introduced recently. The daily polypharmacy possession ratio (DPPR) calculates the days covered with polypharmacy day by day. First results of validation showed that various characteristics of polypharmacy, e.g., medication switching, duplication, and overlapping, which could not be included in the above named methods, could be accounted for by the DPPR [82].

Due to the many different adherence measurement methods and measure calculation methods, the congregation of studies about adherence and adherence-enhancing interventions has been difficult [83,84]. In this thesis, we used patient self-report, pharmacy refill claims, and electronic measurement methods (POEMS), and calculated adherence measures by MPR.

Dimensions and consequences of non-adherence

"Prescribed medications help to control symptoms and slow disease progression, enabling the person to maintain their health and live independently for as long as possible with an optimal quality of life." [85]

Non-adherence starts at filling a prescription: Within 15'961 patients receiving a first-time prescription, primary non-adherence was 31.3% [86]. New users had a lower filling rate (34.3%) than patients switching treatment within a pharmacologic class (11.6%) [86]. After the first filling, persistence subsequently decreases with rates varying for different conditions, e.g., with 60% for bisphosphonates, 61% for statins, 66% for angiotensin-receptor blockers, and 72% for oral antidiabetics [87] (measured by pharmacy refill claims). This is consistent to a review, which compiled electronic adherence data over 95 studies on different conditions reporting a persistence of 60% at one year [59]. Persistence rates can be associated with execution rates: the poorer the execution the lower the persistence [59,88]. Non-execution ranged around 10% in patients on antihypertensive treatment, with 42% of omissions of a single day's dose, 15% up to two days, and 43% of three or more days, defined as drug "holidays") [88]. Almost half of the patients had at least one drug holiday a year. There were particular weekdays on which dosing omissions occurred more frequently for a third of patients, mostly weekend days. Patients who took their medication in the morning executed their treatment more correctly than patients with evening or variable doses [88]. Similarly, taking adherence and timing adherence were more correct for once-daily regimens than for 2-times, 3-times, and 4-times daily regimens within rates

of 93.0%, 85.6%, 80.1%, and 84.4% for taking adherence and 76.9%, 59.3%, 35.9%, and 18.8% for timing adherence, respectively [89]. Higher time variability existed in midday and evening doses compared to morning doses and in weekend doses compared to weekday doses in patients with 100% taking adherence to polypharmacy [75].

Non-adherence occurs in all situations where medication self-administration is required, independently of medical condition, severity, and accessibility to health resources [37]. A review summarizing adherence rates for several conditions over 50 years showed mean adherence rated for HIV of 88.3%, for arthritis of 81.2%, for cancer of 79.1%, for seizures/brain disorders of 78.4%, for cardio-vascular diseases of 76.6%, and for diabetes of 67.5%, among others [90]. In phase I to III clinical trials, non-adherence results in inaccurately adjusted dosing and an underestimation of adverse reactions. Still, patients participating in clinical trials usually adhere better to treatment than in real-life [59,91]. Non-adherence represents the missing link between effective therapy and effective disease management.

Non-adherence has been associated with impaired effectiveness and safety of treatments leading to a variety of adverse health outcomes. Inability to reach treatment goals lead to drug resistance in HIV and tuberculosis [80,92]. Treatment failure has also been described in elderly patients with chronic conditions [93] and in transplantation, constituting a major risk factor for transplant rejection in the latter [94]. In statin treatment, non-adherence leads to inappropriate dose escalation [95]. Disease progression due to treatment failure leads to increased hospitalization [96] and mortality [97] in HIV. Non-adherence to antihypertensive medications constitutes an independent risk factor for stroke related hospital admissions and deaths [98]. Furthermore, evidence has accumulated that patients with cardiovascular diseases who are poorly adherent to cardio-protective therapy had a higher risk of vascular events, hospitalization and mortality [99-103]. Even in secondary prevention of myocardial infarction, these observations persisted [104]. Corresponding results could be shown for patients with diabetes mellitus type 2, and asthma [105,106]. Additionally, non-adherence was associated with adverse drug events [107,108] and was found as one of the largest determinants of hospitalization due to preventable drug related problems [12,109]. Further risks are more intense relapses, medication dependence, rebound effect, toxicity, and accidents (e.g. with antidiabetics, antieplieptics) [37].

Impaired health outcomes may be the consequence but also the cause of non-adherence. Quality of life, for example, has been reported to be influenced from two sides. On one hand regular medication intake guarantees the attenuation of first dose effects and leads to adequate symptom control in epilepsy [110], HIV [96,111,112], and chronic obstructive pulmonary disease [113]. In these cases, higher adherence led to increased quality of life. On the other hand, the high pill burden, missing flexibility in

daily life and increased adverse reactions with high adherence decreased quality of life [15,114]. Patients with diabetes mellitus type 2 experiencing low tolerability with the treatment reported low quality of life as a reason for low satisfaction and adherence [115] and several factors associated with the maintenance of adherence were identified, e.g., treatment fatigue and burnout, social support problems, and emotional and self-efficacy problems, which in the end motivated the patients for non-adherence.

Finally, due to intensified treatment, increased healthcare utilization, medication waste, and loss of productivity, substantial economic costs arise [96,116-121]. The global impact of non-adherence in 186 countries was estimated to range between U$172 and 371 billion [117]. In the United States of America, non-adherence accounts for up to U$100 billion in health care and productivity costs which constitutes approximately 10% of the total annual healthcare budget [116] and the English National Health Service (NHS England) reported losses of £900 per year because of non-adherence within five clinical conditions [122]. Across five European countries, increasing the percentage of patients being adherent to antihypertensive treatment to 70% was estimated to lead to a reduction of cardiovascular related healthcare costs by €332 million [123]. In Switzerland, antihypertensive treatment costs were disproportionately high because of non-adherence [124]. In studies on diabetes mellitus type 2 and HIV patients, adherence was shown to reduce costs due to decreased healthcare utilization [96,118] and hospitalization rates [119]. These savings outweigh the costs generated through increased medication use and adherence-enhancing intervention programs [125].

The collective burden of non-adherence allows the assumption that an effective adherence-enhancing intervention 'may have a far greater impact on the health of the population than any improvement in specific medical treatment' [126].

Adherence-enhancing interventions

"Current methods of improving medication adherence for chronic health problems are mostly complex, labor-intensive, and not predictably effective". [127]

Manifold interventions have been explored, specifically for single clinical conditions, e.g., HIV, depression, diabetes mellitus, and hypertension [50,128-131] or focusing on the delivery of the intervention by specific health-care professionals [51,84,128,129].

Kripalani et al. [132] proposed a taxonomy for types of adherence interventions in a literature review investigating interventions for patients on chronic conditions, including:

- Informational: Education and instruction about disease and/or medication, e.g., oral, telephone, written, or audiovisual education; didactic group class; instructional material.

- Behavioral: Strategies to influence behavior, e.g., skill building by a health care professional; pillboxes, calendars, a change in packaging, other reminders; simplifying/tailoring the medication regimen; rewards and reinforcement.
- Social/family: Social support strategies, e.g., support groups and family counseling.
- Combined: Combination of the groups described above.

The review included 37 studies on 13 informational, 10 behavioral, and 15 combined interventions. A significant improvement of at least one adherence measure was reported in 20, and of corresponding clinical outcomes in 11 studies. Successful interventions were behavioral, with or without combined elements (simplifying medication regimen, feedback and monitoring), contained multiple of the same elements delivered over time, or were combined including elements from different types.

An extensive Cochrane review [126] analyzed 78 trials on the effectiveness of adherence-enhancing interventions. The review presented a vast variety of applied interventions with 19 categories. Only 36 of 87 reported interventions in long-term treatments significantly improved adherence and 26 also had an effect on improving clinical outcomes. Combined complex interventions were mostly successful comprising combinations of comprehensive patient instructions and counseling, reminders, close follow-up, supervised self-monitoring, rewards for success, family therapy, couple-focused therapy, psychological therapy, crisis intervention, and manual telephone follow-up. A common characteristic was the more frequent interaction of healthcare professionals with patients. Two studies on patients with complex regimens, i.e. polypharmacy did not show improved outcomes (i.e. adherence, re-hospitalization rates).

The literature on interventions specifically designed to improve adherence to polypharmacy is scarce. Independently living patients with polypharmacy were reported to benefit from dose-dispensing aids with regular follow-up [133] and from engaging in self-management, mainly delivered by pharmacists [85]. The modes of delivery of adherence-enhancing interventions were more beneficial if they were performed personally at hospital discharge and by a pharmacist at the pharmacy [134].

The effect of electronic medication packaging, i.e., adherence recorder, audiovisual alarm, liquid crystal display, and/or real-time monitoring, ranged from a decrease of 2.9% to an increase of 34.0% in adherence [135]. Electronic devices embedded in complex interventions and the combination of digital displays with alarms were most frequently associated with improved adherence [135]. Electronic packaging devices combined with feedback on the patient's adherence performance was assumed beneficial. This was particularly observed by a meta-analysis including 79 studies on adherence-enhancing interventions measured by electronically compiled dosing histories [136]. They observed increased adherence of 14.1% in the intervention groups compared to the control groups.

Interventions with a cognitive-educational or a feedback element showed significant effects of improved adherence.

Some interventions targeting adherence through medication optimization improved patient satisfaction and health related quality of life [46,113,115]. Usually intensive, complex interventions were estimated to be more effective, but simple interventions were more cost-effective [137,138]. Quality of pharmaco-economic studies and reported economic outcomes in studies on adherence-enhancing interventions were insufficient to make a clear statement on the cost-effectiveness of adherence-enhancing interventions [83,139,140]. Compared to the enormous costs caused by non-adherence, adherence-enhancing interventions are generally thought to be cost-effective [37].

Overall, the evidence of adherence-enhancing intervention remains scarce and their effect on adherence and economic, clinical and humanistic outcomes, if assessable, is moderate. Persistent criticism concerns the poor methodological quality, the large heterogeneity of the results, the small sized study population and the short study duration. Many studies did not suffice the ethical standards for adherence research proposed by the National Heart Lung and Blood Institute [141], which demand the report of benefits for the patients through the measurement of patient-relevant outcomes (i.e. clinical and humanistic outcomes) in trials investigating adherence-enhancing interventions. Often, promising interventions were too complex and diverse to attribute the only moderate effect sizes to a single element. To date, it is suggested that the effect of the interventions might be augmented by tailoring the elements of the intervention to the patients' individual necessities and needs [62,142]. To enable such interventions, patient individual factors of non-adherence have to be assessed before delivering it.

Although complex interventions were usually suggested to yield larger effects, the reviewers doubted their integration into daily practice because of poorly described intervention details and unavailable resources. To be implementable in clinical practice, adherence interventions have claimed to be simple, easy to use, continuous and cheap [37,143]. These requirements are fulfilled by interventions supporting medication self-management e.g. dose-dispensing aids. In a meta-analysis, dose-dispensing aids were one among three intervention elements showing positive moderation on the overall effect size of adherence [144]. Various authors have suggested dose-dispensing aids to enhance adherence in unintentionally non-adherent patients with polypharmacy by optimizing medication self-management [1,62,65,145,146].

Dose-dispensing aids

"Calendar packaging of medications for long-term use is intuitively attractive as a simple adherence strategy, but only a paucity of clinical trials have assessed its adherence benefits systematically, and essentially none has evaluated its potential for harm." [147]

Dose-dispensing aids represent a simple technical option and require little resources on the patient's as well as on the provider's side. They are easy to use, cheap, support medication self-management through adherence (self-) monitoring and constituting a reminder for medication intake, and thus might prolong independent living , save time, costs, healthcare resources (e.g., home care nursing), and medication waste [1,126,145,148,149]. Due to the missing of a Medical Subject Heading, there is a variety of synonyms used in the literature (**Table 2**).

Table 2. Synonyms used for dose-dispensing aids in alphabetical order.
Of note: This list makes no claim to be complete.

Blister packaging	Pill organizer	Easyblist®
Calendar (blister) packaging	Pill packaging	Medidos®
Drug packaging	Special medication packaging	Nomad®
Drug reminder packaging	Unit dose packaging	Pharmis®
Pillbox	Unit of use packaging	Webster® pack
Pill calendar	Brand names	Venalink®
Pill container	Dosett®	MTS®

Dose-dispensing aids consist of a certain number of compartments, containing solid, oral medication for specific dosing times. They can roughly be divided into three groups [77]:

- **Multicompartment adherence aids** are reusable plastic boxes, which come in many different shapes and colors. Usually, they provide compartments for seven days with or without sub-compartments for additional dosing times per day. They are filled either by the pharmacy or by the patient (**Figure 7**).
- **Multidrug punch cards** are disposable frame cards with plastic compartments, sealed with a foil backing. Typically, they provide 28 compartments, but other models from 4-35 compartments exist too enabling the individualized packaging of polypharmacy according to a prescribed dosing regimen. On the front side, the medication is visibly packaged and labelled with patient and pharmacy information and marked with the dosing times (morning, lunch, evening, night; Monday-Friday). The adhesive medication plan at the backside labels brand name, dose, administration number, dosing frequency, size, color, imprint, batch number, and expiration date of each packaged medication. Multidrug punch cards are filled by pharmacy staff, by a specialized company, or an automated system (**Figure 8**).

- **Blister pouches** are little sealed unit-dose bags containing one or multiple medication and usually coming in a sequential line of pouches with perforated limits. They are produced by an automated system, often by a specialized company and sometimes at the pharmacy. Unlimited dosing times per day can be packaged for a requested time of use (**Figure 9**).

Figure 7: Multicompartment adherence aids (top left: Dosett®; top right: Medi-7®).

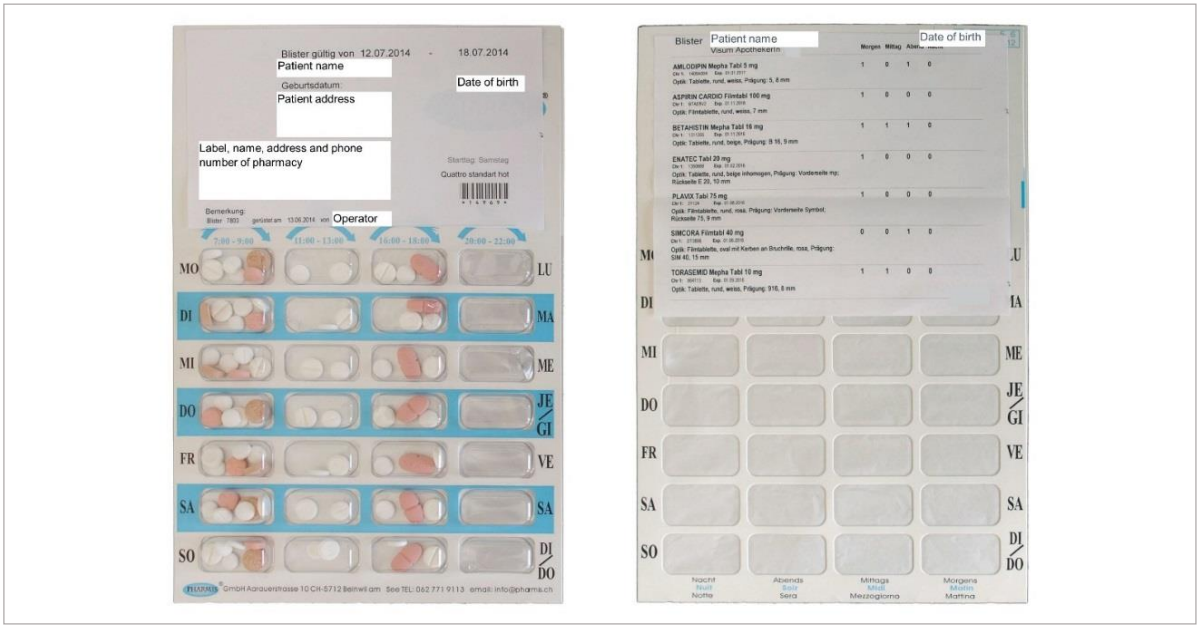

Figure 8: Multidrug punch cards front (left) and back (right).

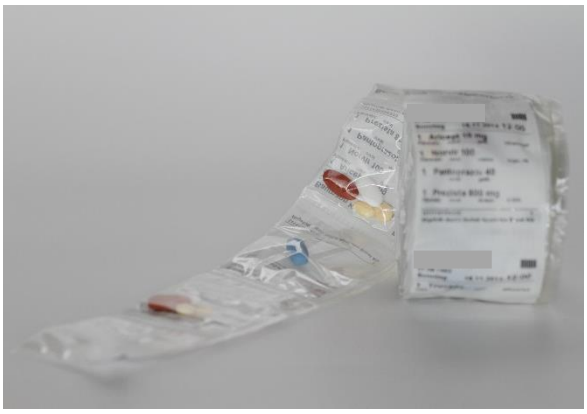

Figure 9: Blister pouches (Medifilm®).

Advantaged and disadvantages of the specific groups are illustrated in **Table 3**.

Table 3. Advantages and disadvantages of dose-dispensing aids.		
Multicompartment adherence aid	Advantages	• Independent filling by the patient • Reusability • Medication self-monitoring possible • Visual intake reminder
	Disadvantages	• Lack of hygiene • Restricted number of dosing times • Risk of deteriorated stability and compatibility of deblistered medication • Risk of inaccurate filling by the patient
Multidrug punch card	Advantages	• Hygiene • Medication self-monitoring possible • Visual intake reminder • Electronic monitoring possible • Not open to manipulation
	Disadvantages	• Not reusable / waste • Restricted number of dosing times per day • Risk of deteriorated stability and compatibility of deblistered medication • Risk of handling difficulties by the patients • Risk of fewer contact to health care professionals • Risk of fading knowledge about packaged medication
Blister pouch	Advantages	• Hygiene • Unrestricted dosing times per day • Separable unit-doses • Electronic monitoring possible • Can be integrated in an automated dosing system • Not open to manipulation
	Disadvantages	• Not reusable / waste • Risk of deteriorated stability and compatibility of deblistered medication • Risk of fewer contact to health care professionals • Risk of fading knowledge about packaged medication

The *dose-dispensing service* is defined as 'the repackaging of solid oral medication by a health-care provider, mostly in a community pharmacy or hospital pharmacy, to assist patients in the management of their polypharmacy' [77]. It ideally should be integrated in a pharmaceutical care service, with instruction and counseling of the patient, information for his/her caregiver(s), and regular follow-up, i.e. medication review of the packaged and unpackaged medication [77,150] (**Figure 10**).

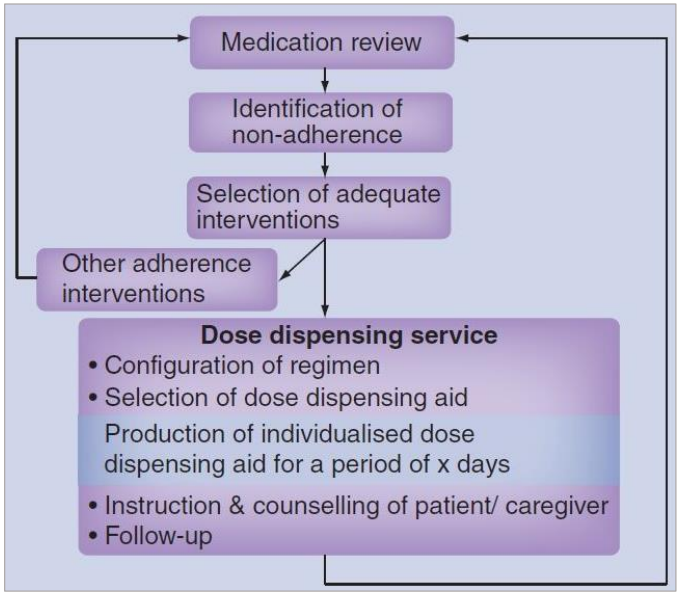

Figure 10: Workflow of dose-dispensing service from Hersberger et al. [77].

Dose-dispensing aids are widely used in practice. Although acknowledged for facilitating medication self-management, their use is not without risks (**Table 3**, disadvantages) and their widely spread use has been criticized. Difficulties with handling were described in several studies, leading to the dangerous action of emptying the content of the dose-dispensing aid into regular pill bottles [32,146,151,152]. The other concern was about the patients loosing contact to health-care professionals and a fading knowledge of medication. The authors feared a loss of skills and autonomy of the patients, which could limit the safe administration of their medication [152-154]. However, despite declined knowledge of patients using pre-packed dose-dispensing aids, their adherence appeared to be better than patients self-managing their medication [154]. In fact, adverse events of dose-dispensing aids resulting in harm for the patients have never been studied in randomized controlled trials [147], representing a security gap.

Prior systematic literature reviews have investigated the impact of dose-dispensing aids on adherence and economic, clinical and humanistic outcomes. They univocally stated a moderate effect of dose-dispensing aids on adherence and clinical outcomes, but declared the evidence to be insufficient to

draw firm conclusions [147,155,156] (detailed information is provided in Chapter 2). One retrospective propensity score matched study including 9'266 patients in the 'real-world' setting reported significantly improved adherence and persistence rates with a single-pill combination in reminder packaging.

In this thesis, we focused on multidrug punch cards to optimize medication use by support of the patient's medication self-management and thus to reach appropriate polypharmacy.

Multidrug punch cards

In Switzerland, multidrug punch cards represent one possibility for a dose-dispensing service. The devices are filled and dispensed at the community pharmacy. A specific software assists the production by archiving patient data, documenting prescriptions, verifying the medication filled through barcode scanning, and by composing data from the database to a label that is fixed on the card (**Figure 8**) [157]. Health insurances are obliged to reimburse this dose-dispensing service with CHF 21.60 per week, if the patient has a prescription for over three different medications per week and for a dose-dispensing aid (according to the collective agreement LOA IV [158]). Multidrug punch cards as a single or as an element of a composite intervention significantly improved adherence [49,159,160] and clinical outcomes [49,160,161]. Additionally, they are assumed to promote interdisciplinary collaboration, since the medication plan is actively managed by the pharmacist and drug related problems can be solved instantly. Continuity of care, which is known to improve medication safety and adherence, is given by the provision of the all medication through the same community pharmacy [37,162]. To date, studies on multidrug punch cards used mainly pill count for adherence measurement. With the availability of POEMS, which can be affixed on the back of a multidrug punch card, it becomes possible to measure adherence to polypharmacy electronically.

In this thesis, we focused on (electronic) multidrug punch cards as an adherence-enhancing intervention to improve patient-relevant outcomes in primary care patients with polypharmacy.

Rationale and approach

The global health situation demands polypharmacy for many clinical conditions, especially in multimorbid patients. Within the momentary demographic changes, many patients are concerned with polypharmacy, which constitutes a considerable risk factor for non-adherence. Non-adherence has been of increasing concern because it impairs clinical conditions and quality of life, and it generates exceeding healthcare costs. Despite numerous tested interventions, evidence has been limited through methodological flaws, heterogeneity of outcome measures, and lack of patient-relevant outcomes. Dose-dispensing aids, like multidrug punch cards, were designated elements of successful

adherence interventions. They aim at enhancing adherence through optimization of medication self-management in unintentionally non-adherent patients with polypharmacy.

The goal of this thesis was to investigate the effect of multidrug punch card use on adherence to polypharmacy and patient-relevant outcomes in primary care patients. We approached this goal in three steps.

In a first step (A), we used the methodology of evidence mapping to provide an overview on a whole topic area and to identify evidence gaps. We used a tool [163] appraising methodological quality specifically designed for public health studies of various study designs. Further, we aimed at extending the information of the evidence by assessing the completeness of reporting of intervention details (PROJECT A1).

In a second step (B), a real life picture of current pharmacy practice in adherence support and of primary care patients using multidrug punch cards in daily life was aspired. Pharmaceutical care interventions delivered at community pharmacies have been successful in improvement of adherence. PROJECT B1 aimed at quantifying and qualifying patient-centered counseling, especially explicit adherence counseling, in daily pharmacy practice. Adherence-enhancing interventions were claimed to be simple, easy to use, continuous, inexpensive, and implementable in clinical practice. Multidrug punch cards are suggested to suffice these requirements. They were introduced in Switzerland in 2002 as a dose-dispensing service provided by community pharmacies. With PROJECT B2, we intended to evaluate integration of multidrug punch cards into community pharmacy practice. Multidrug punch cards are suggested to optimize medication self-management in unintentionally non-adherent patients. Little is known about the characteristics, preferences, and experiences of primary patients using multidrug punch cards in daily life. Lately, concerns about handling difficulties and fading medication knowledge have been expressed and warn from a wide spread distribution of such aids. Hence, PROJECT B3 aimed at the exploration of current multidrug punch card user in Swiss primary care.

In a third step (C), we affixed POlypharmacy Electronic Monitoring System foils on multidrug punch cards to measure adherence to polypharmacy and to give feedback on adherence behavior. Having the research gaps identified in PROJECT A1 and the results of PROJECTS B1, B2 and B3 in mind, we aimed at developing and piloting a randomized controlled trial investigating the intervention of electronic multidrug punch card use for all oral solid medication and individualized feedback sessions on electronic dosing histories on adherence and patient-relevant outcomes (PROJECTS C1 and C2). The described steps and projects with corresponding objectives are listed below.

A EVIDENCE MAP OF DOSE-DISPENSING AIDS

PROJECT A1: EFFECT OF DRUG REMINDER PACKAGING ON MEDICATION ADHERENCE: A SYSTEMATIC REVIEW REVEALING RESEARCH GAPS

To review and map the evidence of dose-dispensing aids in improving adherence and economic, clinical, and humanist outcomes; to identify research gaps providing a rationale for future research.

B ADHERENCE SUPPORT IN CURRENT PHARMACY PRACTICE AND MULTIDRUG PUNCH CARD USE BY PRIMARY CARE PATIENTS

PROJECT B1: ADHERENCE COUNSELING DURING PATIENT CONTACTS IN SWISS COMMUNITY PHARMACIES

To determine the degree and nature of counseling delivered at community pharmacies, focusing on adherence counseling; to assess the community pharmacists' opinions about adherence counseling.

PROJECT B2: FIRST EVALUATION OF PHARMIS® BLISTER PACKAGING PROVIDED BY PHARMACIES IN SWITZERLAND

To explore the integration of multidrug punch card service in contemporary community pharmacy practice, assessing experiences, benefits, and expenditures.

PROJECT B3: MULTIDRUG PUNCH CARDS IN PRIMARY CARE: A MIXED METHODS STUDY ON PATIENTS' PREFERENCES AND IMPACT ON ADHERENCE

To assess the acceptance, preferences, and experiences of multidrug punch card users in primary care and the device's impact on adherence; to profile the primary care patient benefitting most of multidrug punch card use and thus to facilitate targeted adherence interventions.

C EFFECTIVENESS OF MULTIDRUG PUNCH CARD USE IN PRIMARY CARE PATIENTS – A PILOT STUDY

PROJECT C1: ELECTRONIC MULTIDRUG PUNCH CARDS TO IMPROVE CLINICAL AND HUMANISTIC OUTCOMES IN PATIENTS AFTER HOSPITAL DISCHARGE

To develop and pilot a randomized controlled trial investigating the effectiveness of electronic multidrug punch cards and feedback on electronic dosing histories in improving adherence and in extending time to hospital readmission and major therapy adjustment in primary care patients after hospital discharge.

PROJECT C2: SUCCESS OF A SUSTAINED PHARMACEUTICAL CARE SERVICE WITH ELECTRONIC ADHERENCE MONITORING IN A DIABETIC PATIENT OVER 12 MONTHS

To report in detail of the first long-term electronic monitoring of adherence to polypharmacy.

Clarification of terms: Due to the absence of generally accepted terms, different synonyms were used in:

- PROJECT A1: *'drug reminder packaging' was used instead of 'dose-dispensing aids'. The term 'humanistic outcomes' refers to the definition given by Kozma et al. [174]: "Consequences of disease or treatment on patient functional status or quality of life measured along several dimensions", e.g., physical function.*
- PROJECT B2: *'Pharmis® blister' was used instead of 'multidrug punch card'. 'Ambulatory patient(s)' was used instead of 'primary care patient(s)'.*
- PROJECT C2: *'electronic records' was used for the electronic dosing history generated by POlypharmacy Electronic Monitoring System (POEMS).*

A Evidence map of dose-dispensing aids

Project A1

Effect of drug reminder packaging on medication adherence: a systematic review revealing research gaps

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Abstract

Background: This was a systematic review of the literature in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Evidence mapping was used to reveal the effect of drug reminder packaging on medication adherence, to identify research gaps and to make suggestions for future research.

Methods: PubMed, Embase, CINAHL and PsycINFO were searched with an end date of September 2013 using the Medical Subject Headings (MeSH) term 'medication adherence' and 20 different search terms for 'drug reminder packaging', limited to the English and German languages. Additional references were identified through cross-referencing. All prospective controlled trials with an intervention using drug reminder packaging for patients taking at least one medication without the assistance of a health-care professional were included in the evidence mapping of the effect of drug reminder packaging on adherence and outcomes according to the Economic, Clinical and Humanistic Outcomes (ECHO) model.

Results: A total of 30 studies met the inclusion criteria: 10 randomized controlled trials, 19 controlled clinical trials and 1 cohort study. Drug reminder packaging had a significant effect on at least one adherence parameter in 17 studies (57%). The methodological quality was strong in five studies. Two studies provided complete information. Clear research gaps emerged.

Conclusions: Overall, the studies showed a positive effect of drug reminder packaging on adherence and clinical outcomes. However, poor reporting and important gaps like missing humanistic and economic outcomes and neglected safety issues limit the drawing of firm conclusions. Suggestions are made for future research.

***Keywords**: medication adherence, patient compliance, polypharmacy, drug reminder packaging, multicompartment adherence aid, pillbox, multidrug punch card, blister pouch, dose-dispensing service.*

Background

Adherence is defined as the extent to which a patient's behavior matches the agreed recommendations from the prescriber [37]. Reported rates vary from 4.6% to 100% of patients of all age classes with different medical conditions and on long- or short-term treatments [37,90]. Mean adherence rates for specific diseases are 88.3% for HIV infection, 76.6% for cardiovascular disease, 67.5% for diabetes mellitus and 58% for psychosis patients [90,164]. Adherence depends on patients' capability (e.g., physical, cognitive and economic) and willingness to initiate and execute their treatment plan: if either is insufficient, unintentional or intentional non-adherence will be the consequence [65,165]. Non-adherence is known to impair clinical, economic and humanistic outcomes [12,83,103,105,125,166,167] (*the meaning of 'humanistic outcomes' is declared in 'clarification of terms', p. 42*). In a study across five European countries, increasing the percentage of patients adhering to antihypertensive treatment to 70% was estimated to lead to a reduction of cardiovascular related health-care costs by €332 million ($461 million) [123]. Reasons for non-adherence are highly individual and complex. Therefore, individual needs and necessities have to be assessed to find the optimal aid for each patient.

Drug reminder packaging, such as weekly pillboxes or multidrug punch cards, is widely used in everyday practice. It usually consists of a certain number of compartments containing solid oral medication for specific dosing times. Compared to other adherence-enhancing programs, such as patient counseling, education or motivation [126], drug reminder packaging is a simple technical option and requires little resources on the patient's as well as on the provider's side. The provision of drug reminder packaging aims at enhancing adherence by facilitating medication organization and intake, by decreasing medication errors and by (self-) monitoring medication intake. Various authors suggest that drug reminder packaging supports mainly unintentionally non-adherent patients, e.g., geriatric patients and patients with complex drug regimens [62,65,145,146]. Previous reviews with restrictive inclusion criteria investigated the effect of reminder packaging on adherence and were inconclusive [147,155,156]. This review uses evidence mapping [168,169] to analyze data from a different perspective, highlighting methodological strength and completeness of information as well as research gaps, to identify areas for future research.

Methods

A systematic review was conducted, complying with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement. We proceeded by following the evidence mapping methodology in four steps: question development, question prioritization, evidence search and selection, and data extraction [168].

Question development and prioritization

The study question was deduced from previous reviews. An evidence report was composed after a preliminary literature search. Keywords were defined based on the results of this search. Experts were consulted to prioritize the question.

Literature search

PubMed, Embase, CINAHL and PsycINFO were searched for articles published up until September 2013. The keywords used in the search strategy were the Medical Subject Headings (MeSH) term 'medication adherence' and 20 different terms for 'drug reminder packaging': unit dose*, reminder pack*, unit of use pack*, pill organiser, pill organizer, medication packaging, medication container, pill container, pill box, pillbox, pill calendar, calendar pack*, calendar blister pack*, doset*, dosset*, blister pack*, pill pack*, special packaging AND medication, drug pack*, webster pack. The search was restricted to the English and German languages. Abstracts were screened and full text articles of potential hits were retrieved. References of retrieved articles were screened for relevant cross-referenced articles.

Study selection and data extraction

The full text of potentially relevant articles was reviewed. Inclusion criteria were any prospective controlled study design, with at least one outcome being adherence, economic, clinical or humanistic, with drug reminder packaging as an intervention in any adherence-enhancing program, for patients taking one or more oral medication (prescribed or over-the-counter) without the help of a health-care professional. Trials were excluded if they were performed in developing countries or if they used drug reminder packaging with incorporated electronic features (e.g., the Medical Event Monitoring System). Drug reminder packaging included reusable multicompartment adherence aids (plastic pillboxes with several compartments per day or per week filled by the patient or pharmacy staff), non-reusable multidrug punch cards (frame cards with plastic cavities, sealed with a foil backing, with typically 28 compartments, filled by pharmacy staff, by a specialized company or an automated system) and non-reusable unit-of-use packaging (e.g., blister pouches attached to form flexible chains, with an unrestricted number of separated daily dosing times, filled by automated systems) [77].

Data extracted included the author, publication year, study design, duration of the intervention and follow-up, description of the participants (e.g., age, clinical conditions and number of medications), outcomes, method of adherence measurement, type of drug reminder packaging and additional interventions. The literature selection and analysis of methodological issues were performed independently by two reviewers. Consensus regarding the results was reached by discussion.

Methodological quality and completeness of information

The methodological quality of the studies was assessed using the tool for quantitative studies developed for public health topics by the Effective Public Health Practice Project (EPHPP) group [163]. In

brief, the tool is applicable to a variety of study designs other than randomized controlled trials (RCTs), such as pre- and post-cohort studies and case-control studies, and it has been validated [170]. It assesses eight components: (1) selection bias, (2) study design, (3) confounders, (4) blinding, (5) data collection method, (6) withdrawals and dropouts, (7) intervention integrity and (8) analysis. Components 1 to 6 were rated as strong, moderate or weak. Based on the rating of the components, studies were described as of weak, moderate or strong methodological quality [163,171]. The tool was adapted to the review question. The component '(4) blinding' was not assessed because it is not applicable in studies investigating adherence with drug reminder packaging. The rating of criterion '(5) data collection method' focused on adherence outcomes [65]. Data collection was considered 'valid and reliable': (a) if the calculation of the medication possession ratio, the calculation of the medication refill frequency, therapeutic drug monitoring or a validated questionnaire were applied as a single method; (b) if pill count or clinical parameters were combined with at least one additional adherence measurement method (e.g., therapeutic drug monitoring) and (c) if appointment keeping was combined with at least two additional adherence measurement methods.

Following the recommendations of the CONSORT (Consolidated Standards of Reporting Trials) statements for non-pharmacological treatment [172] and the Cochrane Handbook [173], eight additional criteria were selected to assess completeness of information (**Table 1**). One point was accredited per reported criterion. 'Completeness of information' was defined as the sum of the points divided by eight, resulting in rates from 0 (no item on completeness of information available) to 1 (all items on completeness of information available). The packaging was defined as 'described' if the design (daily, weekly or monthly) and the number of cavities were reported. Criteria 7 and 8, concerning medication not packed in the drug reminder packaging, were not applicable if it was stated that all medication was packed into a drug reminder packaging device. Results were calculated according to the adjusted denominator.

Table 1. List of additional criteria for completeness of information.
Each available criterion is accredited with 1 point; completeness of information is calculated as the sum of the points divided by the number of all applicable criteria.

1	Description of drug reminder packaging
2	Description of medication packaging of the control group
3	Description of intervention conditions
4	Description of control conditions
5	Description of all medication used in both groups
6	Specification of all medication packed in the drug reminder packaging
7	Specification of medication not packed in the drug reminder packaging
8	Handling of medication not packed in the drug reminder packaging

Outcomes

Any measurement estimating taking adherence (i.e., an indicator of taken medication) was extracted as an adherence outcome. The Economic, Clinical and Humanistic Outcomes (ECHO) model [174] was used to classify further study outcomes. Therapeutic drug monitoring, biomarker and physiological measurements were categorized as clinical outcomes, unless they were part of a composite adherence outcome. A listing of costs was considered as an economic intermediary outcome if compared between groups. Patient surveys on handling, opinion or satisfaction with drug reminder packaging were considered as humanistic intermediary outcomes if comparison between groups was given.

Results

Of the total 855 identified references, 30 fulfilled the inclusion criteria. The PRISMA flow diagram of study inclusion and the PRISMA checklist are provided in Additional files 1 and 2, respectively (supplementary material). According to the EPHPP assessment tool for study design, 10 studies were RCTs, 19 controlled clinical trials and 1 was a cohort study (one group with a pre- and post-intervention comparison). Compared to the previously published reviews [147,155,156], a total of 13 studies were additionally included, from which 7 were controlled clinical trials, 5 RCTs and 1 was a cohort study.

Overall, the mean number of participants was 191 (range 14 to 2,081 participants). They were on average 62 years old (range 38 to 87 years, not described (n.d.) in five studies), took an average of 3.9 medications (range 1 to 9 medications, n.d. in 12 studies) and were treated for hypertension (7), diabetes mellitus type 2 (3), geriatric conditions (3), Helicobacter pylori infection (2), HIV (2), vitamin supplementation (2), chronic mental illness (2), hypercholesterolemia (1), epilepsy (1), pain relief in cancer patients (1), anticoagulation (1), and Chlamydia infection (1). Medical conditions were not described in six studies of mainly elderly multimorbid patients. The mean study duration was 5.4 months (range 7 days to 14 months, n.d. in three studies). **Table 2** is a summary of the studies (*attached at the end of the article*).

Effect on adherence

Considerable variation exists between studies regarding definitions, measures and calculations of adherence. Taking adherence was estimated in 27 studies (90%). Pill count (15 studies) and patient self-report (12 of which 1 was electronic) were the most used measures. Other methods included refill data (6), therapeutic drug monitoring (5), appointment keeping (2) and clinical measures (2). Eleven studies used composite adherence measures. The calculation of adherence was unclear in three studies [151,175,176].

A significant effect of drug reminder packaging was reported in 17 studies and concerned at least one of the measured adherence parameters. Six of these 17 studies were not incorporated in the previous reviews (**Table 2**).

Twelve studies reported significant adherence improvement in the group with drug reminder packaging as part of a multiple intervention strategy [49,159,176-185]. The effect on adherence was also significant when drug reminder packaging was a single intervention [160,182-189]; however, it was less pronounced in direct comparison with multiple interventions [182-185].

Methodological quality and completeness of information

Methodological quality was rated as strong for 5 studies, moderate for 12 and weak for 13. Overall, weaknesses were in the methods used for data collection (mostly not valid and not reliable) and the report of confounders and their comparison between groups (insufficient or missing). The most accurate standard in statistical analysis, the intention-to-treat analysis, was applied by seven studies. The number of studies with strong and moderate methodological quality doubled after 1996, the year of the first publication of the CONSORT statements [190], while the number of weak methodological quality studies diminished by a factor of 3.

Completeness of information ranged from 0 to 1.0 with a mean score of 0.3. Two studies [49,185] gave complete information for all required details. Reported criteria for the completeness of information are depicted in **Figure 1**. Criteria 7 and 8 were not applicable for 5 studies [49,159,183-185] and practically non-existent in all 25 remaining studies (criterion 7: 0; criterion 8: 1). Information on the person in charge and place of intervention were often missing from the description of the intervention and control conditions. **Figure 2** shows the included studies according to their methodological quality, completeness of information and outcome measures.

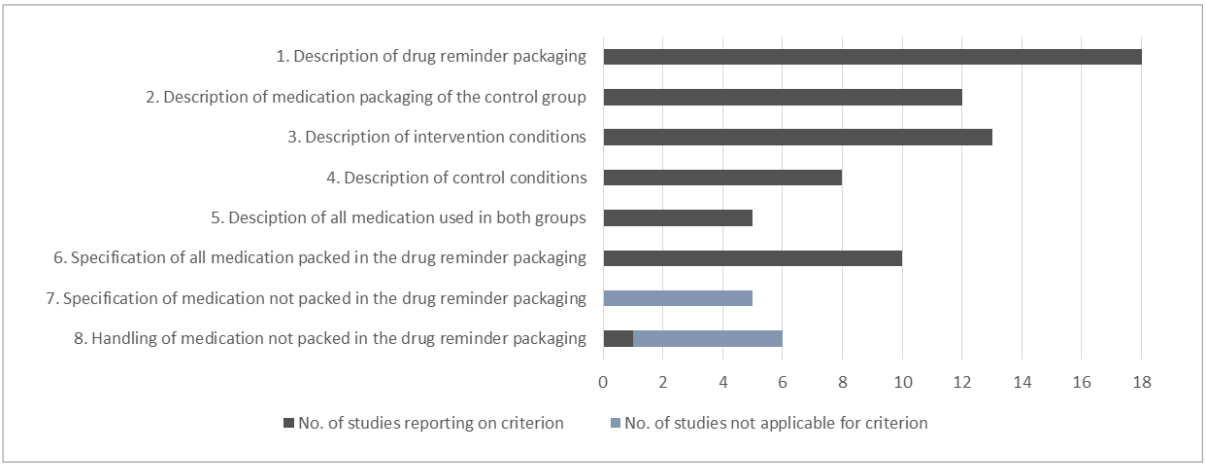

Figure 1: Distribution of the eight criteria defined for the completeness of information (n = 30 studies).

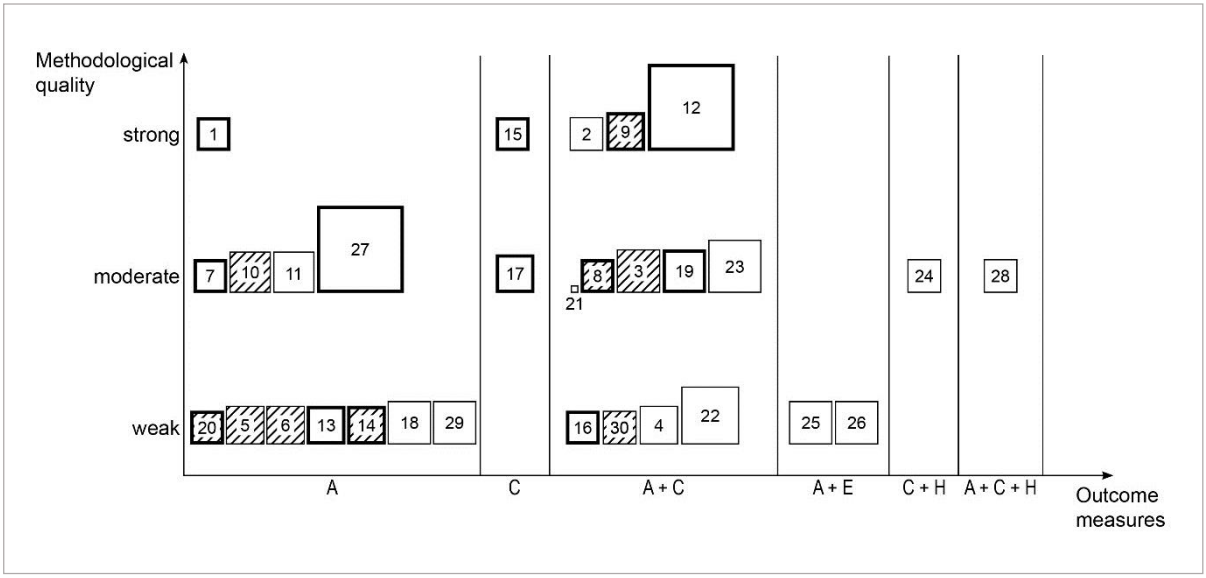

Figure 2: Consolidation of results of outcomes, methodological quality and completeness of information. Each box represents one study numbered as in **Table 2**, plotted in a segment of reported outcome(s) and at a height based on its methodological quality. Completeness of information is indicated by the size of the box, with values between 0 (e.g., study no. 21) and 1 (e.g., study no. 12). Bold frames are for the additionally included studies compared to previously published reviews [147,155,156]. No filling indicates at least one outcome was statistically significant and shading indicates none of the outcomes were statistically significant. A, adherence; C, clinical outcome; E, economic outcome; H, humanistic outcome.

Outcomes

Two studies assessed direct costs as intermediary economic outcomes [183,184] and there was a significant increase in prescription costs. However, a cost-effectiveness analysis that would qualify as an economic outcome according to the ECHO model was not reported.

Clinical outcomes were measured in 16 studies using one or several parameters: blood pressure (6), glycosylated hemoglobin (HbA_{1C}) (2), psychiatric symptoms (2), low-density lipoprotein cholesterol (LDL-C) levels (1), pain reduction (1), number of seizures (1), plasma levels of anticonvulsant drugs (1), viral load (1), CD4 cell count (1), number of opportunistic infections (1), hospitalizations (1), percentages of sub-therapeutic international normalized ratio (INR) values (1), time within the therapeutic INR range (1) and ^{13}C-urea breath test (1).

Of these 16 studies, 7 were not incorporated in the previous reviews. Five of the seven additional studies showed a statistically significant effect [49,175,188,191,192]. In one study, LDL-C levels and blood pressure were significantly reduced after eight months compared to the baseline for patients using drug reminder packaging (LDL-C: −4.8 mg/dl, P = 0.001; systolic blood pressure: −6.9 mmHg, P = 0.005; diastolic blood pressure: −2.5 mmHg, P = 0.04) [49]. In a study with diabetes mellitus type 2 patients, HbA_{1C} was significantly reduced (−0.74%, P < 0.0001) and patients who took ≥5 tablets/day, ≥3

hypoglycemic drugs/day and were <55 years old had the largest benefit from drug reminder packaging [191]. In other studies, pain reduction was effective in cancer patients (P < 0.0001) [192], the number of opportunistic infections and hospitalizations decreased significantly in HIV patients (P < 0.05) [188], the percentages of sub-therapeutic INR values with oral anticoagulation (warfarin) decreased (P = 0.04) and time within the therapeutic INR range increased significantly (P = 0.03) [175]. Of the ten studies with multiple adherence-enhancing strategies in the intervention group, six showed significantly improved clinical outcomes [49,175,181,182,192,193]. The clinical outcomes of all studies are presented in **Table 2**.

Two studies reported humanistic outcomes [159,161]. The usability of drug reminder packaging was rated significantly higher than the usability of usual packaging [161]. Safety issues related to the intervention were addressed by two studies [159,181].

Clear gaps emerged from the overall results. Aside from methodological weaknesses (under-reporting of quality issues) and incomplete information (under-reporting of control settings and specification of medication), economic outcomes (cost-effectiveness), humanistic outcomes and safety issues are lacking.

Discussion

Although more than half of the studies included in this review reported significant effects, only three studies were graded as methodologically strong. Drug reminder packaging had a significant effect on adherence in a geriatric population [177], for chronic mental illness [178] and for cardiovascular disease [49]. The overall effect of drug reminder packaging on adherence parameters remains inconclusive, as reported by previous reviews with more restrictive selection criteria [147,155,156]. Three studies reported a significant effect on adherence but not on clinical outcomes [159,178,182]. Thus, the question of how much adherence is necessary for altering treatment success is raised and there is a requirement to present the clinical benefits for the patients [194]. We observed that drug reminder packaging offers a broad field of application and is mostly used for polypharmacy. As a consequence, disease-unspecific, generalizable clinical outcomes like morbidity or re-hospitalization rates would provide viable and comparable results rather than measures of disease-specific clinical parameters. Only two trials investigated such outcomes [188,195], with one showing that drug reminder packaging significantly reduced the mean hospitalization rate.

We included five RCTs in the evidence map that were excluded by three previous reviews [147,155,156] because of their multiple intervention design. In a direct comparison (factorial trials), the effect was higher with multiple interventions, which is consistent with previous findings [126,155]. Yet, the evidence is limited, for these trials were graded as weak in methodological quality.

The overall methodological quality of the studies included is poor and thus evidence for the effect of drug reminder packaging on adherence is low. We used a quality assessment tool that is applicable to a variety of study designs and was specifically developed to provide research evidence for studies on public health services with a focus on behavior change education [163]. In comparison to previous reviews, we were able to include four additional studies of strong methodological quality [49,177,191,196]. However, information on intervention and control settings was incomplete in three of these additional studies (completeness scores: 0.13, n = 2; 0.25, n = 1). As a consequence, being graded as strong and complying with all the criteria for completeness of information was observed in one out of the 30 studies included [49]. It therefore represents a thin basis for informed clinical decision support.

The increasing number of methodologically strong trials after 1996, the year when the CONSORT statements were released, is intriguing and probably follows from under-reporting in studies published before 1996. Various authors indeed stated that complete reporting of methodological quality according to the CONSORT criteria was inadequate, but that poor reporting did not necessarily correlate with the quality of how the trial was conducted [197-200]. The CONSORT statements of non-pharmacological treatment require 'precise details of both, the experimental treatment and the comparator' [172] and omission of trial details has been shown to lead to decreased uptake of trial results into clinical practice [201,202]. Thus, to obtain valuable and reliable study results, high methodological quality and detailed information are crucial.

Most studies were designed as RCTs, which provide the most reliable results through the minimization of confounding. However, RCTs might not be the appropriate design for all research questions and settings, especially in the field of behavior research. Alternative designs might be worth considering. Firstly, randomized allocation of study participants to a predefined intervention may not be practicable since tailored interventions, in respect of patients' needs and abilities, are expected to be the most effective [126]. Secondly, in studies on survival outcomes for HIV patients, investigating adherence-enhancing strategies in a randomized controlled fashion has been declared to be ethically difficult [203,204]. The reason for this declaration was the assumption that allocation to the control condition equaled withholding a tool, which could possibly lead to higher survival rates through an optimal clinical response due to increased adherence [203,204]. Thirdly, behavioral interventions are often complex and can only be controlled poorly under real-life conditions and therefore randomization might not be practical in a primary care setting [205]. Consequently, confounding could even persist despite randomization. Alternatives to conventional randomization designs, i.e., randomization at the patient level, include pre- and post-cohort studies, historical control studies, pre-randomized designs and cluster randomization [206].

More studies could be included and research gaps identified using our approach of evidence mapping. Patient-relevant disease-unspecific long-term clinical outcomes, e.g., (re-)hospitalization, admission to a nursing home, etc., were neglected. Economic outcomes as defined by Kozma et al. [174] were not reported in any study on drug reminder packaging. This may be due to the fact that drug reminder packaging is generally supposed to be inexpensive, and thus cost-effective. Humanistic outcomes were measured in two studies [159,161], which is insufficient for judging whether a condition optimally treated through drug reminder packaging leads to increased quality of life. Improved adherence could lead to increased adverse events as well. However, safety issues were reported by two studies only [159,181]. Patient satisfaction and other aspects of safety, such as opening medication packaging, confusion with new packaging and decreased ability to identify one's own medication [148,153,207,208], were hardly mentioned by the studies.

Our study has strengths. First, evidence mapping allows the inclusion of more studies and gives an overall view of the subject. Second, the tool used to assess methodological quality is independent of study design (EPHPP) and was developed specifically to assess studies within the scope of public health. Third, with completeness of information, a further element for judging quality is added. Fourth, the consolidation of adherence outcomes and economic, clinical and humanistic parameters allows an overall presentation and highlights research gaps. Our study has limitations also, such as the language restriction, which led to the exclusion of articles considered relevant. Information may also have been missed due to the exclusion of studies performed in developing countries.

A suggestion for future research is to develop methodologically strong studies reporting complete information to clarify the effect of drug reminder packaging on medication adherence.

Conclusions

New information was extracted from the 30 studies included and several studies had statistically significant and relevant results for adherence and clinical outcomes with drug reminder packaging. However, firm conclusions cannot be given for the effect of drug reminder packaging on adherence, mainly because the studies lack methodological quality and the information was incomplete. The main research gaps concerned economic, disease-unspecific clinical outcomes and humanistic outcomes. Safety issues and satisfaction with the intervention were marginally reported. Researchers of behavioral interventions might consider alternative study designs for similar research questions, without neglecting methodological issues and reporting important details. Future research should aim at filling the observed gaps with a focus on patient safety and the benefit to patients as well as on implementable and valuable interventions. Drug reminder packaging should be distributed with respect to patient needs, requests and abilities.

Supplementary material *(available on CD-R or on request)*

- PRISMA flow diagram
- PRISMA check list

Abbreviations

CI: confidence interval; CONSORT: Consolidated Standards of Reporting Trials; ECHO: Economic, Clinical and Humanistic Outcomes; EPHPP: effective public health practice project; HbA_{1C}: glycosylated hemoglobin; HIV: human immunodeficiency virus; INR: international normalized ratio; LDL-C: low-density lipoprotein cholesterol; MeSH: medical subject headings; n.d.: not described; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses; RCT: randomized controlled trial.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

FB designed the review protocol, carried out the literature search, extracted data from selected studies, conducted quality assessments and drafted the manuscript. ES reviewed the literature search and the quality assessment. KS participated in the conception of the review and revised the manuscript critically for intellectual content. KEH participated in the design of the review, helped to draft the manuscript and revised it critically for intellectual content. IA participated in the design of the review, helped to draft the manuscript and revised it critically for intellectual content. All authors read and approved the final manuscript.

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Table 2

Table 2. Summary of the 30 included studies.

No	Author	Design	n	Duration	Intervention	Drug reminder packaging	Outcomes	Effect	Methodological Quality	Compl. of Information
1	**Ascione** [177] (1984)	cct	158	n.d.	Drug reminder packaging, counseling	n.d.	**A**: Self-report*:	Unclear	Strong	0.13
2	Azrin [178] (1998)	cct	39	2m	a. Drug reminder packaging, counseling with family member vs. b. Drug reminder packaging, counseling vs. c. Psychoeducational condition	Multicompartment adherence aid	**A**: Pill count*: **C**: Symptoms Checklist 90-R:	a. vs. baseline: 95.03 vs. 76.24 (p<0.05, Ø CI) b. vs. baseline : 92.01 vs. 69.52 (p<0.01, Ø CI) c. vs. baseline: n.s. n.s.	Strong	0.13
3	Becker [209] (1985)	cct	180	12m	Drug reminder packaging	Multidrug punch card	**A**: Pill count, self-report, self-report + bp: **C**: Bp:	n.s. n.s.	Moderate	0.38
4	Binstock [193] (1988)	cct	112	12m	a. Counseling vs. b. Drug reminder packaging, counseling vs. c. Drug reminder packaging, counseling, other aids vs. other interventions	n.d.	**A**: Self-report: **C**: sbp*, dbp*:	a., b., c.: n.s. b. vs. a.: 133/80mmHg vs. 148/89mmHg (p<0.01, Ø CI) c. vs. a.: 134/84mmHg vs. 148/89mm Hg (p<0.01, Ø CI) b. vs. c.: n.s.	Weak	0.25
5	Crome [210] (1980)	cct	26	10d	Drug reminder packaging	Multicompartment adherence aid	**A**: Pill count:	n.s.	Weak	0.25
6	Crome [211] (1982)	cct	78	4w	Drug reminder packaging	Multidrug punch card	**A**: Pill count:	n.s.	Weak	0.25
7	**Eshelman** [186](1976)	cct	100	n.d.	Drug reminder packaging	n.d.	**A**: TDM*: Pill count: Self-report:	"Adherent" patients: 97% vs. 69% (p<0.05, Ø CI) n.s. Unclear	Moderate	0.13
8	**Fairley** [179] (2003)	rct	43	5m	Drug reminder packaging, counseling, other aids	Multicompartment adherence aid	**A**: Self-report*:	Total Morisky-Score: 3.3 vs. 2.9 (p=0.006, Ø CI)	Moderate	0.13

Table 2. Summary of the 30 included studies.

No	Author	Design	n	Duration	Intervention	Drug reminder packaging	Outcomes	Effect	Methodological Quality	Compl. of Information
								Rate of patients with a Morisky-Score of 0: 29% vs. 49% (p=0.04, Ø CI)		
							C: CD4-cell count, viral load:	n.s.		
9	**Henry** [196] (1999)	cct	119	10d	Drug reminder packaging, counseling, other aids	Multidrug punch card	**A**: Pill count + self-report:	n.s.	Strong	0.25
							C: ^{13}C-UBT:	n.s.		
10	Huang (TRACE) [187] (2000)	rct	184	2m	Drug reminder packaging	Multicompartment adherence aid	**A**: Pill count, self-report, TDM:	n.s.	Moderate	0.38
11	Huang (VITAL) [187] (2000)	cct	297	Unclear	Drug reminder packaging (multidrug punch card vs. multicompartment)	Multidrug punch card, Multicompartment adherence aid	**A**: Pill count*:	Patients who took >90% of pills taken: 93% vs. 87% (p=0.05, Ø CI)	Moderate	0.38
							Self-report*:	Positive answer to question 'forgot to take pills': 21% vs. 31% (p=0.05, Ø CI); self-report total score n.s.		
							TDM:	n.s.		
12	**Lee JK** [49] (2006)	rct	200	14m	Drug reminder packaging, counseling, regular follow-up	Multidrug punch card	**A**: Pill count*:	95.5 vs. 69.1 (p<0.001, Ø CI)	Strong	1.0
							C: sbp*:	Drug reminder packaging vs. baseline: -6.9mmHg (p=0.005, CI -10.7- (-3.1) mm Hg)		
							dbp*:	Drug reminder packaging vs. baseline: -2.5 mm Hg (p=0.04, CI -4.9-(-0.2) mm Hg)		
							LDL-C*:	Drug reminder packaging vs. baseline at 8m: - 4.8mg/dl (p=0.001, CI -7.8-(-1.9) mg/l) Drug reminder packaging vs. baseline at 14m: n.s.		

Table 2. Summary of the 30 included studies.

No	Author	Design	n	Duration	Intervention	Drug reminder packaging	Outcomes	Effect	Methodological Quality	Compl. of Information
13	**Lee M** [180] (1999)	rct	125	14d	Drug reminder packaging, counseling, other aids	Multicompartment adherence aid	**A**: Pill count*:	ITT1 (patients unavailable for follow-up took 100% [cg] resp. 0% [ig] of drugs): No. of patients with >60% of pills taken: n.s. Patients with > 90% of pills taken: 87% vs. 71% (p<0.05, Ø CI) ITT2 (patients unavailable for follow-up took 0% [cg + ig] of drugs): Patients with >60% of pills taken: 94% vs. 78% (p<0.05, Ø CI) Patients with > 90% of pills taken: 87% vs. 59% (p<0.01, Ø CI)	Weak	0.25
14	**MacDonald** [151] (1977)	rct	165	3m	Drug reminder packaging, counseling	Multicompartment adherence aid	**A**: Unclear	-	Weak	0.25
15	**Maier** [191] (2005)	rct	2081	6m	Drug reminder packaging	Multicompartment adherence aid	**C**: HbA_{1C}*:	- 0.74% vs. -0.53% (p<0.0001, Ø CI)	Strong	0.13
16	**McPherson-Baker** [188] (2000)	cct	42	5m	Drug reminder packaging	Multicompartment adherence aid	**A**: MRC*:	75.8% vs. 39.3% (Ø p, CI) Drug reminder packaging vs. baseline: 75.8% vs. 46.8% (p<0.01, Ø CI)	Weak	0.13
							Appointment keeping*:	76.1% vs. 73.3% (Ø p, CI) Drug reminder packaging vs. baseline: 76.1% vs.56.7% (p<0.05, Ø CI)		
							C: (here as proxies for adherence)			
							Mean hospitalizations*:	0.33 vs. 1.04 (p<0.05, Ø CI)		
							Opportunistic infections*:	Reduction with increased medication intake (Ø numbers given, p<0.05, Ø CI)		

Table 2. Summary of the 30 included studies.

No	Author	Design	n	Duration	Intervention	Drug reminder packaging	Outcomes	Effect	Methodological Quality	Compl. of Information
17	**Miaskowsky** [192] (2004)	cct	174	6w	Drug reminder packaging, counseling, other aids	Multicompartment adherence aid	**C**: Pain reduction*: Appropriate prescriptions*: Change in total amount opioids prescribed and taken:	Relieve in average, worst and least pain: Ø numbers given, (p<0.0001, Ø CI) Patients with appropriate opioid analgesic prescriptions vs. baseline: 37.0% vs. 28.3% (p=0.008, Ø CI) Prescribed: Ø numbers given, (p<0.0001, Ø CI) Taken: Ø numbers given, (p<0.001, Ø CI)	Moderate	0.25
18	Murray [189] (1993)	cct	36	6m	Drug reminder packaging	Unit-of-use packaging	**A**: Pill count*: Self-report:	92.6 vs. 79 (p<0.0001, Ø CI) No. of pat reporting all medication taken: 9 vs. 8 (Ø p, CI)	Weak	0.38
19	**Nochowitz** [175] (2009)	pre-, post-cohort	14	3m	Drug reminder packaging, other aids	Multicompartment adherence aid	**A**: Pill count (+/- self-report if pills were not available): **C**: INR*:	n.s. Sub-therapeutic INR values (<2) vs. baseline: 35% vs. 60% (p=0.04, Ø CI) Time spent in therapeutic range vs. baseline: 56% vs. 32% (p=0.03, Ø CI)	Moderate	0.38
20	**Park** [212] (1992)	cct	61	2w	Drug reminder packaging ± organizing chart, factorial	Multicompartment adherence aid	**A**: Electronic self-report:	Unclear	Weak	0.13
21	Peterson [181] (1984)	rct	53	4m	Drug reminder packaging, counseling, other aids	Multicompartment adherence aid	**A**: MRF*: TDM*: Appointment keeping: **C**: Seizure frequency*:	"Adherent" patients: 88% vs. 50% (p<0.01, Ø CI) Patients within therapeutic range vs. baseline: 88% vs. 48% (p<0.005, Ø CI) n.s. Frequency of seizures vs. baseline: 2.5 vs. 6 (p<0.01, Ø CI)	Moderate	0

Table 2. Summary of the 30 included studies.

No	Author	Design	n	Duration	Intervention	Drug reminder packaging	Outcomes	Effect	Methodological Quality	Compl. of Information
22	Rheder [182] (1980)	cct	100	3m	Drug reminder packaging ± counseling, factorial	Multicompartment adherence aid	**A**: Pill count*:	No. of pat who took ≥95% of pills: Drug reminder packaging ± mi > mi, Ø numbers given (p<0.01, Ø CI)	Weak	0.63
							C: bp*:	Drug reminder packaging + mi vs. baseline: Ø numbers given (p<0.02, Ø CI) Drug reminder packaging vs. baseline: n.s.		
23	Schneider [160] (2008)	rct	85	12m	Drug reminder packaging	Multidrug punch card	**A**: MPR *:	0.93 vs. 0.87 (p=0.039, Ø CI)	Moderate	0.5
								Patients with their prescription refilled on-time (± 5d): 80.4% vs. 66.1% (p=0.012, Ø CI)		
							C: dbp*:	No. of patients with decreased dbp at 12m: 12 vs. 4 (p=0.031, Ø CI)		
							sbp:	n.s.		
							Absolute change in bp:	n.s.		
							Long-term outcome measures:	n.s.		
24	Simmons [161] (2000)	rct	68	8m	Drug reminder packaging	(Multi-) drug punch card	**C**: dbp*:	- 5.8mmHg vs. 0.1mmHg (p=0.0041, Ø CI)	Moderate	0.13
							sbp:	n.s.		
							HbA_{1c}*:	- 0.95% vs. -0.15% (p=0.026, Ø CI)		
							H: Usability*:	77% vs. 27% (p<0.001, Ø CI)		
25	Skaer (NIDDM) [183] (1993)	cct	258	12m	Drug reminder packaging ± refill reminder (rr), factorial	Unit-of-use packaging	**A**: MPR*	Drug reminder packaging vs. cg: 0.71 vs. 0.58 (p ≤ 0.05, Ø CI) rr+drug reminder packaging vs. cg: 0.87 vs. 0.58 (p ≤ 0.05, Ø CI) rr+drug reminder packaging vs. drug reminder packaging: 0.87 vs. 0.71 (p ≤ 0.05, Ø CI)	Weak	0.33

Table 2. Summary of the 30 included studies.

No	Author	Design	n	Duration	Intervention	Drug reminder packaging	Outcomes	Effect	Methodological Quality	Compl. of Information
							E:	Drug reminder packaging vs. cg:		
							Prescription expend.* :	+$74.09 (p ≤ 0.05, Ø CI)		
							All other expend.:	n.s.		
								rr+drug reminder packaging vs. cg:		
							Prescription expend.* :	+$124.86 (p ≤ 0.05, Ø CI)		
							Physician expend.* :	-$66.79 (p ≤ 0.05, Ø CI)		
							Laboratory expend.*:	-$18.05 (p ≤ 0.05, Ø CI)		
							Hospital expend.*:	-$107.69 (p ≤ 0.05, Ø CI)		
							Total expend.*:	-$67.67 (p ≤ 0.05, Ø CI) (per capita)		
26	Skaer (BP) [184] (1993)	cct	304	12m	Drug reminder packaging ± refill reminder (rr), factorial	Unit-of-use packaging	**A**: MPR*	Drug reminder packaging vs. cg: 0.67 vs. 0.56 (p ≤ 0.05, Ø CI)	Weak	0.33
								rr+drug reminder packaging vs. cg: 0.79 vs. 0.56 (p ≤ 0.05, Ø CI)		
								rr+drug reminder packaging vs. drug reminder packaging: 0.79 vs. 0.67 (p ≤ 0.05, Ø CI)		
							E:	Drug reminder packaging vs. cg:		
							Prescription expend.*:	+48.17$ (p ≤ 0.05, Ø CI)		
							All other expend.:	n.s.		
								rr+drug reminder packaging vs. cg:		
							Prescription expend.*:	+104.39$ (p ≤ 0.05, Ø CI)		
							Physician expend.* :	-78.41$ (p ≤ 0.05, Ø CI)		
							Hospital expend.*:	-89.54$ (p ≤ 0.05, Ø CI)		
							Laboratory expend. :	n.s.		
							Total expend.* :	-75.28$ (p ≤ 0.05, Ø CI) (per capita)		

Table 2. Summary of the 30 included studies.

No	Author	Design	n	Duration	Intervention	Drug reminder packaging	Outcomes	Effect	Methodological Quality	Compl. of Information
27	**Solomon [185]** (1988)	cct	372	7d	Drug reminder packaging ± videotape ± telephone interview, factorial	Unit-of-use packaging	**A**: Self-report (non-compliance score)*:	Drug reminder packaging vs. cg: 30.2 vs. 50.7 (p<0.001, Ø CI) Drug reminder packaging + video-tape vs. cg: 5.5 vs. 11.1 (p<0.001, Ø CI)	Moderate	1.0
28	Valenstein [159] (2009)	rct	118	12m	Drug reminder packaging, counseling, other aids	Multidrug punch card	**A**: MPR* : CAM*: (MPR + self-report + TDM) **C**: Psychiatric symptoms: **H**: Patient satisfaction, quality of life :	At 6m: 0.91 vs. 0.64 (p < 0.0001, Ø CI) At 12m: 0.86 vs. 0.62 (p<0.0001, Ø CI) At 6m: 26% vs. 9% (p=0.0003, Ø CI) At 12m: 17% vs. 9% (p=0.06, Ø CI) n.s. n.s.	Moderate	0.17
29	Ware [176] (1991)	cct	84	3m	Drug reminder packaging, counseling	Multidrug punch card	**A**: Self-report + pill count*:	Patients taking all prescribed doses: At discharge: 86.7% vs. 66.7% (p=0.03, Ø CI) At 10d: 69% vs. 41% (p=0.02, Ø CI) At 1m : 64.4% vs. 38.5% (p=0.03, Ø CI) At 2m : 57.8% vs. 28.2% (p=0.01, Ø CI) At 3m: 48.9% vs. 23.1% (p=0.03, Ø CI)	Weak	0.38
30	Winland-Brown [195] (2000)	cct	61	6m	Drug reminder packaging	Multicompartment adherence aid	**A**: Pill count: **C**: bp, INR, TDM, mood stabilization, HbA_{1C}: Physician visits: Hospital admission:	n.s. Not reported Mean (per patient) vs. baseline: 1.5 vs. 1.5 (Ø p, CI) No. of patients vs. baseline: 7 vs. 4 (Ø p, CI)	Weak	0.13

Table 2. Summary of the 30 included studies.

No	Author	Design	n	Duration	Intervention	Drug reminder packaging	Outcomes	Effect	Methodological Quality	Compl. of Information
							Home visit:	No. of patients vs. baseline: 0 vs. 0 (Ø p, CI)		
							Transition to a higher level of care:	Not reported		

The 13 additionally included studies compared to previous reviews [147,155,156] are designated in bold. **A**, adherence outcomes; (s/d)bp, (systolic/diastolic) blood pressure; **C**, clinical outcomes; CAM, composite adherence measure; cct, controlled clinical trial; cg**,** control group; Compl., completeness; ^{13}C-UBT**,** ^{13}C-urea breath test; d**,** days; E, economic outcomes; expend., expenditures; **H**, humanistic outcomes; ig, intervention group; INR, international normalized ratio; m, months; mi**,** multiple interventions; no, number; n.s., not significant; rct, randomized controlled trial; TDM, therapeutic drug monitoring; vs., versus; w**,** weeks; *, significant change.

B Adherence support in current pharmacy practice and multidrug punch card use by primary care patients

Project B1

Adherence counseling during patient contacts in Swiss community pharmacies

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Abstract

Purpose: Numerous studies showed the effectiveness of pharmaceutical care in improving medication adherence in primary care patients. However, in daily pharmacy practice, the provision of pharmaceutical care appears to be limited. We aimed at quantifying the content of counseling by community pharmacy staff during patient contacts, especially adherence counseling, and at investigating pharmacist views about their practice of adherence counseling.

Patients and methods: A Master's student in Pharmacy observed patient contacts at selected community pharmacies in the region of Basel, Switzerland. Content of counseling was manually ticked on a checklist with predefined themes (administration, dose, effect, and adherence). Pharmacists working in the pharmacy were interviewed on triggers, topics, and barriers in adherence counseling.

Results: In 20 community pharmacies and during a total of 148.1 hours, 1,866 patient contacts were observed. During the 1,476 patient contacts including the dispensing of one or more medications, counseling was provided to 799 (54.1%) patients; with 735 (49.8%) patients counseled about administration, 362 (24.5%) about dose, 267 (18.1%) about effect, and 99 (6.7%) about adherence. Significantly more patients received counseling when they obtained prescribed versus over-the-counter medication (P=0.002), a new prescription versus a repeat prescription (P<0.001), or when they were served by a pharmacist versus by another staff member (P<0.001). Of the 33 interviewed pharmacists, all except one reported actively approaching patients for adherence counseling. Triggers included medication-related and patient-related factors. The pharmacists named predominantly product-centered topics of adherence counseling. The most cited barriers were rejection of counseling by the patient and lack of time.

Conclusion: Half of the patients receiving one or more medications were counseled, and only 6.7% of all contacts included explicit adherence topics. Future studies should clarify how barriers to adherence counseling at the community pharmacy can be overcome.

***Keywords**: pharmaceutical care, community pharmacy, medication adherence*

Introduction

Pharmaceutical care has been defined as "…the pharmacist's contribution to the care of individuals in order to optimize medicines use and improve health outcomes,"[39] and the pharmacist has been designated as part of the health care team for added value in the health care system.[42,52,213] Pharmaceutical care activities practiced by community pharmacies have been shown effective in improving medication adherence.[44-51] Face- to-face counseling during dispensing of medication is part of pharmaceutical care.[42] Counseling can include providing education to patients (eg, about therapy, their condition), intervening in a patient's drug therapy (eg, optimizing intake times), and ultimately, helping improve medication adherence.[214] Previous studies reported significantly improved adherence and persistence through targeted counseling by community pharmacists.[215-217]

Counseling practice in community pharmacies has been reported to be limited. In a pan-Europe comparison in 2009, the mean total score of pharmaceutical care provision, expressed as a percentage of the total score achievable, ranged from 31.6% to 52.2%.[218] Patient counseling was reported to be only a minor task in every day practice in the community pharmacy,[219-222] and communication was predominantly nonmedical or product-centered, instead of patient-centered.[223-225]

At the dispensing of prescription medication, Swiss pharmacists are reimbursed for providing counseling on dose, frequency, administration, duration of use, storage, and potential adverse effects.[226] Introduced in 2005, this was the first acknowledgment of cognitive services delivered by community pharmacists to improve the patients' use of medication. Additionally, the provision of a dose-dispensing aid by the pharmacy is reimbursed.[227]

To our knowledge, the current counseling practices in Swiss community pharmacies have not yet been addressed, especially the content of adherence counseling. The aim of this study was to quantify the content of counseling by community pharmacy staff during patient contacts, with a specific focus on adherence counseling, and to investigate the views of community pharmacists about their practice of adherence counseling.

Materials and Methods

Of 106 community pharmacies in the region of Basel, Switzerland, community pharmacies that had participated in previous studies[228,229] were approached consecutively, according to a random number list, until the sample size of 20 was reached. This number was calculated to enable approximately 2,000 patient contacts, assuming that counseling would take 5 minutes and one investigator could observe approximately 100 patients during 8 hours. We did not perform analysis of health communication between pharmacy staff and patients, but rather observed and quantified the content of counseling. A Master's student in Pharmacy observed the patient contacts of the pharmacy staff in sequential

order during 1 day at each pharmacy. The observation began at the entrance of one patient into the pharmacy and lasted until the departure of this patient; thereupon, the student observed the next patient who entered the pharmacy. Information about the staff member serving the patient, the number of dispensed medications, and content of counseling were manually ticked on a checklist. The checklist enabled ad hoc coding of the patient contacts by allocation into two categories ("medication on prescription" and "medication over the counter"), as well as the coding of four themes ("administration", "dose", "effect", and "adherence") and 12 topics of adherence counseling. The latter were deduced from published recommendations (**Table 1**).[230] Observation time and characteristics of the pharmacy and the team were simultaneously assessed. At the end of the observation time, an interview was performed with all present pharmacists, consisting of two closed-ended questions (active approach to patients about adherence and frequency of active approach per month) and three open-ended questions (triggers, topics, and barriers in adherence counseling).

We defined explicit adherence counseling as provision of patient-centered information that directly addresses the spectrum of adherence problems, including unintentional (ie, the patient is physically or cognitively unable to adhere) and intentional nonadherence (ie, the patient is not willing to adhere); this included the use of targeted questioning ("have you missed any pills in the past week"), offer of refill reminders and dose-dispensing aids, reinforcement, etc.[230] We defined implicit adherence counseling as provision of product-centered information, eg, information on administration or dose. This information does not directly address adherence but might prevent unintentional nonadherence.

Coded patient contacts were quantified and analyzed statistically within the sample of patients obtaining one or more medications. Answers from the interviews were categorized and analyzed quantitatively. We used SPSS V. 20 (IBM Corp., Armonk, NY, USA) for Windows for descriptive and comparative (χ^2-test) calculations. A P-value of ≤0.05 was considered statistically significant. Missing data were excluded from analysis.

Results

During February and March 2010, 21 community pharmacies were approached, 20 took part in the study, and one pharmacy declined participation without specification of a reason. The pharmacies were located in the city center (eight), in residential districts (eight), and in shopping centers (four). Of a median of 9.25 opening hours (range 8.75–11.5), 7.5 hours (range 6.5–7.75) were observed per day and pharmacy. The observation day was equally distributed over the weekdays (Tuesday [five]; Monday, Wednesday, and Thursday [four]; and Friday [three]). The median number of working staff members was two pharmacists, three pharmacy technicians, and one apprentice, respectively.

During the total observation time of 148.1 hours, 1,866 patient contacts were observed, of which 21 resulted in a referral to the physician, 18 in further inquiry by phone or fax with the physician, and eight in a refusal of dispensing. A total of 1,476 patient contacts included the dispensing of one or more medications, constituting the basis sample for statistical analysis (**Figure 1**). Of 2,789 products dispensed, 1,742 (62.5%) were on prescription and 1,047 (37.5%) were "over the counter" (OTC). Counseling was provided to 799 (54.1%) patients, with 735 (49.8%) patients counseled about administration, 362 (24.5%) about dose, 267 (18.1%) about effect, and 99 (6.7%) about adherence (**Figure 2**). The total number of observed counseling events was 1,800, with most patients receiving counseling on two (55.4%) or three (21.2%) themes. Explicit adherence counseling (n=130) mostly included comprehensive instruction (49 [37.7%]) and counseling on knowledge of disease and medication (36 [27.7%]) (**Table 1**). Significantly more patients solely obtaining prescription medication were provided with overall counseling compared with those solely obtaining OTC medication (57.3% vs 50.2%) (χ^2=7.1, P=0.002; n=1,402). In the same groups, the single theme "effect" was observed significantly more often in patient contacts with the dispensing of OTC than in patients contacts with the dispensing of prescription medication (31.3% vs 6.3%) (χ^2=148.3, P<0.001; n=1,402). There was no significant difference in frequency of adherence counseling for prescription vs OTC medication (7.1% vs 5.9%) (χ^2=0.9, P=0.17; n=1,402).

Focusing on the 757 patients solely receiving prescription medication, 421 (55.6%) had a new prescription, 293 (38.7%) requested a repeat prescription, 26 (3.4%) had both, and 17 (2.2%) were not specified (**Figure 1**). The pharmacy staff provided overall counseling to significantly more patients with new prescriptions compared with patients with repeat prescriptions (74.1% vs 33.8%) (χ^2=115.0, P<0.001; n=714). There was no significant difference in frequency of adherence counseling in these two groups (new vs repeat prescriptions: 7.1% vs 4.4%, respectively) (χ^2=2.2, P=0.14).

Of all patients receiving one or more medications (n=1,476), 368 (24.9%) were served by a pharmacist, 1,075 (72.8%) by another staff member (eg, pharmacy technician or apprentice), and 33 (2.2%) by a combination of both. Significantly more patients received counseling when they were served by a pharmacist compared with other staff members (62.1% vs 51.2%) (χ^2=14.1, P<0.001). Adherence counseling was provided to twice as many patients when served by a pharmacist compared with other staff members (10.7% vs 5.2%) (χ^2=14.2, P<0.001).

Of 390 patients who did not receive a medication at the observed contact (eg, buying dose-dispensing aids, ordering out-of-stock medication), 42 (10.8%) received counseling.

Interview

Among the 20 community pharmacies, 33 pharmacists participated in the interview (with median two and range of one to three pharmacists per pharmacy) and were mainly women (69.7%), with a median age of 41 (range 25–68) years and a median duration of 14 (range 1–43) years after university graduation. They worked with a median of 90% employment at the community pharmacy (range 40%–100%). All pharmacists except one reported actively asking patients about their adherence, and 20 (60.6%) did so on a daily basis. **Figures 3** and **4** illustrate named triggers and topics of adherence counseling. Barriers included rejection by the patient (15 [45.5%]), lack of time (12 [36.4%]), lack of patient data (seven [21.2%]), lack of checklists and demo material (six [18.2%]), lack of confidential room (five [15.2%]), lack of remuneration (three [9.1%]), and "Other" (19 [57.6%]).

Discussion

Counseling was provided to half of the patients receiving one or more medications and occurred more frequently when the medication was on prescription, on a new prescription, or if patients were served by a pharmacist. The content of the counseling mostly included information on medication administration and dose. Only 6.7% of the patients obtaining medication received explicit adherence counseling, significantly more of them if the pharmacist was involved in the dispensing. However, most pharmacists seemed motivated to provide adherence counseling. They named a lot of triggers but also barriers to start adherence counseling and mostly named topics for adherence counseling, which only implicitly addressed the issue.

Due to easy access, regular patient visits, the possibility to monitor medication refill frequency, and the competences of the pharmacist, the community pharmacy seems to be a predestined place for counseling about adherence. In our study, we showed that if pharmacy staff counseled, they counseled about more than one theme, indicating motivation and assumption of responsibility for safe and effective medication management. If only looking at prescription medication, unsurprisingly, dispensing of first prescriptions largely predominated in the number of patients provided with counseling. A considerable percentage (74.1%) of these patients were counseled. Apart from the need to ensure the patient's knowledge at first use, the patient filling a first prescription also seems to expect more counseling, which might result in facilitating counseling.[231] Still, explicit adherence counseling plays a very small part in both situations, dispensing of a new and of a repeat prescription. Because the pharmacist is able to detect nonadherence in patients with long-term therapy, eg, by analyzing medication refill frequency, we expected adherence counseling to occur more in patients with repeat prescriptions.

Evidence that community pharmacy interventions have been successful in improving health outcomes and adherence have accumulated,[44-50,232-235] and two Cochrane reviews concluded that the

pharmacists' cognitive services were beneficial for safe and effective medication use.[51,52] However, our study confirms results of earlier studies showing that community pharmacies provided limited pharmaceutical care services,[218,220,236-238] indicating a problem of implementation in daily practice. Studies on counseling in community pharmacies were conducted using patient and pharmacist surveys, observation, and simulated patient visits.[239,240] They mostly reported on pharmacists' behavior only, with a total counseling rate of 8%–100%.[240] Similar to our study, predominant categories of counseling were administration and dose, and hence were more product- than patient-centered.[223-225,240] A large proportion of communications (26%–40%) between pharmacists and patients was reported to be nonmedical.[237,238] The only observational study specifically investigating adherence counseling was performed with pharmacy students, who had a lack of specific training in adherence management and of resources, and therefore reported not to address adherence in counseling sessions.[241] A German study showed that pharmacists documented "evidence of nonadherence" in only 1.6% of all assessed drug-related problems during patient contacts in community pharmacies, indicating that the pharmacists had difficulties in identifying nonadherence.[242]

We showed that pharmacists provided more counseling than pharmacy staff, which confirms the results of another study.[236] Differences may arise from the more detailed knowledge about therapy and disease, more intense training, and from the assumption of the responsibility for safe and effective medication use by the patients. This knowledge and attitude, however, should be transferred to the whole pharmacy team.

In our study, the comparison of observed counseling practice (observed adherence counseling of 6.7%) with pharmacists' interview responses (60.6% indicated actively approaching patients with adherence issues every day) reveals a discrepancy between our definition and the pharmacists' opinions about the topics of adherence counseling. We defined the topics more explicitly, whereas the most frequently named topics by the pharmacists were implicit. Several problems could arise from the implicit approach. First, the patients might not understand the purpose of the counseling and reject it. Second, while some unintentional nonadherence problems might be clarified with counseling on administration and dose, intentional nonadherence might be completely overlooked. Literature has described habits of pharmacists mainly asking standardized questions, eg, "Do you have any questions?"; at the same time, authors have suggested a more considerate and individualized approach according to patients' needs, and the necessity of engaging patients in counseling.[225,243,244] Such an approach would include a more direct addressing of adherence. Further, almost all topics on our predefined list of explicit adherence counseling were named by the pharmacists, indicating that they were familiar with most of the topics, though less frequently addressed them during the observed patient contacts.

The most frequently reported barrier was rejection of the offered counseling by the patients. This has also been shown in other studies, with 41%–63% of patients declining offered counseling.[231,237] Expectations of patients have been shown to not coincide with the recent development of the pharmacist's role.[244,245] Qualitative studies reported patient tendency to rely solely on the physicians, recommendations and to deny the pharmacists' competences.[246,247] This attitude persisted even in patient-centered consultations[248] and was confirmed by a recent study that collected data over 15 years.[249]

It seems logical that patients with prescribed medications obtain more counseling, on one hand because the medication plan usually is more complex, including long- and short-term medication for serious diseases, hence counseling might be more relevant. On the other hand, the counseling about prescribed medication is remunerated by a medication tax of CHF 4.20 (= US$ 4.60) per prescribed item. Nevertheless, lack of adequate remuneration was only named by 9.1% of the pharmacists as barrier for adherence counseling. Remarkably, counseling was also given without product sale.

Apart from the structural factors discussed above, several procedure-related factors were identified, which hinder pharmacists in counseling, and patients in asking questions. Time constraints pose such a barrier.[241,249-251] However, surveys on pharmacists' activities revealed that pharmacists were mainly occupied with traditional product-centered activities, such as business management, logistics, and product assembly, than with patient-centered activities, like counseling.[219,221,222] In our study, we observed that pharmacists had fewer patient contacts in relation to their presence compared with the rest of the staff. Consequently, the problem could be designated as time mismanagement, and reconsiderations of staffing and of assignment of responsibilities might be a solution.

Another barrier to patient-centered, individualized counseling is the lack of privacy, named by the pharmacists in our study and also reported elsewhere.[236,246,251] Most people certainly are uncomfortable discussing their sensitive health problems next to a line of others at the counter. The traditional conceptualization of the pharmacy accommodations reminds patients more of a shop[247] than of a health care center and hence is not supportive in promoting counseling.

The limitations of our study firstly include the restriction to one region in Switzerland. Secondly, the methodology of observation has been reported to yield variable results but a more holistic picture of counseling practice.[240] We chose a minimally obtrusive method to observe the counseling, in order to prevent the introduction of biases. However, the open approach of the pharmacies and the presence of an observer could have triggered pharmacy staff to engage more in counseling practice than usual (Hawthorne effect).[252] Thirdly, the ad hoc coding without review by second person could have limited the results' reliability. Fourthly, due to the observational setting, we could not evaluate the rate of

overall offered counseling. With the most named barrier for adherence counseling being the rejection of counseling by the patients, we can assume higher counseling rates at higher acceptance of counseling.

Conclusion

The unique position of the community pharmacy in the health care chain and the competencies of pharmacists make the community pharmacy a predestined place for medication and adherence counseling. Pharmacists are motivated to provide counseling but experience several structural and procedural barriers in delivering it. In our study, half of patients collecting one or more medications received counseling, which was predominantly product-centered, and only 6.7% of the patients received adherence counseling. This study revealed insufficient knowledge and gaps in the provision of explicit adherence counseling by pharmacists. Future studies should explore the pharmacist–patient interaction in depth and clarify how barriers to adherence counseling in the community pharmacy can be overcome.

Disclosure

The authors report no conflicts of interest in this work.

Annex

- A1.1 Assessment of pharmacy characteristics
- A1.2 Checklist for recording of counseling
- A1.3 Pharmacist interview

Acknowledgement

We would like to thank Irene Rüfenacht (MSc Pharm) for her participation in conceptualization of the project and data collection, and Gülistan Karatas (MSc Pharm) for data entry.

Authors' contributions.

All authors participated in conceptualizing the study. FB analyzed data and drafted the manuscript. IA and KEH revised the draft critically for intellectual content.

Tables and Figures

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Table 1: Definitions and numbers of observed counseling events by counseling domains and topics of explicit adherence counseling		
Counseling domain	**Definition**	**No. of observed counseling (Prescription / OTC)**
Administration	Counseling on basic administration issues (e.g. with respect to meals)	435 / 317
Dose	Counseling on dosage, dosing times, intervals, and duration of medication therapy	418 / 226
Effect	Counseling about the effects of the medication	53 / 221
Adherence	Explicit adherence counseling according to the list of topics	73 / 57
Topics of explicit adherence counseling		
Morisky question	Asking the explicit question: "Do you ever forget to take your medication?"	0 / 0
Adherence	Directly addressing adherence, assessing the patients attitude towards adherence, and mentioning the importance of adherence	8 / 2
Positive reinforcement	Acknowledging and encouraging the patients on efforts for adherent behavior	2 / 0
Motivation	Assessing motivation of patient to be adherent and, if necessary, providing support	2 / 2
Organization	Offering facilitation of medication management through stick-on labels, diaries, timers, dose-dispensing aids, phone reminders, organization of social support etc.	9 / 2
Appointment keeping	Reminding the patient of appointments (with physician, refill, monitoring)	1 /1
Psychological barriers	Among others: Forgetfulness, fear of side effects	3 / 0
Physical barriers	Among others: Impaired vision and dexterity, difficulties with swallowing	4 / 0
Instruction of product	Providing comprehensive verbal information on use of the medication in the context of adherence	31 / 18
Written Information	Providing written information on the medication	2 / 5
Knowledge about disease / therapy	Explaining the relation between medication therapy and disease / necessity of therapeutic intervention	10 / 26
(Self-) Monitoring	Instructing the patient about how to perform (self-) monitoring, inclusive instruction on interpretation of monitored parameters	1 /1

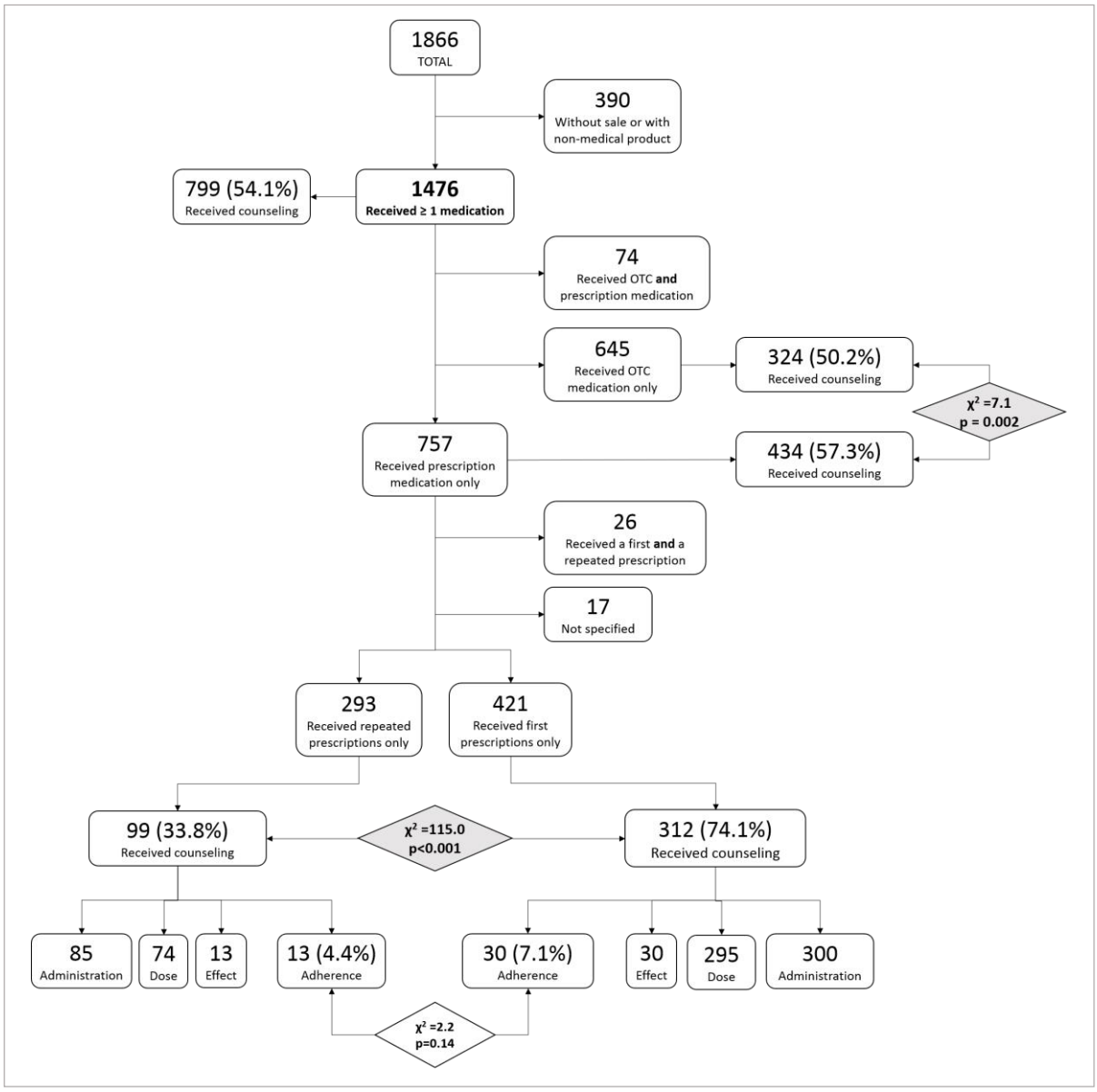

Figure 1: Patient numbers and allocations by category and domain.

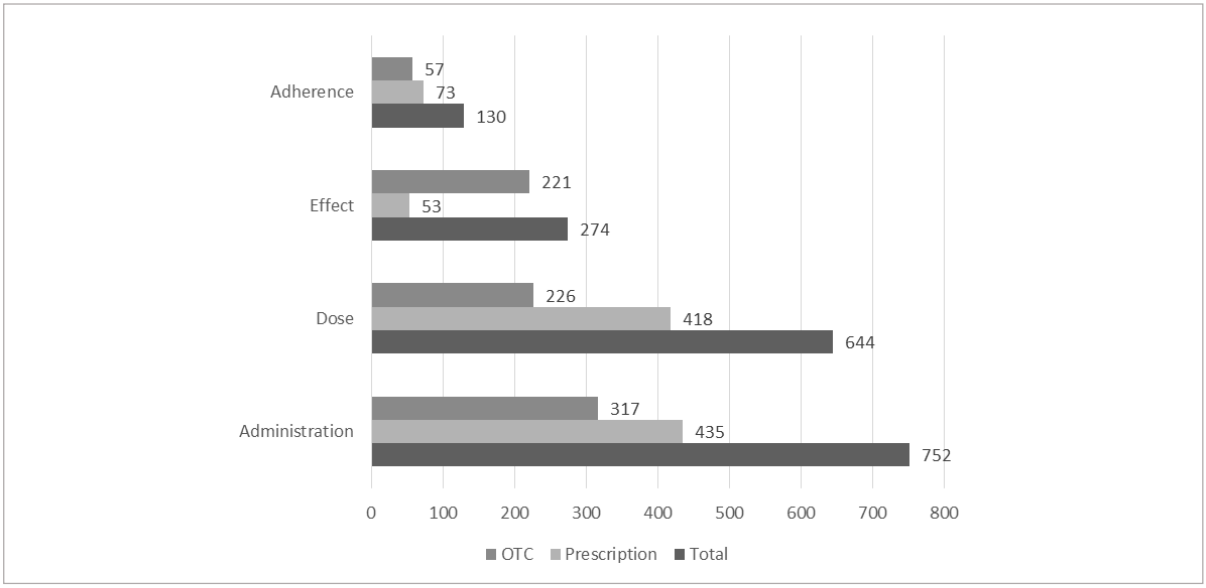

Figure 2: Numbers of observed counseling events about administration, dose, effect, and adherence in total and according to dispensing category (prescription / OTC) (n_{total} = 1'800).

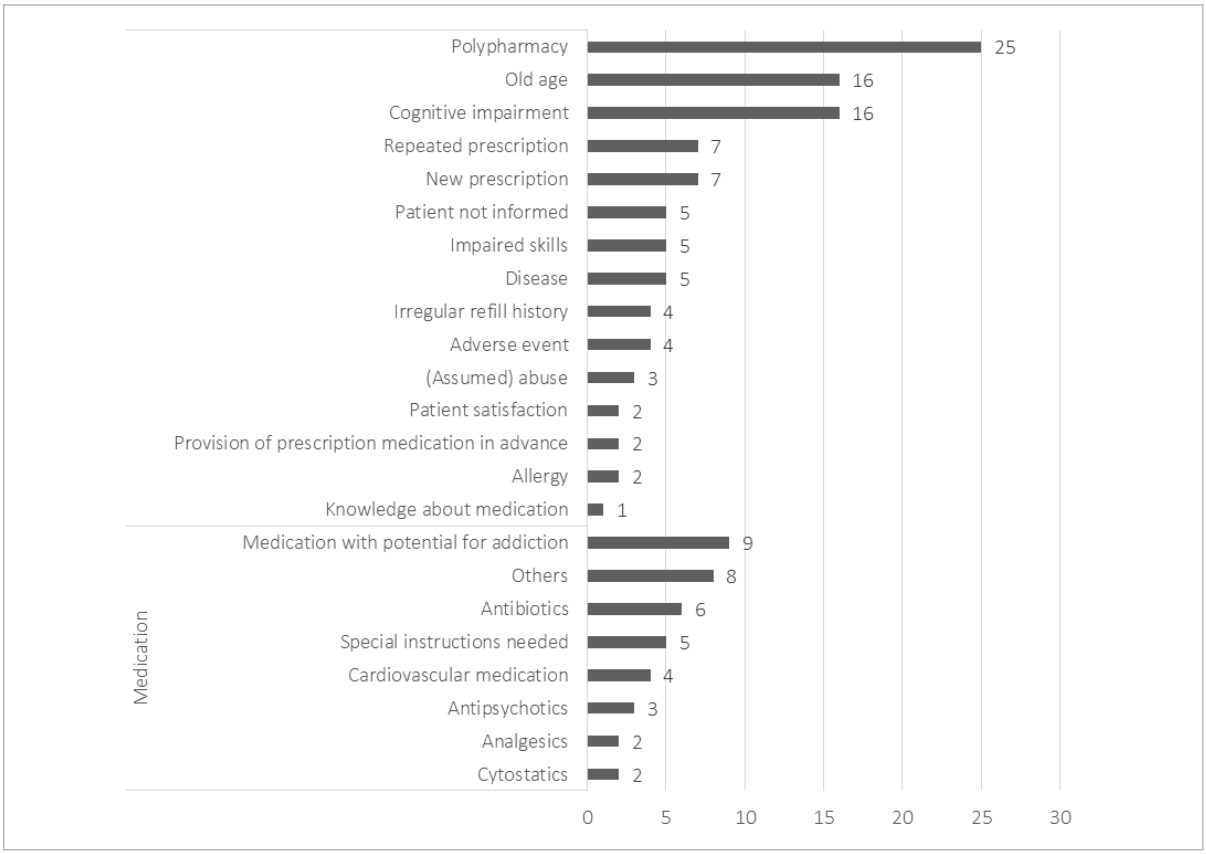

Figure 3: Triggers to start adherence counseling named by 31 pharmacists.

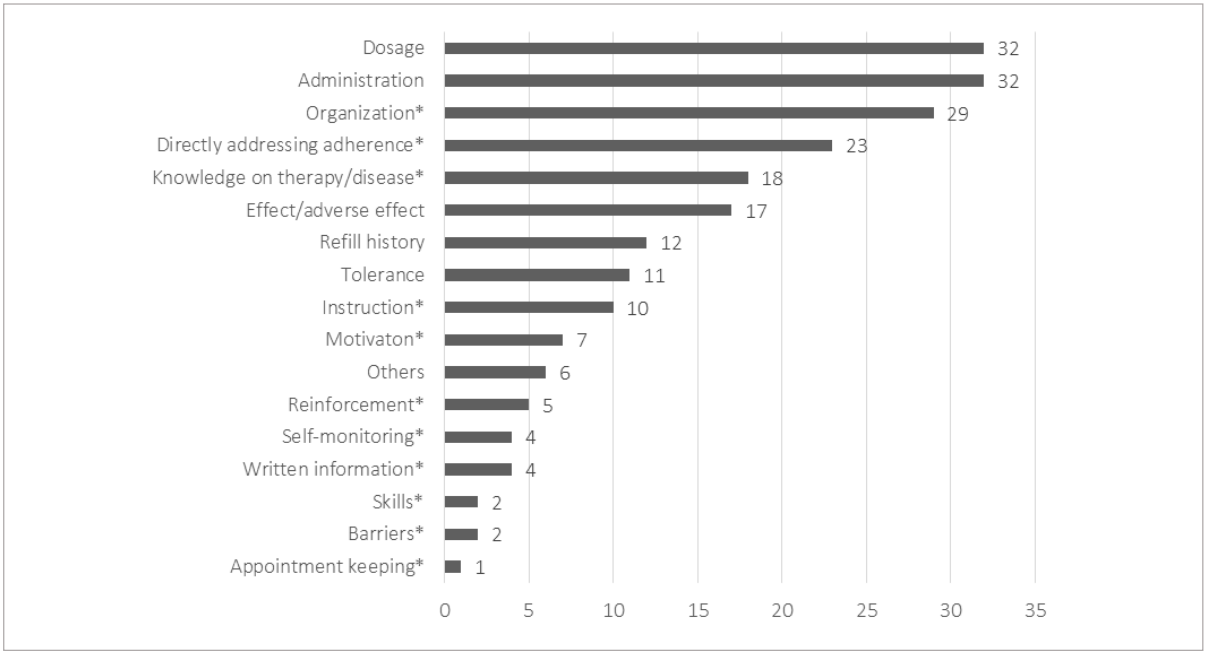

Figure 4: Topics of adherence counseling named by 33 pharmacists. The topics marked with asterisks correspond to the predefined topics of explicit adherence counseling in **Table 1**.

Project B2

First evaluation of Pharmis® blister packaging provided by pharmacies in Switzerland

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Background and Objective

Multicompartment blister packaging is thought to facilitate drug intake and enhance compliance. To date, reviews could not state clear recommendation for their use [147,156,253]. Pharmis® blisters (*herein as synonym for multidrug punch cards*; **Figure 1**) were introduced in 2002 as first weekly blister packaging in Switzerland. They are produced manually with the aid of a software program and have not yet been evaluated. Our aim was to assess experiences, benefits, and expenditures of pharmacies providing this service.

Methods

A national questionnaire based survey was performed including all pharmacies providing Pharmis® blister packaging for ≥ 6 months. Questionnaires were piloted and sent to all pharmacies. They had to be filled out by a pharmacist or a technical assistant. Pharmacies which did not answer in time were contacted by phone. Data was analyzed descriptively by SPSS Vers. 17 for Windows.

Main Outcome Measures

Benefits and experiences were measured on 4-point Likert scales and values like time, expenditures or compliance rate were numeric estimates.

Results

A total of 52 pharmacies provide Pharmis® blisters in Switzerland. The return rate of the questionnaires was 76% (n=40). Pharmacies were situated in the German speaking part of Switzerland (**Figure 1**), mostly in rural and peripheral areas (78%) and were mainly members of a grouping (60%). All were community pharmacies except for one hospital pharmacy.

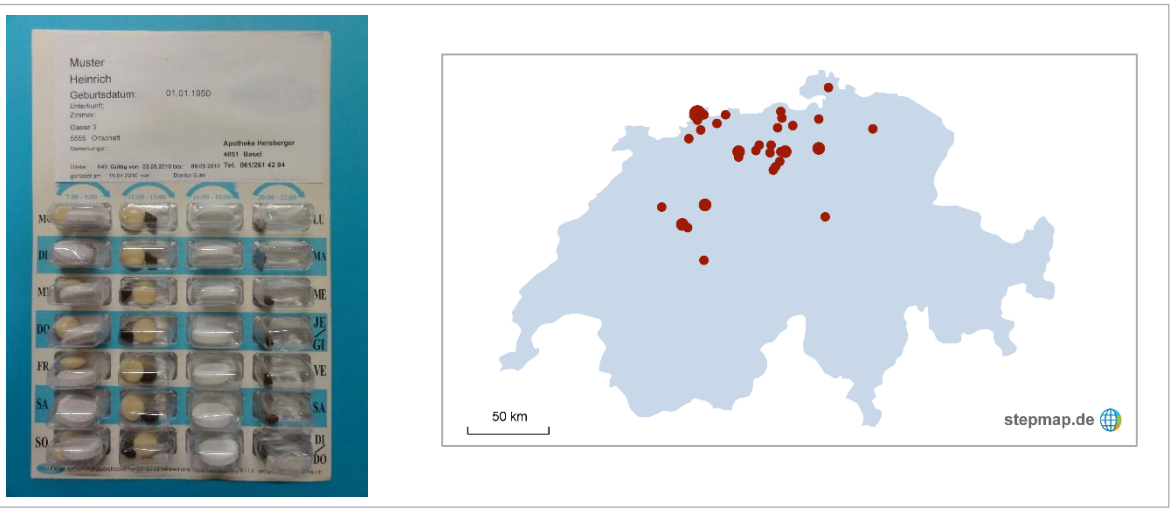

Figure 1: Pharmis blister (left); Distribution of Pharmis® distributing pharmacies in Switzerland; = > 2 pharmacies, = 2 pharmacies, = 1 pharmacy per city, village (right).

Patients

Numbers and distribution of patients see **Table 1/Figure 2**. Thirty pharmacies recommended Pharmis® blisters actively to their patients and reported a success rate of 31% (± 26%, range 0-100%). They recommended Pharmis® blisters to: Patients with multiple medication (29%), patients with compliance problems (14%), elderly patients (11%), overstrained patients (9%), and patients after hospital discharge (6%). Twenty-nine pharmacies (73%) indicated that the patients were very satisfied with Pharmis® blisters. Of 33 pharmacies with ambulatory patients, 31 controlled compliance by pill count, if used Pharmis® blisters were brought back. Pharmacies estimated the taking compliance rate of the ambulatory patients at 93% ± 4%.

Table 1. Number of patients provided with Pharmis® blisters.
No., number; amb, ambulatory..

Total no. of patients	Mean no. of patients per pharmacy (range)	Total no. of ambulatory patients	Mean no. of amb patients per pharmacy;n=33 (range)
1'869	48 ± 39 (1-135)	269	8 ± 8 (1-30)

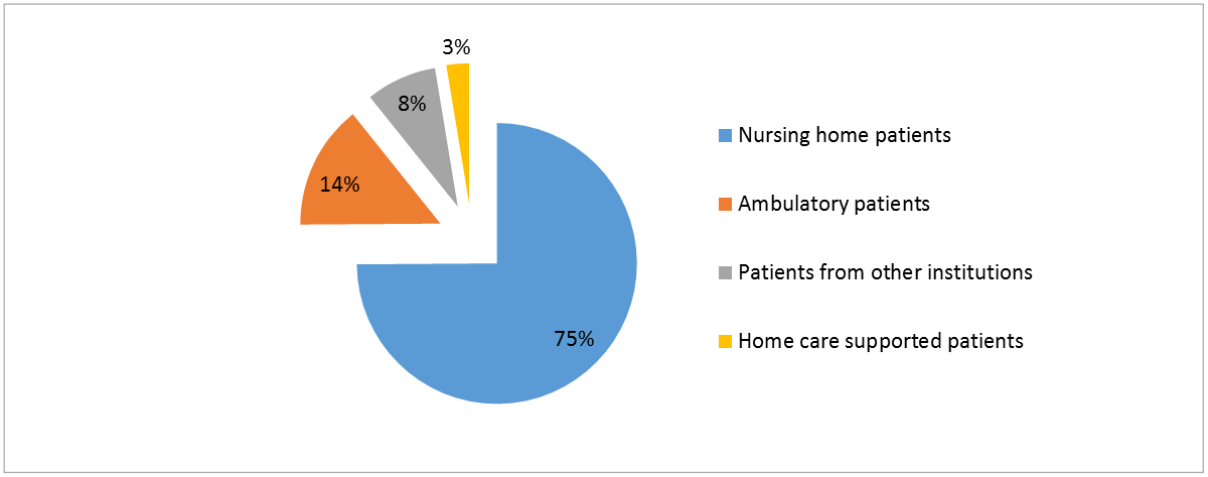

Figure 2: Number and distribution of patients provided with Pharmis® blisters (n=1'869).

Expenditures

Expenditures of time, material, and software for producing one Pharmis® blister was 15.70 CHF (**Table 2**). Space requirements for the production were evaluated as appropriate by 72% of pharmacies. Difficulties in production were mainly due to the software and it was the main point of dissatisfaction, indicated by 32% of pharmacies.

Table 2. Estimation of expenditures per production of one Pharmis® blister.
* neglected for calculation of costs. CHF, Swiss francs; min, minutes; tech. assist., technical assistant.

Production steps	Total duration (min)	Proportion of production steps by staff member (%)			Mean time per production step by staff member (min)		
		Pharmacist	Tech. assist.	Other	Pharmacist	Tech. assist.	Other
Administration	6.8 ± 5.6	25.7 ± 2.9	74.2 ± 32.8	0.1 ± 0.8	1.7	5.0	0
Filling	8.7 ± 4.6	15.1 ± 7.5	80.9 ± 30.4	4.0 ± 16.6	1.3	7.0	0.3
Control	4.3 ± 3.1	94.5 ± 5.5	5.5 ± 15.5	0	4.0	0.2	0
Total time required per staff member (min)					7.0	12.5	0.3
Estimated salaries per hour					60.00 CHF	35.00 CHF	-*
Salary expenditures per blister by staff member					7.00 CHF	7.10 CHF	
Total salary expenditure					14.10 CHF		
Material costs per blister					1.20 CHF		
Software costs per blister					0.40 CHF		
Total expenditures per Pharmis® blister					**15.70 CHF**		

Benefits

The packaging service is remunerated 21.60 CHF per blister if the patient takes ≥ 3 different medications per week and if it is prescribed by a physician. Pharmacies agreed that other benefits arose as well from the introduction of Pharmis® blister service (**Figure 3**). But the gain of new customers, patients, and sales increase were mainly negatively valued. Generally the handling of the software, preparation, filling, and sealing of the Pharmis® blister was rated rather easy or very easy.

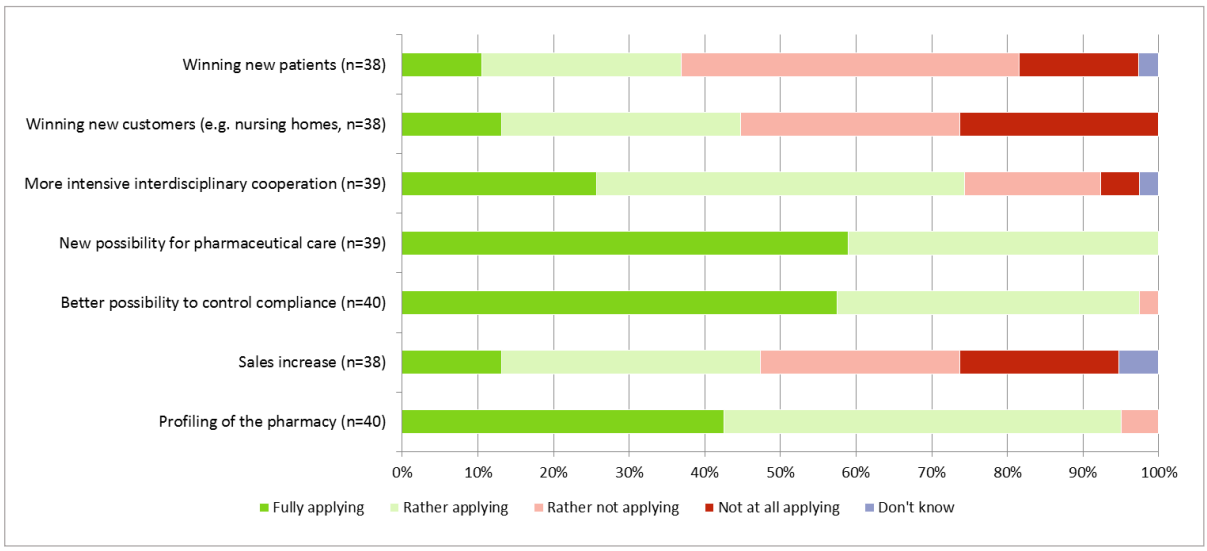

Figure 3: Pharmacies' ratings on benefits perceived after introduction of Pharmis® blisters.

Discussion

Pharmis® blister distributing pharmacies seem to stay regionally limited, grouped around Pharmis GmbH head office. In the French speaking part of Switzerland a French competitive product (Oréus®)

is used. The technology did not break through to the hospital setting because medication is seldom distributed to individual patients. The devices employed in the nursing home setting are thought to relieve the nursing home staff and are not operated by the patients themselves. Only 269 ambulatory patients are provided with Pharmis® blisters. Pharmacies perceived the patients as very satisfied. The pharmacies recommended blisters actively to a specific group of patients. When asked, they said that the acceptance was low in middle aged, mentally sound patients. Pharmis® software was a recurring issue and was described as user-unfriendly. However, benefits seem to outweigh expenditures. In the aspect of compliance enhancement, Pharmis® blisters seems to have an impact since pharmacies estimated remarkably high compliance rates for Pharmis® blister users (93.3%).

Conclusions

- The Pharmis® blister packaging service integrates well into daily work of a community pharmacy.
- Pharmacies estimate high compliance rates for ambulant Pharmis® users.
- Although benefits for pharmacies and patients overweigh expenditures, still few of the community pharmacies in Switzerland provide such service.
- The full potential of Pharmis® blisters in ambulatory care is only little taped.

Annex

- A2.1 Pharmacy survey on multidrug punch card provision

Project B3

Multidrug punch cards in primary care: a mixed methods study on patients' preferences and impact on adherence

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Abstract

Background: Multidrug punch cards are frame cards with 28 plastic cavities filled with a patient's oral solid medication. They are used in primary care to facilitate medication management and to enhance adherence. Main criticism concerned handling difficulties and fading knowledge about medication of patients using them. This study aimed at exploring daily use, preferences and adherence of primary care patients using multidrug punch cards.

Methods: Community pharmacies in Switzerland recruited primary care patients using multidrug punch cards. A mixed methods approach was applied with quantitative interviews performed by telephone and qualitative interviews face-to-face.

Results: Of 149 eligible patients from 21 community pharmacies, 22 participated 2011 in the quantitative and 11 participated 2013/14 in the qualitative interview. Patients were very satisfied with the multidrug punch cards and stated increased medication safety. All considered adherence as very important. Self-reported adherence was 10 (median) on a visual analogue scale (0 = no intake, 10 = perfect adherence). The absence of package inserts and predefined handling difficulties e.g., tablets spiking at removal were not perceived as problems.

Conclusions: Patients are satisfied with the multidrug punch cards, feel safe, mostly have no handling problems and adhere to their treatment. Trust in health-care professionals and patients' experiences emerged as key variables for initiating multidrug punch card use and for medication adherence. This mixed methods study invalidates previous concerns about disadvantages of multidrug punch cards. Health-care professionals should actively recommend them for primary care patients with polypharmacy and poor adherence.

***Keywords**: pharmaceutical care, community pharmacy, medication adherence, primary care, dose-dispensing aids, multidrug punch card, polypharmacy, mixed methods.*

Introduction

Medication management i.e., the patient's ability to self-administrate her/his medication constitutes a major preoccupation in a patient's life [31,254,255]. Physical and cognitive barriers hinder patients from removing medication from the primary and secondary packaging, from preparing it (e.g., handling a measuring cup, tablet-splitting, etc.) and from administering it the right way at the right time in the right dosage [35,207,256]. Medication administration errors including non-adherence and incorrect use belong to the leading causes for adverse drug reactions and related hospitalizations [12,107-109]. Elderly patients with polypharmacy for chronic diseases are at highest risk for such adverse drug reactions [257].

The World Health Organization defined medication adherence as "the extent to which a person's behavior - taking medication, following a diet and/or executing lifestyles - corresponds with agreed recommendations from a healthcare provider" [37]. An average of 50% of patients does not take long-term medication as prescribed [37], either intentionally (when the patient consciously decides not to take the medication) or unintentionally (when the patient is not able physically or cognitively to follow his own intent of taking medication as recommended). Non-adherence increases morbidity and mortality, decreases quality of life and raises healthcare costs [83,99,103,105,125,166,167]. Strategies and aids to enhance adherence have been of major interest [143]. Dose-dispensing aids such as multidrug punch cards and pillboxes have been suggested for unintentionally non-adherent elderly patients with complex medication regimen [62,77,145]. Current literature reviews state an effect of dose-dispensing aids on adherence and clinical outcomes, but robust and reproducible studies are lacking [147,155,258].

Several studies have described handling difficulties with the use of dose-dispensing aids [32,146,151,259]. In one study, six out of fifteen patients put the loose tablets from a dose-dispensing aid back into a bottle because they could not handle the device [151]. Another study reported that patients who elaborated their own medication management system tended to return to it after initiation of a prefilled dose-dispensing aid [32]. Such misuse is critical for patient safety. Medication knowledge has been advocated as essential for patient safety. Often, prepackaged dose-dispensing aids are delivered directly to the patient's home and thus were observed to reduce contact between the pharmacist and the patient. In connection, knowledge about self-administered medication seemed to be poorer in patients with dose-dispensing aids than in patients who manage their medication on their own [153,154]. A recommendation paper of the Royal Pharmaceutical Society criticizes the distribution of dose-dispensing aids to all patients without assessing their capabilities and needs [152]. In Switzerland, one single criterion (intake of >3 different medications) is required by the health insurance to supply reimbursed dose-dispensing service (repackaging of solid oral medication into dose-dispensing aids by a healthcare provider) by the community pharmacy to primary care patients.

Two qualitative studies explored the views of patients using various dose-dispensing aids [32,255]. Findings of these studies indicated that one group of patients saw clear benefits in dose-dispensing aids, whereas the other group felt patronized and restricted in liberty. Some of the patients had handling problems with the devices and troubles with identifying their medication. Both studies concluded that future studies have to clarify which patients benefit most from dose-dispensing aids and how to recognize them in primary care.

Multidrug punch cards are disposable frame cards with plastic cavities, sealed with a foil backing, with typically 28 compartments, filled by pharmacy staff, by a specialized company or an automated system (**Figure 1**). They provide a visual reminder for medication intake, the possibility of adherence self-monitoring and the saving of time, costs, healthcare resources (e.g., home care nursing), and medication waste. Multidrug punch cards were introduced in Switzerland in 2002 together with a documentation software for community pharmacies [157].

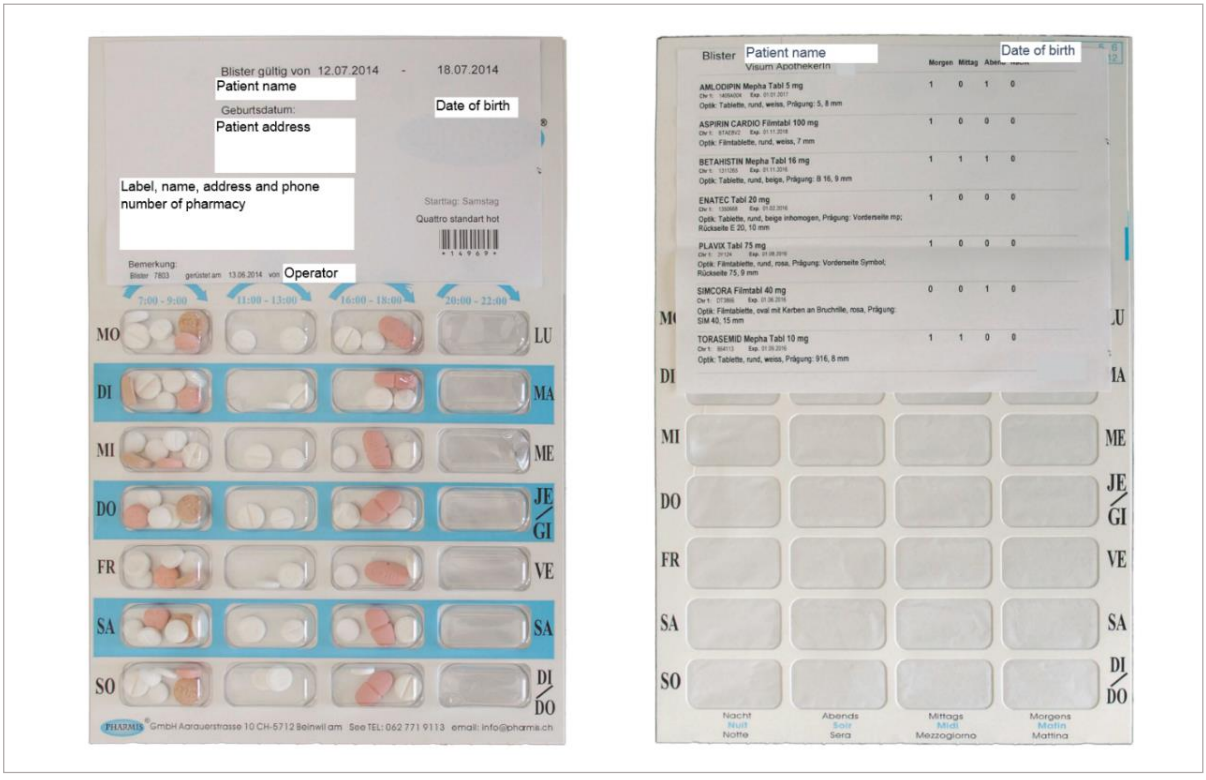

Figure 1: Multidrug punch card. Front side (left): 28 plastic cavities with visible packaged medication and labeling with patient and pharmacy information. Back side (right): 28 cavities sealed with foil and marked with indication of dosing time (morning, lunch, evening, night; Monday–Friday); the adhesive medication plan labels brand name, dose, administration number, dosing frequency, size, color, imprint, batch number, and expiration date of each packaged drug. All specifications are in German.

We conducted a mixed methods study to assess experiences, attitudes and adherence of primary care patients using multidrug punch cards in Switzerland. We aimed at investigating the preferences of primary care patients using multidrug punch cards in daily life, at compiling a profile of the primary care patient benefitting most of the multidrug punch cards' use and thus at facilitating a targeted adherence interventions. The results should advance the rational distribution of multidrug punch cards and connected healthcare services.

Materials and methods

Quantitative interviews were performed in 2011 and qualitative interviews were conducted sequentially in 2013/2014 to clarify the results. A positive notification was obtained by the regional ethic boards. Good Reporting of A Mixed Methods Study (GRAMMS) guidelines were considered [260].

Recruitment and inclusion criteria

In 2011, all community pharmacies in the cantons of Basel-Stadt, Baselland, Aargau and Solothurn (Switzerland) delivering multidrug punch cards to primary care patients were asked to participate in the recruitment of patients for the quantitative interviews. Community pharmacies providing multidrug punch cards to primary care patients in the cantons of Basel-Stadt and Baselland were re-invited in 2013/2014 to recruit patients for the qualitative interview. One pharmacist per pharmacy was instructed for recruitment. Patients were eligible if they had used multidrug punch cards for at least three months, lived independently, administering medications without external help, spoke German and were able to give informed consent. The pharmacists decided upon eligibility of the patients and recruited them by phone or face-to-face at their next visit at the pharmacy. The study team received the contact details of accepting patients and called them to fix a date for the interview. Patient information and the informed consent form were provided through the pharmacy or at the interview. For both interviews, patients were approached in the same manner, irrespective of participation in the first, quantitative interview.

Instruments

A quantitative questionnaire was developed containing five domains (living situation, general questions about the multidrug punch cards, handling, design and medication adherence). Answers were indicated as multiple choice, Lickert-scales, on visual analogue scales (VAS) or were open ended. The questionnaire was validated for feasibility, understandability and consistency of the scales. The questionnaire comprised 31 questions and took 30 minutes to conduct. Demographic parameters included age, sex, living situation, education, status of employment and number of medications. Adherence was measured through patient self-report on a VAS ranging from 0 (taking no medication) to 10 (taking all prescribed medication every day at the right time). The term 'medication adherence' is not colloquially used in Swiss German. We therefore replaced it with 'fidelity to therapy'

[Therapietreue], which we suggested to be more understandable. The term was explained to the patients before patient self-report of adherence by the VAS and discussion about importance of adherence was conducted.

A qualitative topic guide was constructed upon the results of the quantitative questionnaire with themes that remained unclear or contradictory. The topic guide and the course of the interview were piloted with two patients who were not included into the final analysis. Adoption of the multidrug punch cards, acceptance, use in everyday life, design and medication adherence built the five domains. Subtopics were outlined with 19 pre-worded questions. Demographics and adherence were asked in the same manner as in the quantitative interview. Both, the quantitative questionnaire and the qualitative topic guide were applied as interviews. After interviews had been held, the current medication plan was obtained from the corresponding pharmacies.

The quantitative interview was conducted by telephone after informed consent was received by post. One interviewer performed the interview, reading out the questions and the possible answers of the questionnaire. Immediate feedback was requested from the interviewed patient for assurance of ticking the right box.

The qualitative interview was held face-to-face at the patient's home or at the pharmacy in a separate room. FB led the interview and another researcher asked in-depth questions. Each domain was introduced to the patients by a general open-ended question to allow the patients to answer freely. Subtopics that remained untouched were then explored by further questions. The order of the domains and questions followed the patient's answers. The interviews were held in Swiss German and were audiotaped. One research assistant (NR) orthographically transcribed the recordings in German language, preserving dialect expressions. All transcriptions were double-checked by FB.

Analysis

The quantitative interviews were analyzed descriptively by using Microsoft Excel 2013 for Windows (Microsoft Corporation, Redmond, WA, USA). Answers to open questions were categorized and analyzed quantitatively. Missing data were excluded from the analysis. Numbers of valid answers are given for each question.

Transcriptions of qualitative interviews were transferred to MAXQDA V. 11 for Windows (VERBI GmbH, Berlin, Germany). Data were analyzed analogously to a five-stage 'framework approach' developed for applied qualitative research [255,261]. A coding framework was constituted by preliminary coding of five interviews. Domains related to the original topics were structured as main codes and emergent themes formed sub-codes. After verification, the coding framework was applied to all interviews. Coding was performed manually line-by-line by FB. Codes of all interviews were grouped for detection of

associations and patterns. Quotations were selected to illustrate the analysis. They were translated into English by FB and checked by a native English speaker. Original German transcriptions of the quotations are listed in the supplementary material.

Quantitative and qualitative data are presented in direct relation to each other in the Results' section and were integrated by FB on the level of interpretation. Qualitative data were used to complete and explain findings from the quantitative interviews.

Results

Demographics

In 2011, 33 of 266 community pharmacies in the cantons of Basel-Stadt, Baselland, Aargau and Solothurn delivered multidrug punch cards, mainly to nursing home patients. Of the 25 pharmacies supplying primary care patients, 21 participated in the recruitment of the patients for the quantitative interview. They supplied a total of n_{quant}= 149 patients, of whom 25 (17%) were contacted by the study team and 22 (15%) consented to perform the quantitative interview.

In 2013/2014, 13 of 124 community pharmacies in the cantons of Basel-Stadt and Baselland supplied primary care patients with multidrug punch cards and 6 participated in the recruitment of the patients for the qualitative interviews. Of a total of n_{qual}=60 patients, 18 (30%) were recruited and 16 (27%) consented to perform the qualitative interviews. Five patients had to be excluded from the analysis, two because they participated in the pilot study, two because of language difficulties and one because of the use of a dose-dispensing aid other than multidrug punch cards. Reasons for exclusion by the pharmacist for the quantitative and qualitative interviews were (n_{quant}/n_{qual}): cognitive or psychological barrier 30/16; participation rejected 27/13; home care 25/4; language barrier 19/11; patient unreachable 6/6; multidrug punch card use for less than three months 6/3; terminal medical condition 2/0; deceased 2/2; multidrug punch cards abandoned 1/0; reason unknown 6/3. Patient demographics are listed in **Table 1**. Mean durations of the quantitative and qualitative interviews were 28.5 (SD ± 7.5) and 42.8 (SD ± 14.2) minutes, respectively.

Table 1. Demographics of patients participating in the quantitative and in the qualitative interviews.

Patient demographics		Quantitative interview	Qualitative interview
Participants, n		22	11
Age, median (range) [years]		71 (37-96)	76 (27-91)
Sex, n	Female	14	5
	Male	8	6
Living situation, n	Alone	13	10
	With partner	9	1
Education, n	No school graduation	2	2
	Primary school	19	8
	University	1	1
Status of employment, n	Employed	1	0
	Retired / unemployed	21	11
Number of medications, median (range)	In multidrug punch cards	7 (4-13)	7 (4-12)
	Additional (outside multidrug punch cards)	1 (0-4)	1 (0-3)

Reason to recommend multidrug punch cards

According to the quantitative interviews, multidrug punch cards were recommended by pharmacists in 54% of the cases, by physicians in 18%, by relatives in 14% and by others in 14%. Of the 16 patients who had the multidrug punch cards recommended by a pharmacist or a physician, 14 remembered one or several reasons: (new) prescription of numerous medications and / or complex regimen (n=7), facilitation of medication management (n=6), poor adherence (n=6), hospital discharge (n=3) and medication abuse (n=2).

Qualitative interviews largely confirmed these reasons. The medical condition was named as principal reason which finally resulted in getting multidrug punch cards (n=4). The same four patients, who stated that they were confused with their medication or had difficulties in handling it, also declared that non-adherence was a reason for the recommendation of the multidrug punch cards. Difficulty/confusion: *"I always have messy cupboards xxx. I've always had a box with one pill here, one pill there. Packaged like this [in regular packaging], right? Then I just did 'tschak, tschak, tschak' back and forth. And in time it seemed to me, it's not the best solution, is it."* (P7) [xxx = garbled speech, unable to make an educated guess]. Non-adherence: *"Sometimes it's also happened that I've forgotten one [tablet] or so."* (P7). These patients mentioned their problems in the community pharmacy or to a relative, which led to the recommendation of multidrug punch cards. Four patients received the multidrug punch cards on prescription or by arrangement between the general physician (GP) and the pharmacist. Two of them did not remember having talked about it to the GP or the pharmacist prior to the initiation of the multidrug punch cards. One patient explained that it was his own idea to save money, because the size of packages often did not fit his needs. The packaging was proposed as solution by the GP. *"[…] either they [the pharmacy] make packs with only 10 [tablets], and then this doesn't really go far. Or they [the pharmacy] make a pack with 50 or 100 [tablets] and I don't need*

them either. And then, there's a lot lost. And that way [with the multidrug punch cards], I really have only the medication that I need." (P2).

Advantages and disadvantages of multidrug punch cards

In the quantitative interviews, all 22 patients felt well cared for by the pharmacy. All were satisfied with the multidrug punch cards, 20 of them very much. Facilitation of medication management and the reminding of medication intake were the main advantages mentioned. Overall, 67 advantages and 12 disadvantages were named (**Table 2**). Twenty patients liked the design of the multidrug punch cards and agreed fully that it was clearly arranged. The orientation according to the written dosing times was judged as very easy by 21 patients and as easy by one. However, the patients stated uniformly that the functionality was more important than the design. The multidrug punch cards were rated as practical and very robust by all 22 patients.

Table 2. Advantages and disadvantages named by all 22 patients of the quantitative interview in an open-ended question.

Advantages		**Disadvantages**	
Facilitation of medication management	22	Difficult medication removal	5
Reminder for medication intake	14	Missing package insert	3
Clear design	7	High refill frequency	2
Control	6	Waste	1
Medication safety	4	Missing confidentiality	1
Organization	4		
Communication	2		
Facilitation of therapy adjustment	2		
Mentioned once: recycling of medication, space-saving, hygiene, documentation, home delivery, rationing	6		
Total	**67**		**12**

The satisfaction was also high in the qualitative interviews with 55 passages coded with positive expressions about the multidrug punch cards (e.g., *"This is marvelous!"* (P1)). There were no corresponding negative remarks. Most patients said that they much preferred the multidrug punch cards to their prior medication management system. It was a facilitation, not only for medication management, but also for their life: it was less time consuming, they did not have to reflect which 'box' to use at which dosing times and they did not have to store numerous medication boxes. *"This [multidrug punch cards] really simplifies my life!"* (P1). *"Again, one concern less for me!"* (P5). Patients also highlighted the clarity and order of the multidrug punch cards. The layout helped them to orientate themselves. Interviewer: *"And why do you like it, when it [the medication] is packaged like this [in the multidrug punch cards]?"* - Patient: *"You have an overview. […]"* (P8). Few comments concerned the high-level hygiene and the suitability for old and / or forgetful people. Only four

negative comments were issued by three patients: the sound of the multidrug punch cards while handling was displeasing, a long sheet with the medication plan glued on the back was unpractical while removing medication, the assumption that the handling could be difficult for people with disabilities and the lack of package insert and information to identify the tablets. *"The disadvantage, I find a bit is that you don't have an overview of the tablets. Now, I really can't…. Where there is a heart on it [the tablet], I know it is for the heart somehow, but on the whole, I do not know what I here [take]…. Well, everything is written in the back, isn't it, for me. I don't know if they do that in general or not?"* (P4). This comment was stated by a patient who also criticized that he could not understand the information of the medication plan glued on the back, he thought it was written in Latin. On the other hand, the lack of package insert did not trouble other patients and was appreciated as an advantage by several patients.

Handling of the multidrug punch cards

In the quantitative interviews, 21 out of 22 patients were very satisfied with the handling of the multidrug punch cards. Nineteen patients pushed the medication out with their fingers. Of five patients cutting the foil on the backside, four seldom or never had trouble in pushing out the tablets. In total, 14 (64%) patients indicated never having trouble with removing medication from the multidrug punch cards. Eight patients had technical or physical difficulties: tablets spiked at removal (n=5); tablets stuck in the cavity at removal (n=4); dexterity problems (n=3); cavity too fully loaded (n=1).

During the qualitative interviews, patients were asked to demonstrate with a demo multidrug punch card how they removed their medication. All 11 patients removed the mock medication without trouble, but sometimes it spiked. Although some patients admitted that this happened from time to time with their own multidrug punch cards too, they mostly did not see it as a drawback. Some of the patients described problems with removing medications at the very beginning of multidrug punch card use, but they developed their own strategy to overcome these problems. Most patients had not been instructed how to use the multidrug punch cards or did not remember it. They negated the need for it, because they found the multidrug punch cards self-explaining. Four patients reported that they daily removed the content of the cavities in advance into a separate little box or bowl. This was practical to them because they kept the medication ready and could not mix it up, or they had it in their pocket in case they left home. One patient was sure that she would forget the intake in the morning, if she did not prepare the dose the evening before. *"Because I have to prepare them, otherwise I would really…, I have to tell you honestly, I would forget them [the medication]."* (P8). Two patients told that they manipulated the multidrug punch cards for their purpose. The main motivation was cutting the size for storage or transport. *"[…]. If I know, of course, I will leave for three days, then I cut it [multidrug punch card] here."* (P2). One patient also pushed medication into the cavities or took some of the filled

medication out if there was a short-term change in medication therapy. She did not report these therapy changes to the pharmacy until she was sure it was fixed. *"[…]. And after this, just once for this evening I did it, so that I don't have to mess around for a long time, I took the two [tablets] that I have to take anyway, I pushed them in here and the blue one I already pushed out [of the multidrug punch card]. That's how I work with the blister [= multidrug punch card]."* (P1).

Safety issues

In the quantitative interviews, safety and control were named by four and six patients, respectively, as an advantage of the multidrug punch cards (**Table 2**). All 22 patients stated that they felt safer in medication management with the multidrug punch cards than without. All patients agreed fully that they could read the text with the information written and glued on the back of the multidrug punch cards without problems. Three patients admitted that they never read this text. Three patients named the missing package insert as a disadvantage.

The topic safety was explored in-depth in the qualitative interviews. All 11 patients confirmed that the multidrug punch cards made them feel safe in managing medication. The main reasons were the overview of their medication and to be in control of medication intake. It was very important for them to be sure they had the right medication at the right time. *"Yes, I would say there is a kind of safety in it [multidrug punch cards]. Then I'm sure I took the right one, here."* (P2). Some patients mentioned in that context that they believed the medication filling to be correct and that they could rely on the controls of the health-care professionals. Nevertheless, all 11 patients reported that they controlled the tablets immediately after removal by number, shape or color. Two patients felt safe because the medication was incorporated in a package that was hygienic and robust. In relation to medication knowledge, the patients could be divided in two groups (**Figure 2**). Group A was confident to know the name and indication of their medication, could more or less identify the tablets in the multidrug punch cards and stated that they did not need further information or a package insert. Group A/Knowledge: *"I know exactly what I have to take, […]."* (P5). Group A/Package insert: *"Because if I have to read the package insert, either I have to or I want to, I suffer from everything that is written there. And I don't want that at all."* (P1). Group B did not know the name and indication of their medication and could mostly not identify the tablets. All patients of Group B except one did not want more information because they declared not to understand it. The package insert was refused quite fiercely by some patients and was named as a reason for denied medication intake. All patients of group B explained that they were faithful to the pharmacy for years and that they trusted health-care professionals. Trust and fidelity to the pharmacy also coincided with statements of perfect medication adherence. Group B/Knowledge: Interviewer: *„How well do you know which tablet is which, for example?" Patient: "I don't know."* (P9). Group B/Package insert: Patient: *"But what the other one is, I don't know."* -

Interviewer: *"You don't know it. Would you like to know it then? So, do you mind not knowing it?"* - Patient: *"Well, I don't know if I would actually like to know it or not."* - Interviewer: *"That means this fits for you then?"* - Patient: *"You know, this would… if, if this was something that… This would concern me very much. […]"* (P8). Group B/Package insert/trust and fidelity: *„[…]. I trust you and the physicians. I'm not interested in this because I don't understand it anyway. What's in it and what's written on it [in/on the multidrug punch card] and so. No, I never look at it."* (P3). The medication plan glued on the backside of the multidrug punch cards was very much appreciated and was declared to contain enough information about the medication and the user. Some patients saw it as a major advantage in safety because they could give the correct names and dosages of their medication to physicians at first consultation or at admission to the hospital. Two patients told that they requested oral and written information on medication from the pharmacy if they had specific questions. All 11 patients described their contact to the pharmacy to be very good and the pharmacy team to be very friendly.

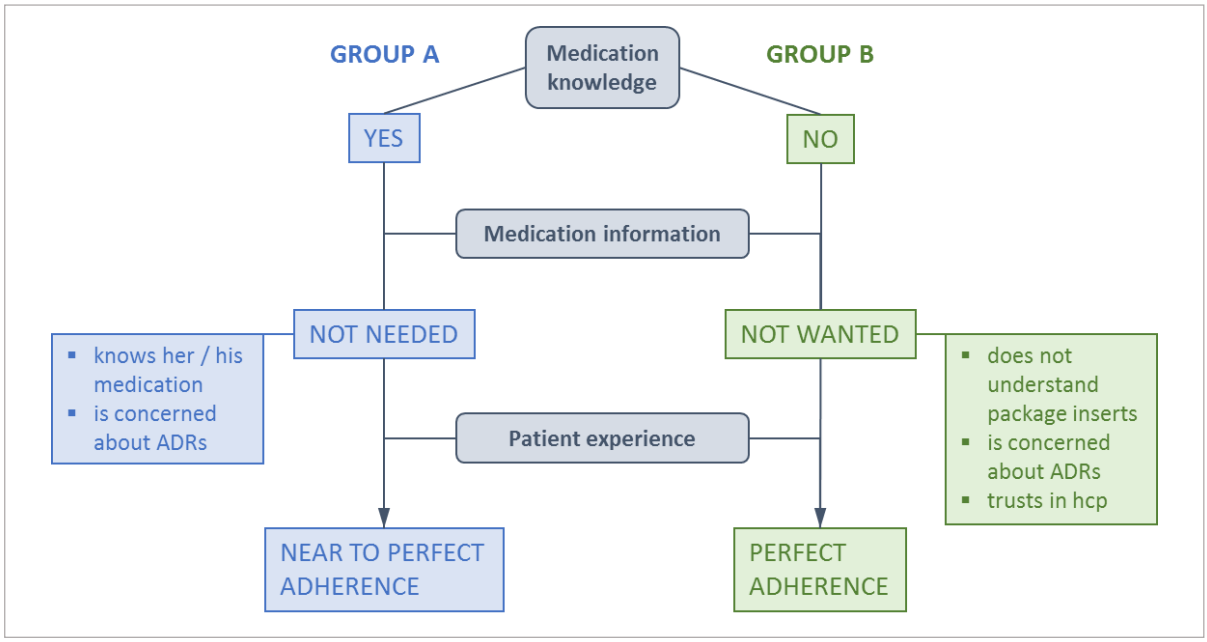

Figure 2: Adherence elements emerging from qualitative interviews. Although all patient stressed perfect adherence, statements of Group A allowed margins for time of medication intake (= near to perfect adherence). 'Medication knowledge' relates to a patients' confidence to appoint the name and/or the indication of the medication and/or to identify the tablets. ADRs, adverse drug reactions; hcp, health-care professionals.

Adherence

In the quantitative interviews, patients indicated that the multidrug punch cards were a tool to remind them of medication intake. Compared to their prior medication management system, 21 patients rated a relative improvement of +37% (SD ± 43%) for taking adherence and 19 patients rated a relative

improvement of +38% (SD ± 43%) for timing adherence after the initiation of multidrug punch cards. One patient estimated his timing adherence to be 13% worse with the multidrug punch cards than without. Median self-reported adherence of the 33 patients participating in quantitative and qualitative interviews was 10 on the VAS (range 3-10).

In the qualitative interviews, all 11 patients stated that they did not know the term adherence [fidelity to therapy, Therapietreue], but three patients could imagine the rough sense of it. *"Yes, I stick to the rules. Which I get ordered, now about the therapy, sort of… yes. I do what I should and not…. Faithful to therapy, like this. Xxx. If you now get medication to calm down, if you… have a fit. Then I would say, fidelity to therapy is really if you just take it at the right moment."* (P6). Others related it to physical therapy because in Swiss German the term 'therapy' [Therapie] theoretically stands for various kinds of therapy, but is colloquially often used for physical therapy. Some patients had no idea of the meaning of the term 'fidelity to therapy'. Two patients remembered that they had a talk with their health-care professionals about adherence, but the majority thought this was self-evident and that they did not need further explanations. All 11 patients declared that medication adherence was very important for them and emphasized their willingness to be adherent. As reasons they indicated that it made sense to follow the physician's directions, that they would benefit from the therapy and that they would suffer from medical consequences if they were non-adherent. One patient even stated that pharmacotherapy was existential for her. All patients who feared medical consequences of non-adherence had a history of an adverse medical event (e.g., heart attack) or suffered from a medical condition, which they had to keep under strict control (e.g., diabetes mellitus, epilepsy). *"I know it [the medication] holds off a lot, when you had two heart attacks, then you know what it means to take medication. Then you really take it [the medication]."* (P9). *"Well, what do I want? There is nothing else for it. It only benefits me, if I take it, right? I don't want to sit in the hospital again."* (P8). Statements about adherence matched Groups A and B defined in the Safety's section. Patients from Group A were more liberal and reported that they were fine with a margin for time of medication intake. Patients from Group B were anxious about leaving out one tablet or taking one dose too late since they were sure to sense immediate consequences. *"If I did not take them, I would feel it. So, I would have to go soon, most likely…, so maybe the second day at most [after missing a tablet], I would already have to go to the physician and say: 'I don't feel well anymore'. So yea, I would feel it."* (P10). Three patients believed that they would forget medication intake if they had to prepare the medication themselves out of the regular packaging, if the multidrug punch card was stored at a hidden place, or if there were more dosing times. Most patients who admitted that they forgot medication intake with their prior medication management system also forgot intake with the use of the multidrug punch cards, but much less than before. The visualization of the doses would reveal their omission and allow them to

make up the intake. One patient had problems remembering the short-term therapy that she was managing besides the multidrug punch cards. Three patients were absolutely sure that they never forgot medication intake. Strategies to remember medication included defining an eye-catching place of storage for four patients, setting an alarm for two patients and embedding medication taking into a ritual or daily routine for four patients. All four patients who had defined a special place of storage reported always seeing it and therefore remembering medication intake. Patients who had the medication intake embedded in their daily routine told that they did not have to remember medication taking as a separate action, it was more like an automatism within their normal activities. They also did not need to control the multidrug punch cards to ensure timely intake. *„It is, it's like automatic, right? When I'm sitting, having my breakfast at the table, then I just do it and then it's done. And then I put it [the medication] into the plate and the matter is settled."* (P5). *"I always take all of them. I always take them how I have to, I don't have to control it."* (P9). For most patients control of intake was an additional step of safety. *"But here [with the multidrug punch card] you have control after all! Here you have it, you are sure that you took the right thing [medication]."* (P11). *„I see it at first sight. I had it, I took it, I know it."* (P2).

Discussion

We combined quantitative and qualitative methods in an explanatory way to investigate the profile of multidrug punch card users in-depth, and the influence of the dose-dispensing aid on their adherence. Our primary care patient using multidrug punch cards reports high level of satisfaction with the multidrug punch cards, few handling difficulties, and high medication safety. She/he declares currently highest medication adherence and improved adherence compared to her/his prior medication management. Our results support the assumption that unintentionally non-adherent patients represent a target population for dose dispensing aids [62,145] and highlight some key variables which health-care professionals may assess while recommending multidrug punch cards to patients with polypharmacy.

The typical independent primary care patient accepting to use multidrug punch cards is over 70 years old, has a low education grade, is retired, lives alone, favors tidiness, rituals and daily routines and is unable or reluctant to leave home. She/he trusts the health-care professionals, is a regular customer of the same community pharmacy, is motivated to conduct a healthy life and has a feeling of high necessity for medication. The association of adherence with the necessity for medication intake is well-known and has been used as an integral part of the 'believes about medicines questionnaire', an instrument to assess adherence [53].

Our patients much preferred the multidrug punch cards to their prior medication management and reported improved adherence of even +37% after the initiation of the device. Significantly increased adherence was also demonstrated by five out of six randomized controlled trials investigating the use of multidrug punch cards in primary care patients [49,159,160,176,211]. Additionally, in two of these studies [49,160] cardiovascular patients with polypharmacy achieved significantly improved clinical outcomes (e.g., blood pressure, LDL cholesterol). Thus, major improvement of adherence and of associated outcomes by the use of multidrug punch cards are likely.

In our study, patients claimed their perfectly adherent behavior to be motivated by a personal experience of benefit if they adhered to the physician's orders or by a fear of medical consequences if they did not. These findings correspond to the role of patients' experiences denoted as crucial for clinical safety and effectiveness [262]. Trust towards the pharmacy emerged also as a reason for high adherence, since the participants expressing trust towards health-care professionals most explicitly, were most accurate with their medication plan. This attitude is characterized as the 'passive medication user', representing one out of three different types of medication intake-behavior [263]. We thus suggest that the population of 'passive medication users' could be a target group for the use of multidrug punch cards. If we add that high fidelity to the pharmacy is associated with increased medication adherence and decreased adverse drug reactions [162], we can suppose that multiple key variables at different levels permit to reach a perfect medication intake behavior (trust in the institution/health-care professionals; perceived benefits of the management system; fear of negative consequences) (**Figure 2**).

Although multidrug punch cards do not feature an explicit reminder function, its storage at a strategic visible place helped the patients to remember medication intake. In particular, it allowed immediate visual control of the intakes, the performed ones as well as the forgotten ones. An advanced strategy seems the integration of the medication intake into daily routine to become an 'automatism'; the patients even did not have to think about medication intake. Habits and routines have long been described to be beneficial for general adherence [57,264] as well as for dose-dispensing aids [255]. As a consequence, recommending multidrug punch cards should include an assessment of the patients' daily habits and routines.

Reasons for recommendation of multidrug punch cards and major advantages assessed in our study e.g., facilitation of medication therapy and improvement of adherence, mostly coincided with results of two qualitative studies on primary care patients using different types of dose-dispensing aids (e.g. pillboxes, multidrug punch cards, etc.) [32,255].

Absence of medication information – due to the dispensing of multidrug punch cards without package inserts – was of minor importance in the quantitative interviews. The in-depth exploration of the qualitative interviews confirmed that the patients were satisfied with a minimum of medication information. Only two patients requested written or oral medication information from the pharmacy. These findings might appear controversial, since a lack of medication information has been related to a reduction of knowledge resulting in a dangerous loss of skills and autonomy of the patient [32,152,153]. Inversely, good medication knowledge was suggested to reduce inappropriate medication administration, adverse events and non-adherence, and hence to increase medication safety [108,265-267]. However, these investigations were not performed within a population using multidrug punch cards. Since their use spares the handling of regular packaged medication, a different type of knowledge seems needed by those patients than the information contained in package inserts. Our assumptions are strengthened by a recent study showing that patients over 65 years with dose-dispensing aids were significantly more adherent (n=119) but less knowledgeable than patients who managed their medication by themselves (n=96) [154]. Finally, since multidrug punch cards per se reduce potential errors of administration to a minimum, a relation to medication knowledge is unlikely.

Handling problems (e.g., difficulty in removing medication, confusing inscriptions when to take the medication, etc.) were claimed to constitute a major reason for reduced medication safety with dose-dispensing aids [32,146,151]. Consequently, the small number of handling problems in the quantitative interviews was surprising. However, the qualitative interviews confirmed the first findings and revealed a major contribution of multidrug punch cards to the patients' feeling of medication safety. The clear design of the multidrug punch cards assured its safe use. Hence, for most patients instruction was dispensable.

For practice, our study implies that medication management and non-adherence should be addressed actively through health-care professionals. The profiling enables selecting the right patients, provides arguments for recommendation and points out relevant issues for advancement of dose-dispensing service. Initially, trust between the patient and the health-care professional has to be established and patients' experiences and habits should be included into adherence counselling. While recommending multidrug punch cards, pharmacists should emphasize the facilitation of medication management and the increased medication safety. Based on our results, other strategies to advance dose-dispensing service and increase safety might be considered e.g., regular medication review of the packaged medication by a pharmacist [150], giving instruction on multidrug punch cards if necessary (anticipation of handling difficulties, integration into life-style, reminder strategies), inclusion of short term medication into the packaging, detailed instruction of separate medication, and regular contact between pharmacy and patient.

Strengths and limitations

The strength of this study was the deeper explanation of ambiguous quantitative data through qualitative interviews. To our knowledge, this is the first study with a mixed methods approach in the field of dose-dispensing aids and their impact on medication adherence.

Our study results are limited through several points. First, our study sample is small. On one hand, this is due to the effective small number of primary care patients, who are using multidrug punch cards without external help. In Switzerland, multidrug punch cards were originally intended for the supply of nursing homes. Only in the last few years, they were recommended to primary care patients. Further, the primary care patients selected by the pharmacists as multidrug punch card users really were the target group for this type of adherence aid (cognitive or psychological barrier, home care, language barrier), but turned out to be inadequate for our study. On the other hand, about half of the adequate patients refused study participation. Telephone interviews constituted a major barrier for recruitment. Conducting interviews at home or at the pharmacy were more acceptable. Second, the high level of satisfaction may reflect a selection bias. We can assume that patients unsatisfied with the multidrug punch cards might not have been willing to consent for interviews, especially if invited by the provider of the unsatisfactory device. Further, the recruiting pharmacist may have approached satisfied users among her/his patients to take part in the study. The problem-free handling of the multidrug punch cards that we observed might be the result of a further selection bias, since we excluded cognitively impaired patients who are known to experience difficulties with the handling of any medication packaging [207,259]. Additionally, because our participants had to use the punch cards at least three months for inclusion, initially encountered difficulties may have been solved already. Third, reporting and interviewer biases may have interfered with study results. Since there were no differences observed by location of interview, the conduction of the interviews at the pharmacy does not seem to have influenced the patients' answers. Fourth, adherence was measured through patient self-report which has been described not to be fully reliable and often overestimated [268]. However, the conformity with similar studies [49,154] endorses our results. Fifth, this study represents the views of patients solely using multidrug punch cards and cannot be generalized to patients using other dose-dispensing aids.

Outlook

Future research should aim at developing studies with larger populations to enable generalization. The development of an assessment tool for non-adherent patients to provide targeted interventions should be a priority. Clarification of the impact of multidrug punch cards on patient-oriented outcomes should be aspired. Younger patients with complex medication regimen should be interviewed about their preferences to clarify the benefit of multidrug punch cards for additional populations.

Conclusions

Characteristics of primary care patients using multidrug punch cards include age over 70 years, low education grade, living alone, appreciation for tidiness and daily routine, trust in health-care professionals, fidelity to pharmacy and motivation for a healthy lifestyle and medication adherence. The patients are satisfied with the multidrug punch cards, feel safe, mostly have no handling problems and adhere perfectly to their treatment. Multidrug punch cards constitute a simplification for their lives, offer a clear overview of hygienically packaged medication, a reminder function and a possibility for adherence monitoring. Key variables for initiating multidrug punch card use and for medication adherence are trust in health-care professionals and patients' experiences. This mixed methods study attenuates previous concerns about disadvantages of multidrug punch cards. Hence, health-care professionals should actively recommend them for primary care patients with polypharmacy and poor adherence.

Annex

- A3.1 Final board decision of the Ethikkommission beider Basel for the quantitative patient interviews
- A3.2 Final board decision of the Kantonale Ethikkommission Aargau/Solothurn for the quantitative patient interviews
- A3.3 Quantitative patient interview
- A3.4 Final board decision of the Ethikkommission beider Basel for the qualitative patient interviews
- A3.5 Topic guide for the qualitative interviews

Supplementary material *(available on CD-R or on request)*

- Pharmacy Information for quantitative and qualitative interviews
- Informed consent form for quantitative and qualitative interviews
- Patient information for quantitative and qualitative interviews
- Original German transcriptions of quotations

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Authors' contributions

All authors conceptualized the study. FB conducted the interviews, analyzed data and drafted the manuscript. KEH and IA reviewed the draft critically for intellectual content.

Conflict of interest

None.

C Effectiveness of multidrug punch card use in primary care patients – a pilot study

Project C1

Electronic multidrug punch cards to improve clinical and humanistic outcomes in patients after hospital discharge

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Internal work report

Index

Abstract

Background: Medication self-management is often impaired in patients with polypharmacy, especially after hospital discharge, leading to medication errors and non-adherence. Non-adherence is widespread in the primary care population and impairs clinical conditions, quality of life, and healthcare costs. Multidrug punch cards are suggested to enhance adherence by optimization of medication self-management. In Switzerland, multidrug punch cards have been integrated in practice of community pharmacies since 2002. Multidrug punch cards can be equipped with POlypharmacy Electronic Monitoring System (POEMS), a novel technique for electronic measurement of adherence to polypharmacy.

Objective: We aimed at investigating the effectiveness of a pharmaceutical care intervention including electronic multidrug punch cards and regular feedback on electronic dosing histories, to improve adherence to polypharmacy and patient-relevant outcomes in primary care patients after hospital discharge. Herein, we report of the results and experiences of a pilot study.

Methods: During 10 months in 2013, patients on an internal medicine's ward at the University Hospital Basel were screened, recruited, and assessed at bedside. All patients received medication counseling and an individualized medication plan prior to hospital discharge. Patients randomized to the intervention group received their oral solid medication packaged in electronic multidrug punch cards and regular feedback on their electronic dosing histories by a study pharmacist. Patients allocated to the control group received usual care. Follow-up visits were carried out at the study pharmacy at three, six, and twelve months after hospital discharge. Primary outcomes were 'time to hospital readmission and major adjustment of drug therapy' and adherence according to medication possession ratio (MPR). The evaluation of the pilot study was based on Donabedian's evaluation model of quality of care.

Results: Of 958 screened patients, 10 consented to participate. One patient accepted the intervention and nine patients were allocated to the control group. The median age of the control patients was 67 years, 5/9 were male, and their baseline median self-reported adherence was maximal. The intervention patient was male, 65 years old, and reported a maximal taking adherence and moderate timing adherence. Over the whole study duration, there was no unplanned hospital readmission. One major adjustment of drug therapy occurred in the intervention patient, which could not be linked to impaired adherence. The mean MPR of the control and the intervention group was 1.01 and 1.18, respectively. Patient satisfaction was high and no harm related to the intervention was registered.

The evaluation showed adequate feasibility of the study design, but a lack in quality and efficiency. Key points for these shortcomings were, e.g., the high exclusion rate, the inadequate time management, the induction of a potential bias by medication counseling during the follow-up assessments.

Conclusions: Because of a lack in efficiency and quality of the pilot study, only ten patients could be recruited and only one patient accepted the intervention. Over the whole study duration there was no unplanned hospital readmission and one major adjustment of drug therapy in the intervention patient. However, the intervention patient maintained perfect adherence and was clinically stable over the whole study year. In the control group, adherence was at a maximum according to self-report and medication possession ratio (MPR). The evaluation revealed major inadequate points, whose improvement might enable the successful study performance.

Introduction

Physical and cognitive impairments of primary care patients pose a barrier for safe and effective medication self-management [35,207,256], i.e., the patient's ability to self-administrate her/his medication [31], leading to adverse drug events, non-adherence, and related hospitalizations [12,107-109]. Elderly patients with polypharmacy for chronic diseases and who are newly discharged from hospital are often prescribed polypharmacy, which puts them at highest risk for such adverse health outcomes [29,257].

Adherence was defined as 'the extent to which a person's behavior – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider' [37]. Typical adherence rates for oral prescription medications are approximately 50-76%. Non-adherence impairs clinical outcomes [65,90], resulting in increased risk of hospital admission [12,105,269]. As consequences of the adverse health outcomes, quality of life decreases [110,112,113] and healthcare costs rise [117,124]. Non-adherence behavior can be categorized into two groups: 1. unintentional non-adherence is when the patients are prevented from correctly executing their treatment plan by physical or cognitive barriers; and 2. intentional non-adherence is when the patients actively decide not to take medication according to treatment plan. Various authors suggest that dose-dispensing aids may represent a simple method to help unintentionally non-adherent patients to optimize their management of polypharmacy [65,145,146 62].

Dose-dispensing aids usually consist of a certain number of compartments containing oral solid medication for specific dosing times and conform to the requirements to be simple, easy to implement, and inexpensive [143]. Recent literature reviews confirmed a positive effect on adherence and clinical outcomes [147,155,258]. However, the evidence support for the use of dose-dispensing aids remains weak because of poor methodological and reporting quality. Further research gaps encompassed economic and humanistic outcomes, safety issues, long-term, disease-unspecific, and generalizable clinical outcomes, and clinical effects on multimorbid populations with polypharmacy. More robust replicable studies were claimed to strengthen the evidence.

Multidrug punch cards are disposable frame cards containing 28 plastic cavities for four dosing times per day and are filled by community pharmacies or manufacturers with all oral solid medication of an individual medication regimen. A specific software assists the production by archiving patient data, documenting prescriptions, verifying the medication filled through barcode scanning, and by composing data from the database to a label that is fixed on the card [157]. The label comprises data of the pharmacy, the patient, and the packaged medication (**Figure 1**). In Switzerland health insurances reimburse this dose-dispensing service (i.e., the repackaging of solid oral medication into dose-dispensing aids by a health care provider) with 21.60 CHF per week with a prescription of ≥ 3 different

medication per week, (according to the collective agreement LOA IV [158]). Preliminary studies showed that the dose-dispensing service with multidrug punch cards integrated well in daily practice at the community pharmacies in Switzerland, but that they were mainly produced for patients in nursing homes [270]. Primary care patients using multidrug punch cards in daily life were very satisfied with them, asserting that they constituted a simplification for their lives and increased their safety [271]. Pharmacists and patients estimated improved adherence with the use of multidrug punch cards [270,271].

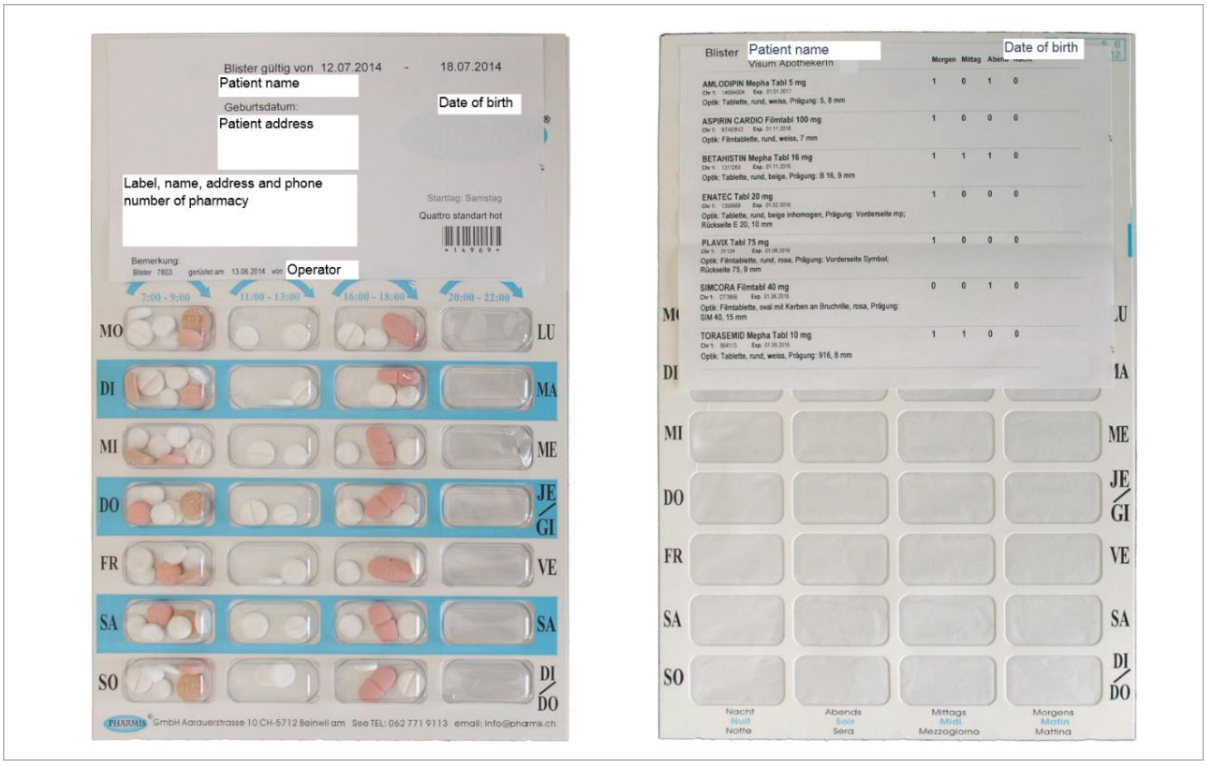

Figure 1. Multidrug punch card, front side (left): 28 plastic cavities with visible packaged medication and labelling with patient and pharmacy information. Back side (right): 28 cavities sealed with foil and marked with indication of dosing time (morning, lunch, evening, night; Monday-Friday); the adhesive medication plan labels brand name, dose, administration number, dosing frequency, size, color, imprint, batch number, and expiration date of each packaged drug.

Electronic measurement of adherence is considered nearest to gold standard [272] and is obtained by Medication Event Monitoring System (MEMS®)[73] or POlypharmacy Electronic Monitoring System (POEMS) [273]. POEMS consists of an adhesive film with conductive properties that can be fixed at the back of a multidrug punch card. It registers date, time, and position of the cavity where drug was removed. Recorded signals are transferred to a database [273]. Whereas MEMS® is limited to monitoring of adherence to one single lead drug, POEMS can be attached to multidrug punch cards enabling the monitoring of adherence to polypharmacy. Many long-term studies on adherence enhancing

interventions with MEMS® and feedback on electronic dosing histories reported significant improvement on adherence [274-278] and one meta-analysis attributed a large effect to the same intervention [136].

In summary, a service to enhance adherence in primary care patients that is simple, economic, and accepted is represented by multidrug punch card service, which is already implemented into daily practice in Swiss community pharmacies. However, multidrug punch cards were not commonly distributed to primary care patients. We propose that this adherence aid could be provided to any patient with polypharmacy, independently of age or condition, to result in improved medication adherence and thus yield clinical, humanistic, and economic benefits. Our study was the first in the attempt to electronically monitor adherence to polypharmacy, which might substantially add to the knowledge about adherence behavior in this complex situation.

Aims and approach

We aimed at investigating the effectiveness of a pharmaceutical care intervention comprising the packaging of all oral, solid medication into electronic multidrug punch cards and regular individual feedback on electronic dosing history, to improve adherence to polypharmacy and to reduce time to hospital readmission and major adjustment of medication therapy in primary care patients after hospital discharge.

We approached this aim by conducting a pilot study to evaluate and to optimize the feasibility, efficiency, and quality of the study. We report herein of the results and experiences of the pilot study (Part C1.1) and of the evaluation (Part C1.2).

Methods

C1.1 Pilot Study

The study was designed as a 12-months prospective randomized controlled trial performed at the University Hospital Basel and the Notfallapotheke Basel (study pharmacy) (**Figure 2**). The trial was performed in line with legal regulations (HMG, VKlin [279]) and the International Conference on Harmonization (ICH) guidelines [280]. The responsible ethic board approved the study protocol. The report of the pilot study is structured following the Consolidated Standards of Reporting Trials (CONSORT) statement [281].

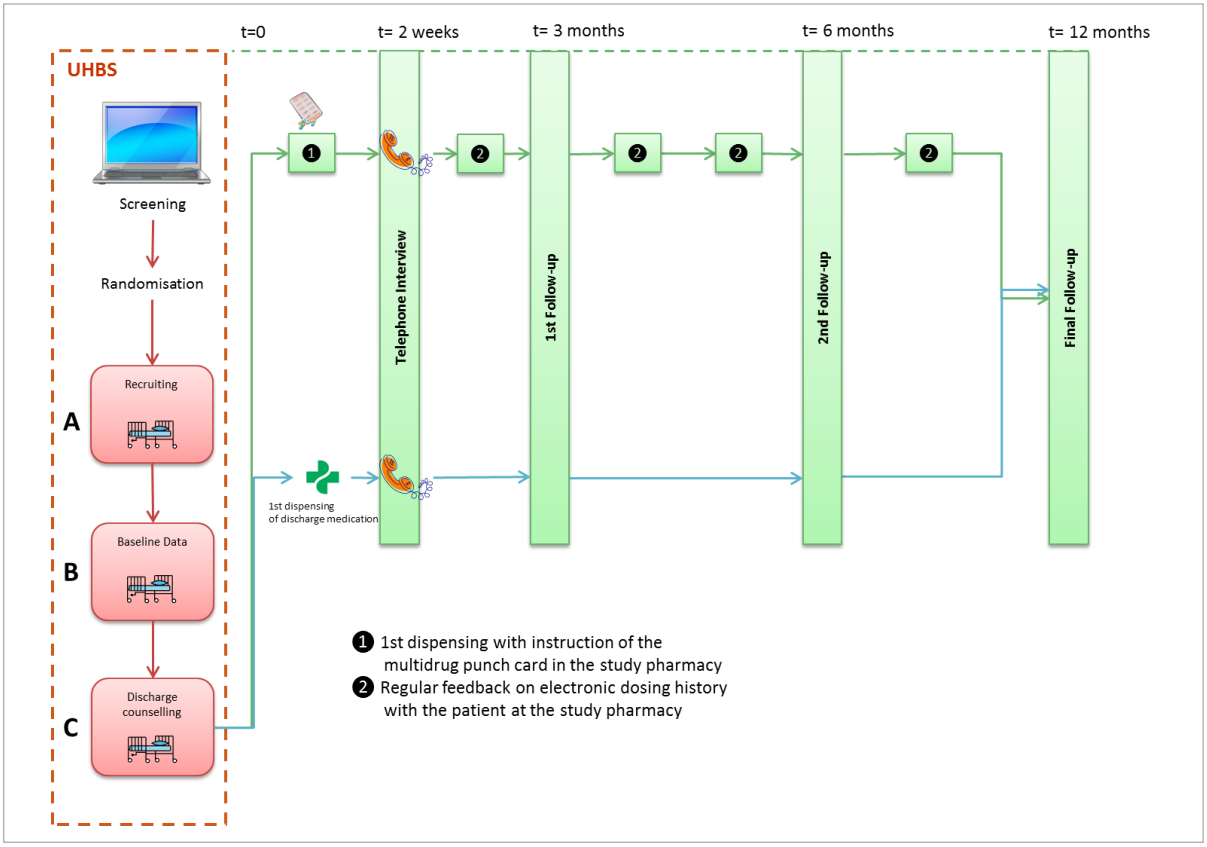

Figure 2: Trial design. T, time; UHBS, University Hospital Basel.

Setting and participants

We recruited eligible patients from an internal medicine's ward at the University Hospital Basel. The screening for eligible patients was carried out in two steps. In a first screening, the electronic case notes from the hospital database (ISMed) of all patients on the ward were screened according to in- and exclusion criteria (**Table 1**). Included patients of the first screening were assigned a consecutive study number. Additional criteria for eligibility were checked in a second screening on the ward with paper case notes. A study pharmacist recruited the included patients from the second screening on the ward. After informed consent was obtained, the patients were randomized and baseline data were assessed at bedside. All patients, irrespective of group allocation, met a study pharmacist for a discharge counseling on all prescribed medications. The counseling was performed by following standardized information sheets, derived from the official drug information [282], with information on indication, long-term benefit, adverse effects and correct use. These elements were described to be preferred by patients [143,283]. An example of a standardized information sheet is given in the supplementary material. At the completion of the counseling, a personalized medication plan was handed out to the patients (supplementary material). Uncertainties raising during the counseling session were clarified with the responsible physician before the leave of the patient. The patient's

community pharmacy and general physician (GP) were informed by fax about the patient's participation in the study. The hospitalization during which a patient was recruited will herein be called 'index hospitalization'.

Table 1. Inclusion and exclusion criteria.
Inclusion criteria
Age > 18 years of age
Literate in German
Capable to give informed consent
Self-management of medication
(Re-)Fill medication at a community pharmacy
Prescription of ≥ 4 different oral solid drugs at discharge
Swiss health insurance
Acceptance of the electronic multidrug punch card use
Exclusion criteria
Pregnancy
Physical impairment (visual or dexterity; as diagnosis or evaluated as such by the responsible nurse)
Cognitive impairment (as diagnosis or evaluated as such by the responsible nurse)
Transplantation
Prescription of vitamin K antagonist at discharge
Non-packable medication (e.g. > 2 non-solid/non-oral medications, > 4 dosing times per day)
Transfer to another institution at discharge (e.g. nursing home, rehabilitation center)
Use of a multidrug punch card or a single dose-dispensing aid (e.g. pouch blister) before hospital admission
Prohibition of the access to patient records of the community pharmacy / general physician

Three important changes were made to the methods after trial commencement:

1. The length and wording of the script for recruiting was shortened and simplified.
2. To augment efficiency of recruiting, the study steps of the hospital phase were adjusted. The extensive screening process was abandoned and the study pharmacist was integrated on regular weekly ward rounds with the physicians, including one to two thirds of the patients of the ward. Eligibility criteria were checked on the spot by consulting paper case notes, physicians, and nurses and in conversations with the patients directly (**Figure 3**). This change was indicated by the study evaluation and carried out in May 2013.
3. The non-acceptance of multidrug punch cards was frequent. To include an adequate number of patients for descriptive analysis, patients were offered to take part in the study in the control group if they rejected the intervention. The randomization process was abandoned in June 2013.

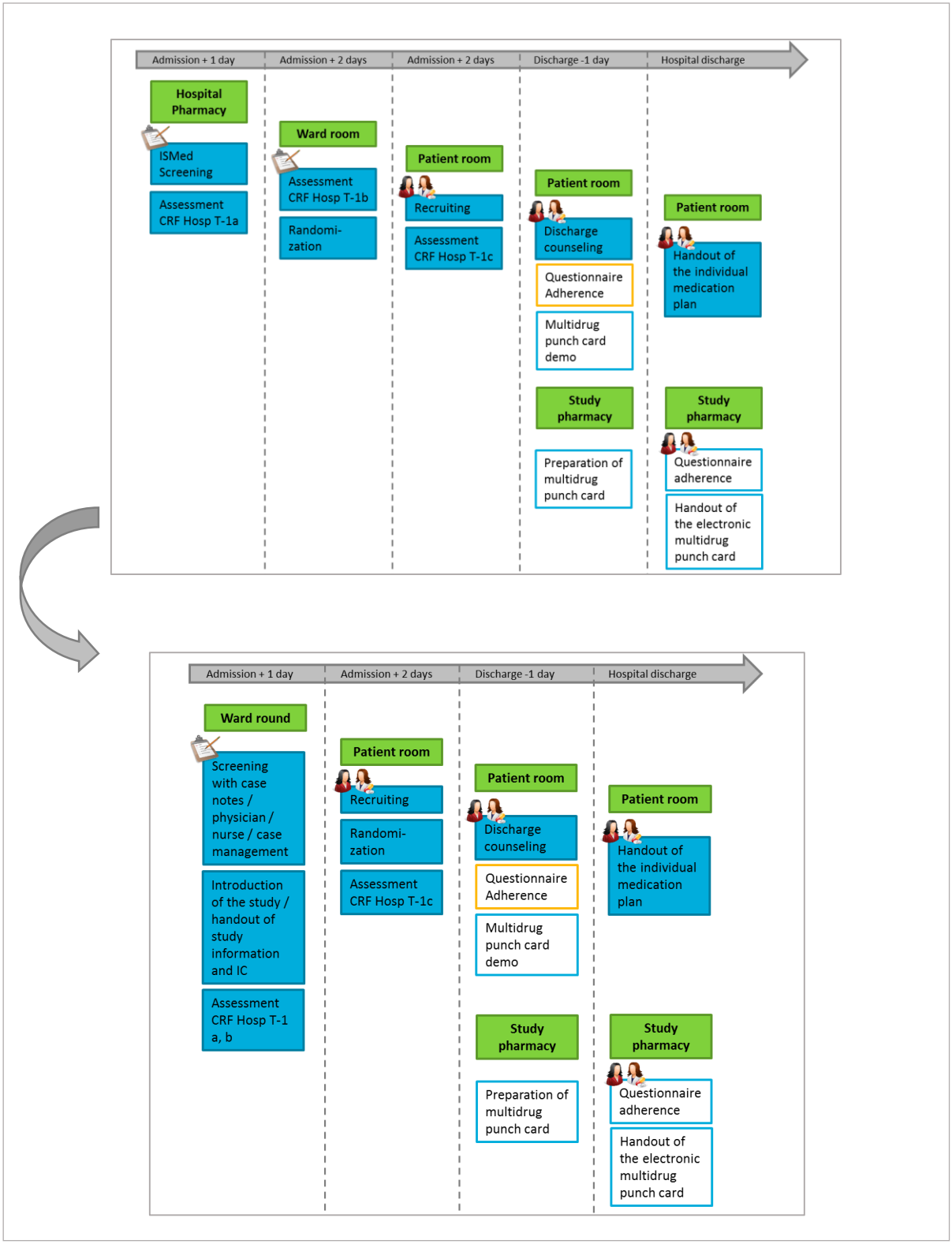

Figure 3: Study steps of the hospital phase, before (above) and after adjustment (bottom). Legend: Green box = location; blue box = study action; clear box with blue frame: study action specific for intervention group; clear box with yellow frame: study action specific for control group. CRF Hosp T-1, case report form hospital T-1, with assessment of a: electronic patient records, b: paper case note data, c: patient interview and questionnaire quality of life; IC, informed consent form; QoL, quality of life

Intervention

Intervention patients received their oral solid medication packaged in individualized electronic multidrug punch cards (**Figure 4**) continually from discharge until the end of the study. The multidrug punch cards were prepared at the study pharmacy by a pharmacist and reviewed by a second pharmacist. POEMS was affixed and activated on the completed multidrug punch card. The production took place under the conditions of Good Manufacturing Practice [284], following a standard operation procedure. At first provision, a study pharmacist instructed the patient in the use of the multidrug punch card and of the medication not included into the device. The capability of the patient to remove medication from a multidrug punch card was tested with a demo. Exchange of the multidrug punch cards took place at the study pharmacy in weekly or multiple weekly intervals. Multidrug punch cards and additional medication (if requested) were handed out by a pharmacist. In regular intervals, the study pharmacist conducted feedback sessions on adherence behavior with charted electronic dosing histories (**Figure 4**), using elements of motivational interviewing, e.g. active listening, reflective listening, affirmation, and summarization to help the patient express his concerns about the behavioral change, enhance his personal motivation, set goals and arrive at a change of plan [285].

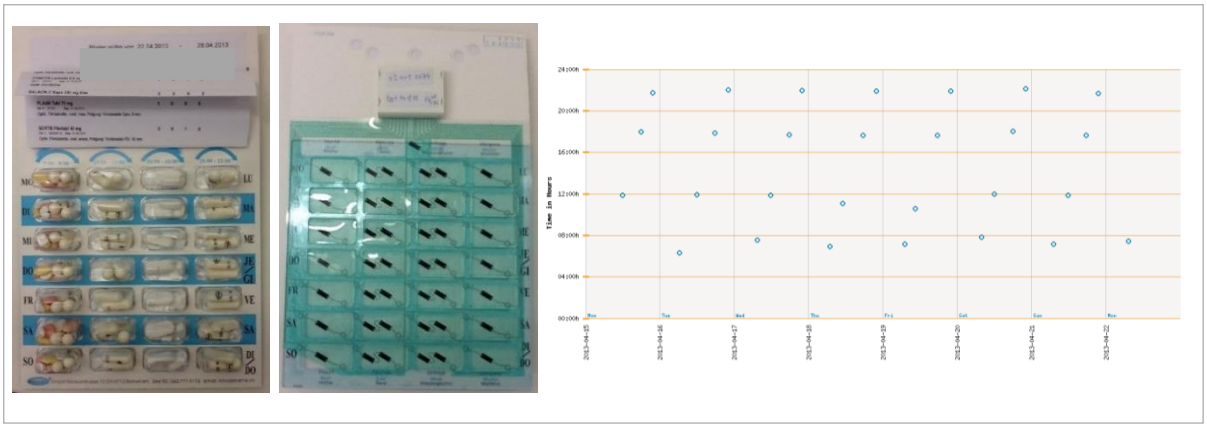

Figure 4. Electronic multidrug punch cards with affixed POlypharmacy Electronic Monitoring System (POEMS) on the backside and charted electronic dosing history over one week with a four-times daily intake (from left to right).

Control conditions

Patients allocated to the control group received their medication in commercial medication packaging and usual care at the community pharmacy of their own choice. Usual care in Swiss community pharmacies comprises management of patient records; validation of prescription; dispensing of the requested medication on prescription and over-the-counter (OTC); providing the most economic generic; interaction check; check of risk factors and contra indications; calling the physician for further

information if needed; check for abuse; counseling on dose, dose frequency, medication administration, duration of medication therapy, storage, and potential adverse reactions [158]. Pharmacies also offer medication review (polymedication check, intermediate medication review according to the Pharmaceutical Care Network Europe [286]) and dose-dispensing service, which are reimbursed by the health insurance. Patients were free to use self-filled medication management aids (e.g., pillboxes), however, dose-dispensing service was not allowed during the study. The patients were advised to always refill their medication at the same community pharmacy to allow retrieval of complete pharmacy claims for adherence measurement.

Follow-up

All patients were contacted by phone call within the first two weeks after discharge and before the next patient contact for a consolidation phone call analog to the 'New Medicines Service' (NMS), developed for community pharmacies in 2011 in the UK [287]. The aim of the phone call was to ensure initiation of medication therapy prescribed at discharge and correct self-management of the medication and the multidrug punch card. Follow-up visits took place at three, six, and twelve months after hospital discharge at the study pharmacy. A study pharmacist performed one interview on the topics of pharmacy visits, GP visits, hospital readmission, medication therapy change, intake of OTC medication, medication management, medication management aids, and adverse drug reactions. The patients filled questionnaires for self-report of adherence and quality of life assessment. Community pharmacies were contacted after every follow-up visit to transmit medication claim records of the patients. At 12 months, one additional questionnaire assessed patient satisfaction and the GP was contacted by fax to transmit laboratory data of the patients. At the last visit, the future management of the medication was discussed and polymedication checks were offered to all patients to evaluate their need for dose-dispensing service by multidrug punch card.

At each follow-up meeting, patients were invited to ask questions about their medication and at request, counseling on indication, benefits, use, and adverse reactions was given analog to the discharge counseling. The experience of adverse drug events (i.e., any injury related to the use of a drug, even if the causality of this relationship is not proven [288]) was asked actively. If unexpected adverse events occurred at another time during the study, patients were able to contact the trial investigators via a hotline number. All reports were treated like any adverse drug event reported in the community pharmacy. According to severity of the symptoms, the study pharmacist counseled the patient about adverse drug event management, advised to discuss the problem with the GP at the next visit, referred the patient to the GP immediately, or phoned the GP for feedback. Every adverse drug event report, hotline contact, and further inquiry with the GP, community pharmacy, a relative, or the study physician was systematically documented

Outcomes

The **primary outcomes** were:

1.1 Composite clinical outcome of time to hospital readmission and time to major adjustment of drug therapy

1.2 Adherence according to Medication Possession Ratio (MPR)

Time to hospital readmission was calculated as the number of days from the day of discharge until the day of first unplanned readmission to any hospital. Time to major adjustment of drug therapy was the number of days from the day of discharge until the day of major adjustment of therapy. Major adjustment of drug therapy was defined as an at least two fold increase in drug dose and/or a prescription of a new drug in the same ATC code class. Events were assessed through patient self-report at every follow-up visit. Major adjustment of drug therapy was verified by pharmacy records. MPR was calculated according to pharmacy claims within the 12 months of study duration as the number of the days' supply obtained over multiple intervals, divided by the duration of the observation period [82]. The observation period was defined as the time between first and last supply for every medication separately, under the assumption that there was no stock available at the first supply. The number of days' supply was the sum of all supplies of the observation period minus the last supply divided by the amount of intake per 24 hours. We included all medications into the calculation that were prescribed over the whole study duration, had a fixed dosing unit (e.g., oral solid forms, inhalers), were prescribed for continuous use (i.e., not upon demand), were refilled at least twice, and with dose and dosing frequency, which were known and remained unchanged over the observation period.

The **secondary endpoints** comprised:

2.1 Adherence according to

2.1.1 Self report: Morisky Medication Adherence Scale (MMAS) score of 0-8, with a maximal score of 8, indicating perfect adherence [67]; visual analogue scales (VAS) of taking and timing adherence ranging from 0: no tablets taken / no tablets taken at the right time, to 100%: all tablets taken / all tablets taken at the right time; elements of the 'Believes about Medicines Questionnaire' (BMQ).

2.1.2 POlypharmacy Electronic Monitoring System: Taking adherence as percentage of taken doses in relation of prescribed doses; timing adherence as average of all recorded intake times according to the prescribed dosing times; correct dosing intervals as percentage of doses taken within 25% of time interval between the prescribed doses.

2.2 Clinical outcomes included the single measurements of time to hospital readmission and time to major adjustment of drug therapy.

2.3 Humanistic outcomes

2.3.1 Quality of life according to the short form 12 v. 2 (SF 12 v. 2): score of 30-70, with a score of 70 indicating best physical/mental health, [289].

2.3.2 Satisfaction with the medication management system and the pilot study: questionnaire containing 37 closed-ended questions with 4-point Lickert-scale answers and seven open ended questions.

Self-reported adherence and quality of life were assessed at baseline and at every follow-up visit. POEMS data were read out continually at every exchange of the electronic multidrug punch cards. The questionnaire for patient satisfaction was administered once at 12 months.

Additional data assessed at baseline included demographic factors, such as diagnoses, prescribed medication at admission and discharge, over-the-counter (OTC) medication, marital status, living situation, education level, employment status, dexterity, health status before index hospitalization, hospital admissions in the three months before the index hospitalization, frequency of GP and community pharmacy visits, prior experiences with adverse events, and financial constraints concerning medication refill. Independency in daily activities was assessed with the Barthel index questionnaire (score of 0-100 with maximal score of 100 indicating total independency) was filled by the investigator with the help of the responsible nurse for the status of the patient at discharge. Laboratory data, e.g., glycosylated hemoglobin (HbA_{1c}), were assessed at discharge from hospital records and at 12 months from the GP's patient records, if available.

Sample size and randomization

Data of the composite endpoint 'time to hospital readmission and time to major adjustment of drug therapy' with the intervention of electronic multidrug punch card were not available. Based on studies examining a tele-monitoring intervention [290], with elderly patients [291], and with myocardial infarction survivors [292,293], we assumed a mean time to hospital readmission + to major adjustment of drug therapy of 200 days for the control group and 240 days for the intervention group (+ 20%). With an assumed standard deviation of 80 days in both groups and a sample size of 150 patients, the resulting power is 86.5% (calculated by a web-tool [294]). A sample size of 150 patients (75 patients per group) was considered sufficient, since a larger sample size would facilitate to reach statistical significance but diminish clinical relevance. The same sample size was also proposed as a conclusion of a review analyzing 78 randomized controlled trials on effectiveness of adherence interventions [126]. A total of 200 patients were planned to be recruited to account for attrition, dropouts, and loss to follow up. For the pilot study, a sample size of 20 patients was determined. Recruited patients were allocated randomly 1:1 into intervention and control groups. Random numbers up to the intended sample size

of 20 (for the pilot study) were generated by a web-tool [295]. A research assistant not involved in the study, packed the allocation information for every patient separately in sequentially numbered envelopes. The envelopes were kept in a closed drawer until the assignment. Two study pharmacists recruited eligible patients and assigned them to the study groups after informed consent was obtained, by opening the envelope with the subsequent number. Due to the nature of the intervention, blinding was not aspired.

Statistics

Due to the small patient sample size recruited during the pilot study, descriptive statistical methods were applied by SPSS v. 20 (IBM, Armonk, New York, USA) and MS Excel 2013 (Microsoft Corporation, Redmond, WA, USA). In the following paragraph, the originally planned analysis is described.

Primary outcome measures will be compared between groups. Secondary outcome measures will be compared between groups and between baseline and follow-up measures. Differences in binary data will be calculated by χ^2-test. The student t-test will be used for normally distributed and the Man-Whitney-U-test for non-parametric means. In order to measure strength of the relationship between the primary endpoint and the group allocation and to test the impact of possible covariate factors, a multiple logistic regression model will be calculated. A p-value of ≤ 0.05 will be considered statistically significant. The analysis will be performed as an intention to treat analysis.

C1.2 Study evaluation

The evaluation was developed according to the 'Planning-Evaluation-Cycle 20', composed of the steps Formulation of evaluation question; Conceptualization; Evaluation design; Evaluation analysis of; Utilization of results in management or decision-making [296].

Formulation of evaluation question

The evaluation had the aim to optimize the feasibility, efficiency, and quality of the study.

Conceptualization

The evaluation was based on Donabedian's evaluation model of the quality of care [297]. According to this model, services are performed in given structures, following defined processes and finally generate an outcome of measurable quality. 'Structure' describes the properties of an environment in which care is performed, including organizational structure, material, and human resources. The category 'process' describes what effectively is practiced. The 'outcome' shows the effects of care on the health of the patients, i.e., improvement of the patient's knowledge, beneficial changes in behavior, and satisfaction. These three parts of quality are directly related to each other, therefore good structure and processes lead to good outcomes. During the evaluation, key elements of structures, processes, and outcomes are measured by indicators. These indicators are suitable

numbers, facts, or parameters, which should be easy to assess in practice and need to be valid, reliable, and sensitive for assessment [298].

These definitions were translated to the pilot study. The desired outcomes in this case were feasibility, efficiency, and quality of the study. Important elements of the pilot study were allocated to the groups of structure and process. For each group, one evaluation method catalogue was developed, containing concrete evaluation questions. At least one indicator and measurement method was defined for every question, indicating answers in scales (e.g. measurement of time), in categories (e.g. Lickert-scales, yes/no), or descriptions and judgment in words (e.g. to open-ended questions). Measurement methods included observation, a questionnaire, and analysis of study databases. Assessments were performed once for structural elements or repetitive over a defined period for process elements.

Evaluation Design

The observation focused on the processes in the hospital, such as the first and second screening, recruitment and discharge, and on structural elements like handling of documents and communication at the University Hospital Basel. Assessment forms with predefined questions according to the study steps were developed. Continuous assessments were measured at five time points.

The perspective of the study team was assessed by a questionnaire based on the questions of the evaluation method catalogues. The questionnaire referred to the whole study duration and comprised the topics a. work within the study team; b. work at the University Hospital Basel and at the study pharmacy; c. work with the documents. Answers were indicated as binary (yes/no) and as four-point Likert scales. Answers could be specified in open comment fields. The same questionnaire was provided to the whole study team with the instruction only to answer the questions concerning their tasks at a short introduction during the study meeting.

Analysis of the databases of both screenings, recruitment, and baseline assessment, containing patients' data from the beginning of the study (21.01.2013) to the 30.04.2013, were on the following topics:

- Fluctuation of patients at the hospital according to electronic database (ISMed)
- The ratio of included and excluded patients after the first screening, the second screening, and after the recruitment
- The reasons for exclusion in the first screening, the second screening, and at the recruitment
- The reasons for rejection of study participation
- Number of multiple assessments

The evaluation was started simultaneously to the commencement of the pilot study.

Analysis

The results of the observation, questionnaires, and database analysis were calculated quantitatively with MS Excel 2007 for Windows (Microsoft Corporation, Redmond, WA, USA). Based on these results, the evaluator answered the questions of the evaluation catalogues and judged the study elements as 'adequate / improvement unnecessary', 'optimizable / minor improvements recommended', and 'inadequate / major improvements necessary'.

The evaluation of the hospital phase was systematically carried out by a master student in Pharmacy during the first period of the pilot study (21.01.2013-30.04.2013) using the above described methods. The evaluation of the primary care phase was conducted by the study coordinator at the termination of the pilot study, based on experiences and analysis of study databases.

Results

C1.1 Pilot study

The pilot study was performed from the 21st of January to the 30th of September 2013.

Participants

Of a total of 958 screened patients, 10 (1.0%) consented to participate in the study. The numbers of the screened and recruited patients and the numbers and reasons for exclusion, lost-to-follow-up, and drop-out are depicted in **Figures 5** and **6**. One patient assigned to the intervention group rejected participation upon discharge but agreed to be included in the control group and therefore was reassigned.

Recruitment

Recruitment started at 21st of January and ended at the abandonment of the pilot study on 30th of September with an interruption from the 25th of March to the 12th of April because of a case of death in the nursing team of the ward. During the flu season, the ward chosen for the recruitment served as pooling ward of patients with infectious isolation and thus was not accessible for recruitment. Therefore, we attempted to change the recruitment ward. However, the change of the ward was not possible, because the head of the ward did not accept recruiting staff due to understaffing of the nurses. For this reason, 58 of the screened patients on this ward (6.2) were lost to follow-up (**Figure 5**). Of the 80 visited patients, 10 (12.5%) consented to participate in the study (**Figure 6**). Reasons for rejection of study participation are shown in **Figure 7**.

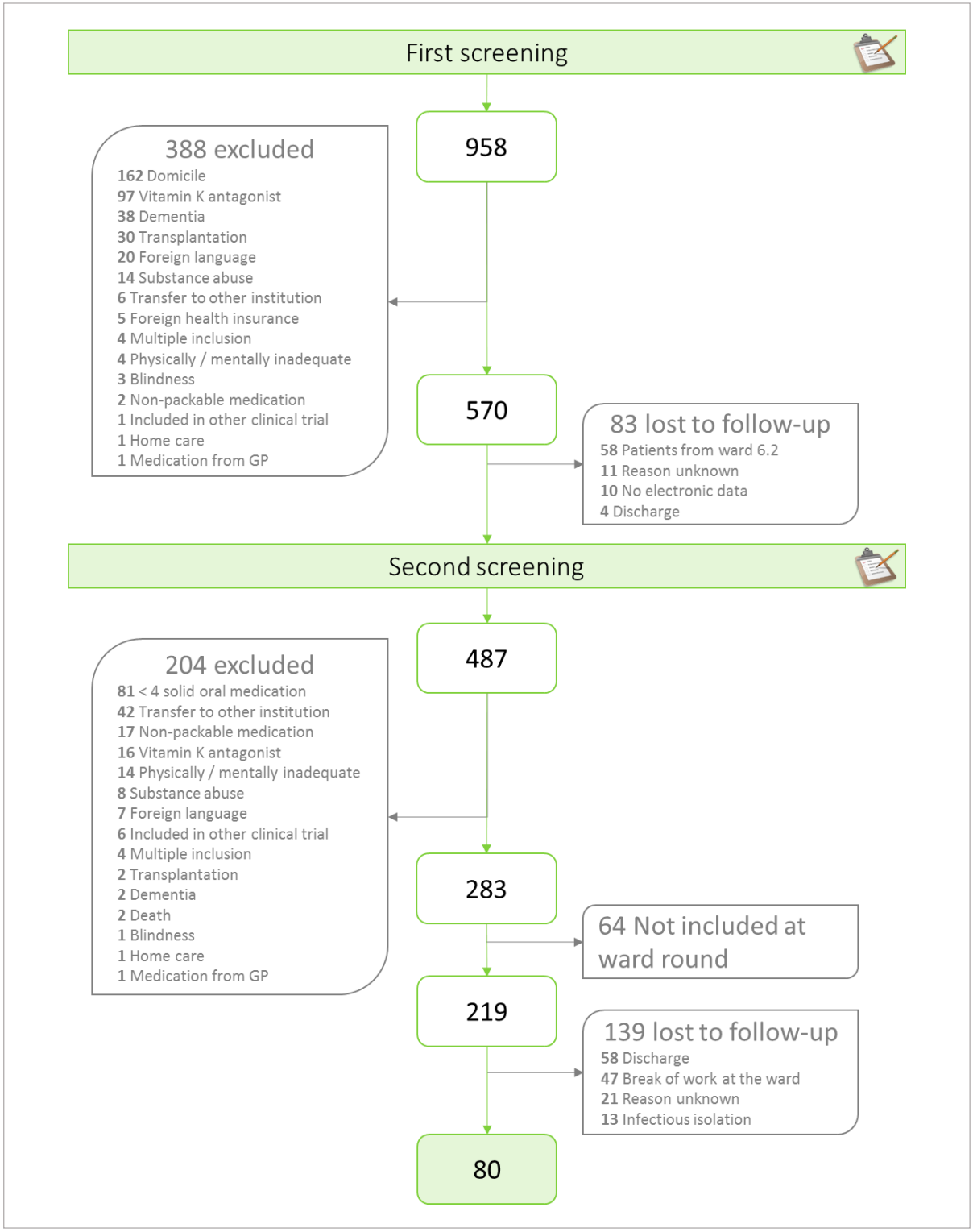

Figure 5: Flow chart of the screening phase of the pilot study with numbers and reasons for exclusion and lost to follow-up. Eighty patients were included for recruitment. GP, general physician.

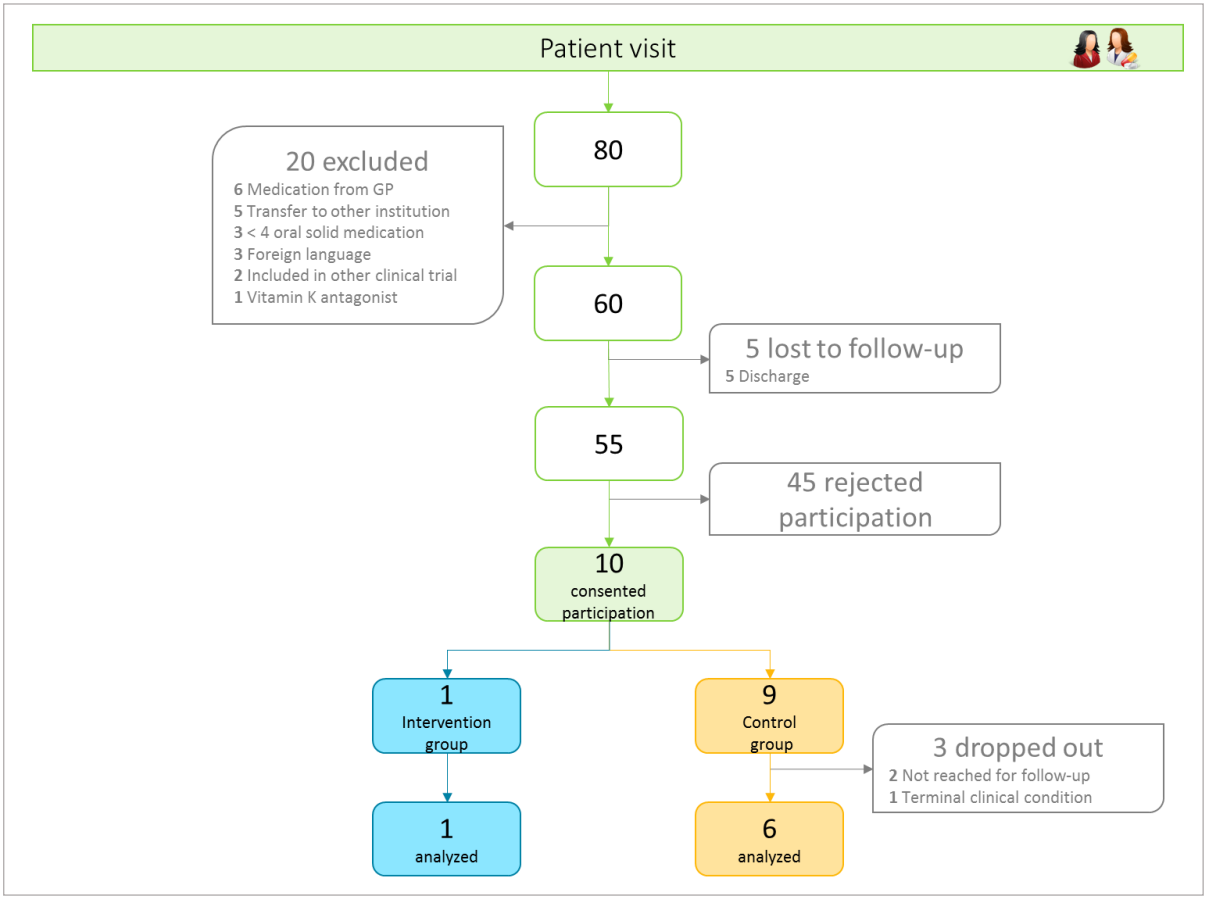

Figure 6: Flow chart of the recruitment of the pilot study with numbers and reasons of exclusion and numbers of patients recruited, allocated and analyzed. GP, general physician.

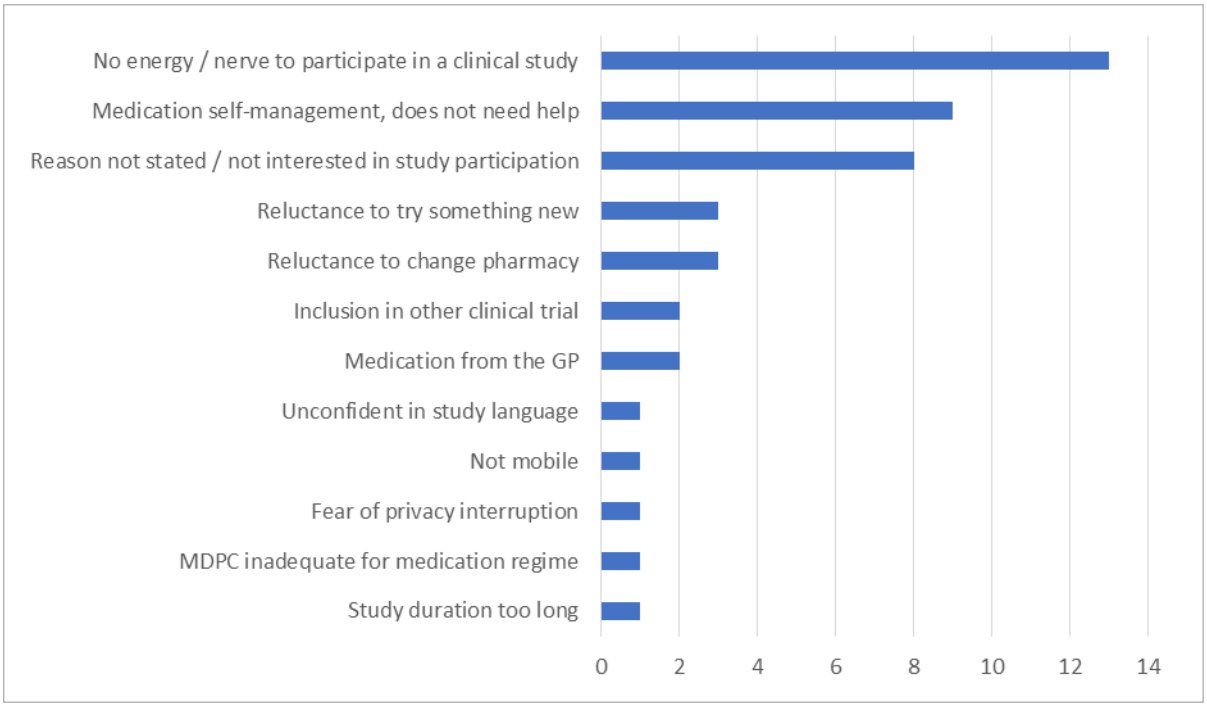

Figure 7: Reasons for rejection of study participation (n=45). MDPC, multidrug punch card. GP, general physician.

Baseline data

Baseline data of the recruited patients are displayed in **Table 2**. All patients were fully independent in daily management according to the Barthel index (score of 100) [299], except for the patient with the fracture (patient ID 2; score of 90). Their health status in the two weeks before index hospitalization was very good (n=2), good (n=6), and moderate (n=2). One patient from the control group had had a hospital admission within the three months before the index hospitalization. In the year prior to the index hospitalization, four patients had visited the GP 1-2 times and six patients 3-6 times. Three patients did not visit a community pharmacy during the previous year, five visited it 3-6 times, and one patient went to the pharmacy 1-3 times per month. Two patients reported prior experiences with adverse drug events and one patient had thought once of not refilling a medication because of financial constraints. Correspondingly, the intervention patient had had no hospitalization in the three months before index hospitalization and reported two planned GP visits, three to six community pharmacy visits, and no experience of and averse drug reaction in the year prior to the index hospitalization.

Table 2. Baseline data of the recruited patients.

* The patient did not use prescribed long-term medications before index hospitalization.

Appl. sci., applied sciences; MMAS, Morisky Medication Adherence Scale; QoL, quality of life; TaA, taking adherence; TiA, timing adherence; VAS, visual analogue scale.

Patient ID	Age [years]	Sex	Living situation	Education level	Employ-ment status	Cause for index hospitalization	Adherence MMAS	Adherence VAS	QoL physical/mental score	No. of drugs at hospital admission	No. of drugs at hospital discharge
Control patients											
1	75	F	With partner	Appren-ticeship	Retired	Hypertensive heart disease	2.5	TaA: 90% TiA: 90%	40 / 51	5	7
2	63	M	With partner	University (PhD)	Employed	Fracture of lumbar spine and pelvis	6	TaA: 96% TiA: 90%	58 / 58	3	10
3	67	F	With partner	University of appl sci	Retired	Glioblastoma	8	TaA: 100% TiA: 100%	40 / 59	6	6
4	68	F	Alone	Business school	Retired	Pain in upper abdomen	8	TaA: 100% TiA: 100%	56 / 62	3	4
5	80	F	With partner	University (PhD)	Retired	Ischemic cerebrovascular insult	8	TaA: 100% TiA: 100%	56 / 54	4	8
6	53	M	With partner	High school	Employed	(N)STEMI / Myocardial infarction	n.a.*	n.a.*	50 / 61	0	5
7	76	M	With partner	Mandat-ory school	Retired	Unspecified arthritis	8	TaA: 100% TiA: 100%	56 / 50	8	10
8	35	M	With partner	Appren-ticeship	Employed	Hematemesis	5.5	TaA: 50% TiA: 70%	54 / 45	1	6
9	57	M	With partner	University of appl sci	Employed	Ischemic cerebrovascular insult	8	TaA: 100% TiA: 100%	58 / 52	6	7
Median (range) / *Sum*	67 (35-80)	*F: 4* *M: 5*	*With partner: 8* *Alone: 1*	n.a.	*Retired: 5* *Employed: 4*	n.a.	8 (2.5-8)	TaA: 100% (50-100%) TiA: 100% (70-100%)	56 (40-58) / 54 (45-62)	4 (0-8)	7 (4-10)
Intervention patient											
10	64	M	Alone	University of applied science	Retired	Staphylococcus aureus sepsis	8	TaA: 100% TiA: 50%	46/42	7	10

Outcomes and estimation

The number analyzed for the control group was n=8, 7, and 6 for follow-up at three, six months, twelve months, respectively. The number analyzed for the intervention group was n=1.

At the phone follow-up, nine of ten patients could be reached and all reported that they could start with the treatment as prescribed at discharge. Seven of nine patients had had a control visit at the GP's and for five patients this had resulted in a change of their medication regimen. All patients felt confident in the administration of their medication. The phone call was performed at a median of 14 days after discharge (range: 4-26 days) with a median duration of 12.5 minutes (range: 7-34 minutes).

Six of the nine control patients and the intervention patient completed the study. One control patient forgot one appointment for follow-up assessment, which was postponed. Otherwise, the patients kept all appointments at the study pharmacy. All control patients self-managed their medication, except for one, who had the help of his wife. Two patients of the control group had home delivery by mail order pharmacy and four received their medication at the community pharmacy. The follow-up visits at three, six, and twelve months took place at a median of 98 days (range: 89-109 days), 188.5 days (171-216 days), and 368 days (365-379 days), respectively, and lasted a median of 19.5 minutes (12 minutes – 1 hour).

Over the whole study period, no patient experienced an unplanned hospital readmission. The intervention patient had one major adjustment of drug therapy, i.e., an augmentation of bisoprolol 2.5mg twice daily to 5mg twice daily, 79 days after hospital discharge. The medication possession ratio (MPR) could be calculated for five of six patients in the control group for a median of four medications (range 1-5). For one patient (patient ID 2), most medications changed during the study period and for the remaining two medications he had too few pharmacy claims (<2) to be included into MPR calculation. The overall MPR of the control group was 1.01 ± 0.10. For the intervention patient, the MPR could be calculated over six medications. Some of the claims had shorter observation periods than others because the patient provided his stock medication for inclusion into the multidrug punch card. The overall MPR of the intervention patient was 1.18 ± 0.11. The MPRs per groups, patient, and medication are listed in **Table 3**.

Adherence measures according to patient self-report, quality of life, clinical outcomes, and the changes of the patient's medications during the study period are displayed in **Table 4**. Results from the 'Believes of Medicines Questionnaire' (BMQ) showed that the patients were rather ambivalent in medication use, in that they acknowledged the necessity but were worried about the consequences of medication use. Detailed answers to BMQ questions and the trends over time are given in **Annex A4.7**. Results from the electronic measurement of adherence by POEMS are reported separately in a case report (page 148).

Table 3. Medication possession ratio (MPR) per medication, per patient and per treatment group.

SD, standard deviation.

Patient ID	Medication included in calculation	Observation period [days]	MPR	Mean MPR / patient	SD
Control patients (n=5)					
1	Rivaroxaban	312	0.94	0.94	n.a.
4	Aspirin®	282	1.04		
	Candesartan / hydrochlorothiazid	282	1.04	1.04	0
5	Alendronate	315	1.07		
	Aspirin®	189	1.04		
	Atorvastatin	279	0.72		
	Vitamin B complex	248	1.11	0.99	± 0.18
6	Aspirin®	302	0.97		
	Atorvastatin	302	0.66		
	Bisoprolol	302	0.99		
	Lisinopril	302	0.99		
	Ticagrelor	302	0.93	0.91	± 0.14
7	Aspirin®	169	1.16		
	Atorvastatin	321	0.93		
	Pantoprazol	244	1.23		
	Ramipril	321	1.25		
	Tizanidin	246	1.22	1.16	± 0.13
Overall MPR of the control group				**1.01**	**± 0.10**
Intervention patient					
10	Aspirin®	375	1.12		
	Atorvastatin	328	1.31		
	Clopidogrel	328	1.28		
	CoAprovel	178	1.10		
	Metfin	341	1.23		
	Pantoprazol	232	1.03	**1.18**	**± 0.11**

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Table 4. Adherence, clinical and humanistic outcomes and medication therapy changes over the study period.

Hc, healthcare; MMAS, Morisky Medication Adherence Scale; n.a., not applicable; OTC, over-the-counter; pack., packable; pat, patient; QoL, quality of life; SF12 v.2, short form 12 version 2; T0, T3, T6, T12, time points of discharge and follow-up visits at three, six, and twelve months.

			Control patients				Intervention patient			
Assessments			**T0**	**T3**	**T6**	**T12**	**T0**	**T3**	**T6**	**T12**
For control patients values are given as median (range)			(n=9)	(n=8)	(n=7)	(n=6)				
Adherence	MMAS,		8 (2.5-8)	7 (4.75-8)	7 (6.75-8)	8 (5-8)	8	8	8	8
	VAS taking adherence		100% (50-100%)	100% (98-100)	100% (96-100%)	99.5% (94-100%)	100%	65%	95%	95%
	VAS timing adherence		100% (70-100%)	100% (95-100%)	100% (80-100%)	95% (90-100%)	50%	75%	95%	85%
Humanistic outcomes (QoL)	SF12 v.2 physical scale		56 (40-59)	47 (33-60)	54 (44-59)	55 (33-58)	46	39	42	48
	SF12 v,2 mental scale		54 (45-63)	53 (44-58)	57 (40-60)	56 (44-63)	42	62	61	58
Clinical Outcomes	Major therapy adjustment		n.a.	0	0	0	n.a.	1	0	0
	Unplanned hospital readmissions		n.a.	0	0	0	n.a.	0	0	0
	Unplanned visits at any hc facility		n.a.	0	0	0	n.a.	0	0	0
	Planned GP visits per patient		n.a.	2 (1-6)	2 (1-4)	3 (1-5)	n.a.	4	3	2
	Pharmacy visits per patient		n.a.	3 (1-7)	2 (0-4)	2 (0-4)	n.a.	9	4	6
	Glycosylated hemoglobin (control pat n=1)		6%	n.a.	n.a.	5.8%	8%	n.a.	n.a.	7%
	Blood pressure [mmHg] (control pat n=5)		141/76 (123/75-154/92)	n.a.	n.a.	131/80 (125/64-142/91)	183/93			193/88
Medication changes	Number of medications per patient		7 (4-10)	6.5 (3-10)	7 (3-11)	5 (3-12)	10	9	9	9
	Number of patients with medication changes		n.a.	6	6	4	n.a.	2	0	0
	Number of medications started per patient		n.a.	0 (0-3)	1 (0-3)	0 (0-1)	n.a.	0	0	0
	Number of medications stopped per patient		n.a.	0.5 (0-4)	0 (0-1)	0 (0-2)	n.a.	1	0	0
	Number of medications changed per patient		n.a.	1 (0-3)	0 (0-2)	0.5 (0-4)	n.a.	1	0	0
	Number of medication by dosage form at discharge per patient	Oral, pack.	5 (4-9)	n.a.	n.a.	n.a.	8	n.a.	n.a.	n.a.
		Oral, non-pack	0 (0-1)	n.a.	n.a.	n.a.	0	n.a.	n.a.	n.a.
		Parenteral	0 (0-1)	n.a.	n.a.	n.a.	2	n.a.	n.a.	n.a.
		Inhaler	0 (0-2)	n.a.	n.a.	n.a.	0	n.a.	n.a.	n.a.
		Skin patch	0 (0-2)	n.a.	n.a.	n.a.	0	n.a.	n.a.	n.a.
	Number of OTC medications		1.5 (0-6)	1.5 (0-7)	2 (0-5)	3 (0-6)	0	0	0	0

All control patients had one or several strategies to remind medication intake encompassing self-filled multicompartment adherence aids (n=4), visual reminders, storage of medication at a strategic place, connection with a daily routine, and integration in daily life. All patients were very satisfied with their strategies of medication management. There was no remarkable difference between control patients, who had their own systems for medication management and the intervention patient, who had the multidrug punch card. The control patients were confident that the system helped them with the correct use of their medication (**Figure 8**). The satisfaction of the intervention patient with the multidrug punch cards is shown in **Figure 9**. The patient reported initial handling difficulties because of strong resistance of drug removal from the cavities that were fully loaded (e.g., morning cavities, which contained eight medications). These problems resolved with time.

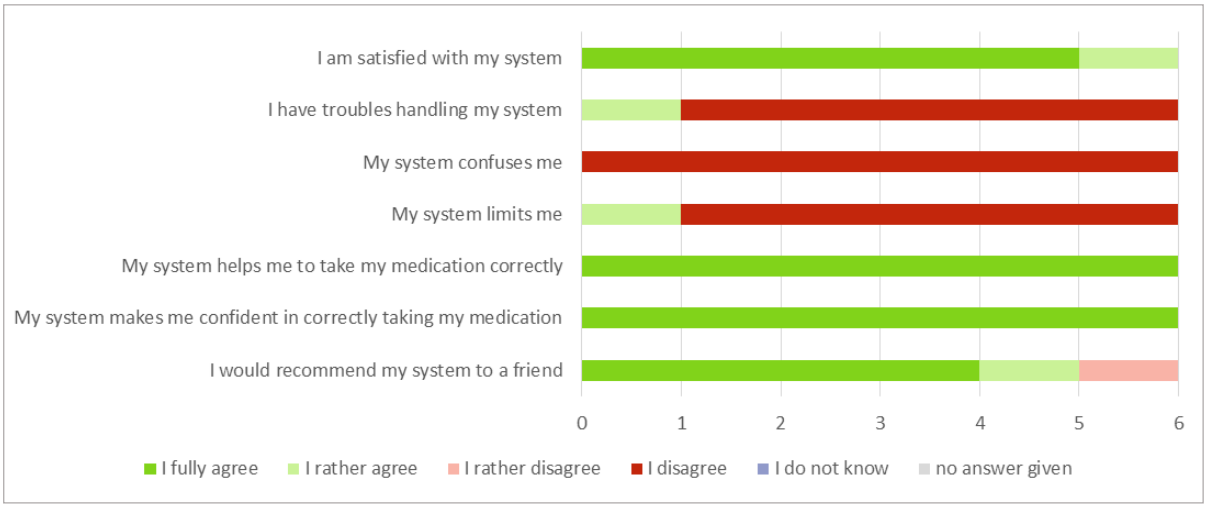

Figure 8: Satisfaction of the control patients with their medication management system (n=6).

Figure 9: Satisfaction of the intervention patient with the multidrug punch card.

At the end of the study, patient 6 of the control group wished to start multidrug punch card service. Patient 1 bought a pillbox, which she filled on her own. All other patients preferred to continue with their previous systems. The intervention patient requested to continue the multidrug punch card service.

Harms

During the whole study, there was no emergency call on the hotline. The intervention patient reported initial handling difficulties with the multidrug punch card, which resolved with time. There was never a danger of failure of medication intake because of the multidrug punch cards. Five of all ten patients stated adverse drug events at one or more follow-up visits, which are specified in **Table 5**.

Table 5. Adverse drug events (ADE) reported during the study, action taken, and outcomes.
ADE, adverse drug event; ADR, adverse drug reaction GP, general physician; T0, T3, T6, T12, time points of discharge and follow-up visits at three, six, and twelve months.

Patient ID	Time of ADE report	Nature of ADE / suspected medication	Action taken	Outcome (assessed at the next follow-up visit)
1	Consolidation phone call	(1) Myopathy/atorvastatin (2) Gastro-intestinal problems, loss of appetite, obstipation, vertigo	(1) Atorvastatin was stopped by the GP prior to the phone call. (2) Counseling about ADE management.	Symptoms improved
	Follow-up T6	Obstipation / amlodipine	Counseling about ADE management	Symptoms persisted, follow-up at the next visit
	Follow-up T12	Loss of appetite, obstipation, loss of hair / antihypertensive medication	Counseling about ADE management	No follow-up
2	Follow-up T3	Edema on lower leg, low body temperature / amlodipine	None - patient reported handling by the GP	No follow-up
5	Consolidation phone call	Increased tiredness	Related to rehabilitation phase after hospitalization	No follow-up
	Follow-up T6	Bad smell in mouth, hypersalvation / atorvastatin	None - patient reported handling by GP	No follow-up
6	Follow-up T3	Increased tiredness / bisoprolol	None - patient reported handling by the GP	Follow-up at the next study pharmacy visit
	Follow-up T6	Increased tiredness / bisoprolol	None - patient reported handling by the GP	Follow-up at the next study pharmacy visit
	Follow-up T12	Increased tiredness / bisoprolol	None - patient reported handling by the GP	No follow-up
9	Consolidation phone call	Bleeds rapidly after marginal injuries, blood smells metallic, dry cough / ramipril	Advise to discuss the ADE with the GP at the next visit (substitution of ramipril)	Symptoms persisted, follow-up at the next study pharmacy visit
	Follow-up T6	Dry cough / ramipril	Advise to discuss the ADE with the GP at the next visit (substitution of ramipril)	Ramipril was stopped at T6 and substituted through valsartan / hydrochlorothiazide

C1.2 Study evaluation

Hospital phase

The evaluation catalogues of the structure and process elements of the pilot study contained a total of 158 questions with corresponding indicators and measurement methods (supplementary material). Single and continuous observations were performed in eleven halve days distributed over twelve working days between 15.04.-30.04.2013. The questionnaire was filled by all four study team members. The databases used for evaluation analysis contained data from 376 patients in the first and 197 patients in second screening during the predefined time period.

Structure evaluation

Considering the fixed times of the ward (e.g. for ward rounds, meals, visiting) and the investigators' experiences, the best time to go on the ward was between 10.00-12.00 a.m. for the second screening and after 3.00 p.m. for recruitment. The walking distances between the different study locations took less than 7 minutes. The response to calls of the hotline was tested five times, of which one was answered, one was called back, and three were not registered.

Access to electronic and paper case notes was always possible, although paper case notes were not always traceable. An average of 5.8 ± 3.5 new patients (range: 1-15) were screened per day in the electronic hospital database. The average stay of a patient at the hospital was 7.4 ± 5.9 days (range: 1-30). The number of days between entry of a patient and his / her assessment at the first screening took 3.2 ± 2.5 days (range: 0-13). The observation showed that the electronic hospital database was not always up to date and that there were discrepancies of the patient numbers (±1), which resolved within one to two days.

Figure 10 charts the flow of the first and second screening during the evaluation period. Major exclusion reasons were domicile, vitamin K antagonist, and dementia in the first screening, and < 4 solid oral drugs, transfer to another institution, and non-packable drugs in the second screening. At the first screening 58.8% of all screened patients were included and at the second screening 49.2% of all patients available for the second screening were included for recruiting. The category 'transfer to other institution' comprised the transfer to another ward, nursing home, rehabilitation center, psychiatry, and women's house. In the first and second screening, 23 and 2 patients were assessed multiple times, respectively (exclusion reason 'multiple inclusion'). The reasons for loss to follow-up because of discharge were non-availability of the patient during hospitalization (e.g., because of acute clinical condition, medical investigation etc.; 13, 34.2%), absence of the study team (12, 31.6%), too short hospital stay (9, 23.7%), and weekend discharge (4, 10.5%).

Of 34 patients included for recruitment, 11 were excluded during the recruiting because of transfer to other institution (4, 8.8%), receiving medication from physician or rejection to change the pharmacy

(3, 8.8%), discharge (3, 8.8%), and < 4 oral solid medications (1, 2.9%). Twenty-three patients rejected the study participation because of several reasons (**Figure 11**). At recruitment, 12.5% of the visited patients were included and consented to participate. Overall, 1 of 94 patients from the first screening was enrolled. There were no drop-outs during the evaluation of the hospital phase of the pilot study.

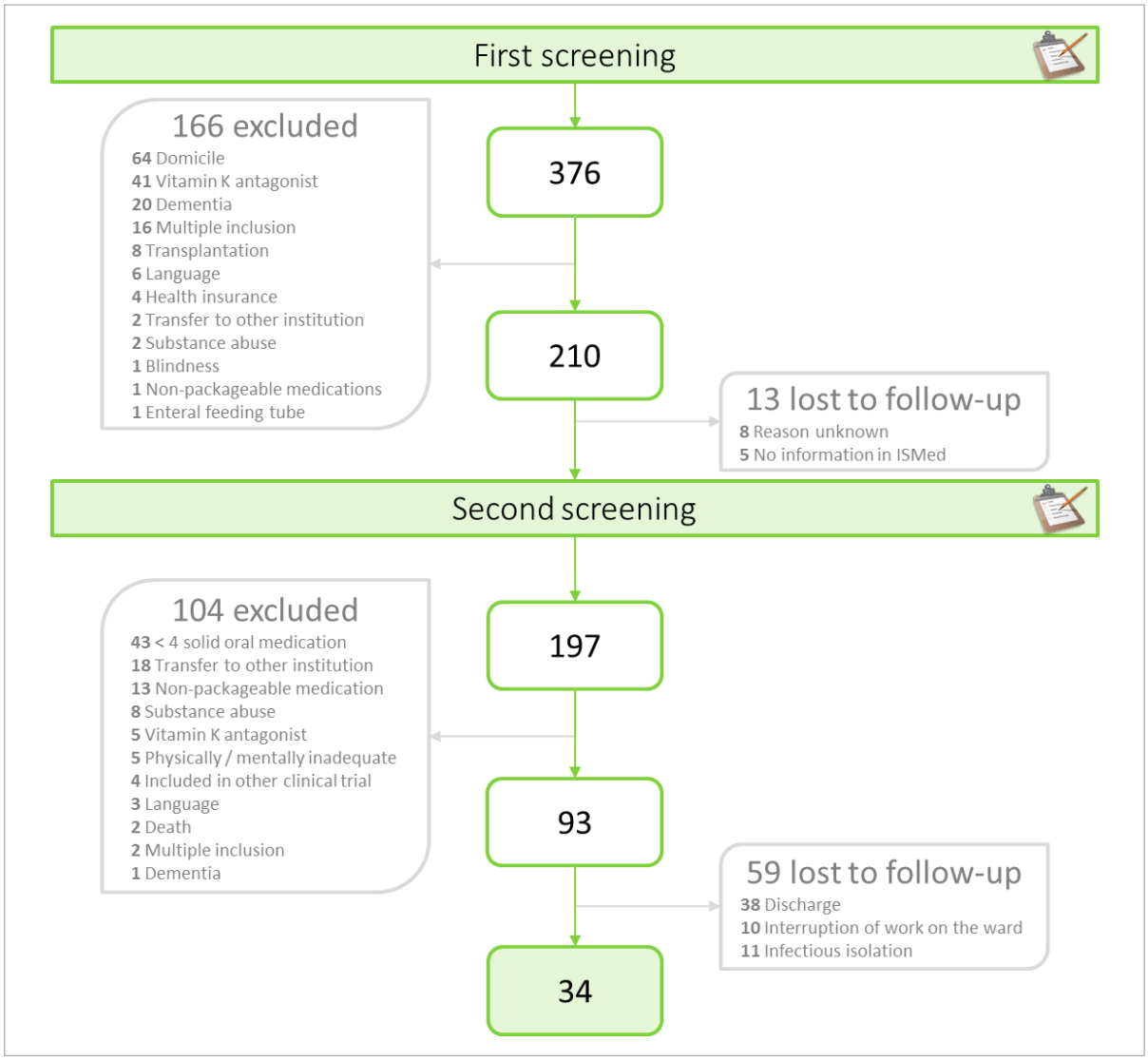

Figure 10: Flow chart of the patients in the first and second screening during the evaluation phase with the numbers and reasons for exclusion and loss of follow-up. Thirty-four patients were included for recruitment (this was an intermediate result of the master thesis and may not be in total accordance with the final adjusted analysis displayed in Part C1.1, Chapter 'Participants'). GP, general physician.

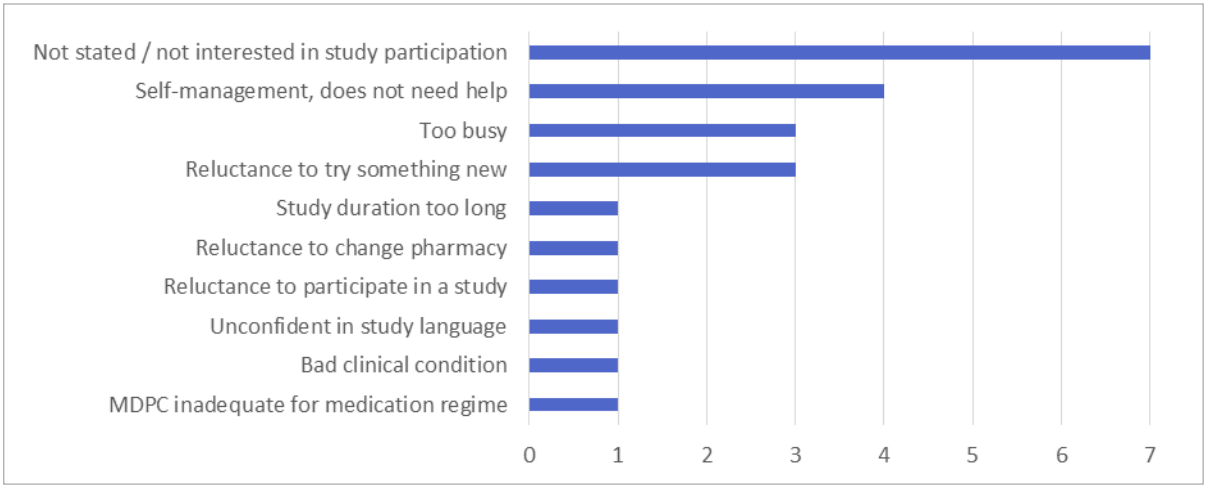

Figure 11: Reasons for rejection of study participation (n=23; this was an intermediate result of the master thesis and may not be in total accordance with the final adjusted analysis displayed in Part C1.1, Chapter 'Participants').

All documents containing sensitive patient data were kept in a separately locked drawer. The study team members rated the place for document storage as inadequate because of inconvenience of access and the lack of clear arrangement in the drawer. The effort to print new documents was judged as low, the items in the case report forms (CRFs) well understandable, and the layout of the CRFs well designed. The structure of the CRFs, applicability and understandability of the predefined questions for the patients were considered as rather good. During observation, the patients asked no questions indicating trouble with the wording.

Within the study team, the role was unclear for one, and the tasks not clearly defined for another team member. Some tasks handed over by the study coordinator were not or only partly manageable because of time or skill requirements. The Standard Operating Procedures (SOP) for the study distributed at the first study team meeting were known by three of four study team members and two persons adhered to them. The information flow was generally judged as too low and a regular updating by e-mail was desired. However, team members agreed that there were adequate possibilities for feedback to and support by the study coordinator. The study team rated the working atmosphere and communication as good at all study locations.

A summary of the structure evaluation of the hospital phase is given in **Table 7** at the end of section 'Process evaluation'.

Process evaluation

The time measurements of the single study steps and per patient in-, exclusion, and assessment are shown in **Table 6**. 'Open patient' means that the patient has not decided about study participation to

that moment. Predefined process schemes were available for the recruitment and the discharge counseling. The schemes were adhered to and uniformity of processes was mostly kept. The time needed by the patients to decide about the participation was 2.0 ± 2.9 days (n=5, range 0-7 days).

Table 6. Time expenditure of study steps and per patient.
CRF, case report form; min, minutes; n.a., not applicable; no., number; SD, standard deviation; T0, time point of discharge

Step of the study		1. Screening	2. Screening	Recruitment	Discharge
Time expenditures and numbers of patients screened and assessed per day					
No. of investigators observed (no. of observations)		2 (11)	2 (8)	2 (6)	1 (1)
Mean duration per day ± SD [min], (range)		42.7 ± 28.6	63.3 ± 25.0	36.8 ± 30.7	48.9
Mean no. of patients assessed per day ± SD		6.5 ± 4.9	10.5 ± 3.7	1.60 ± 0.55	1
Mean no. of included patients per day ± SD		3.6 ± 2.5	2.5 ± 1.1	0.2 ± 0.5	n.a.
Mean no. of excluded patients per day ± SD		2.6 ± 2.7	3.0 ± 1.5	0.6 ± 0.6	n.a.
Mean no. of open patients per day ± SD		0.3 ± 0.5	5.0 ± 1.9	0.8 ± 0.8	n.a.
Time expenditures by patient screening and assessment					
No. of investigators observed (no. of observations)		2 (45)	2 (27)	2 (7)	1 (1)
Mean time expenditure of screening and assessment ± SD [min]	per included patient	5.4 ± 2.0	4.6 ± 1.0	47.5	48.9
	per excluded patient	0.7 ± 0.0	1.8 ± 2.0	3.8 ± 2.0	n.a.
	per open patient	0.4	2.1 ± 2.0	9.4 ± 5.7	n.a.

At the second screening, a patient initially excluded for a criterion of which a change during hospitalization was potentially realistic (e.g., > 4 oral solid medications) and allowed the subsequent inclusion of the patient, was followed-up until discharge. At the moment of change of the criterion, the patient was included to be recruited. Of 10 initially excluded patients followed-up during the observation period, nine were definitively excluded and one patient was still followed-up at the end of the observation phase. The mean time for these follow-ups was 5.9 ± 4.4 days. The initial reasons for exclusion and the reasons for stopping the follow-up are illustrated in **Figure 12**.

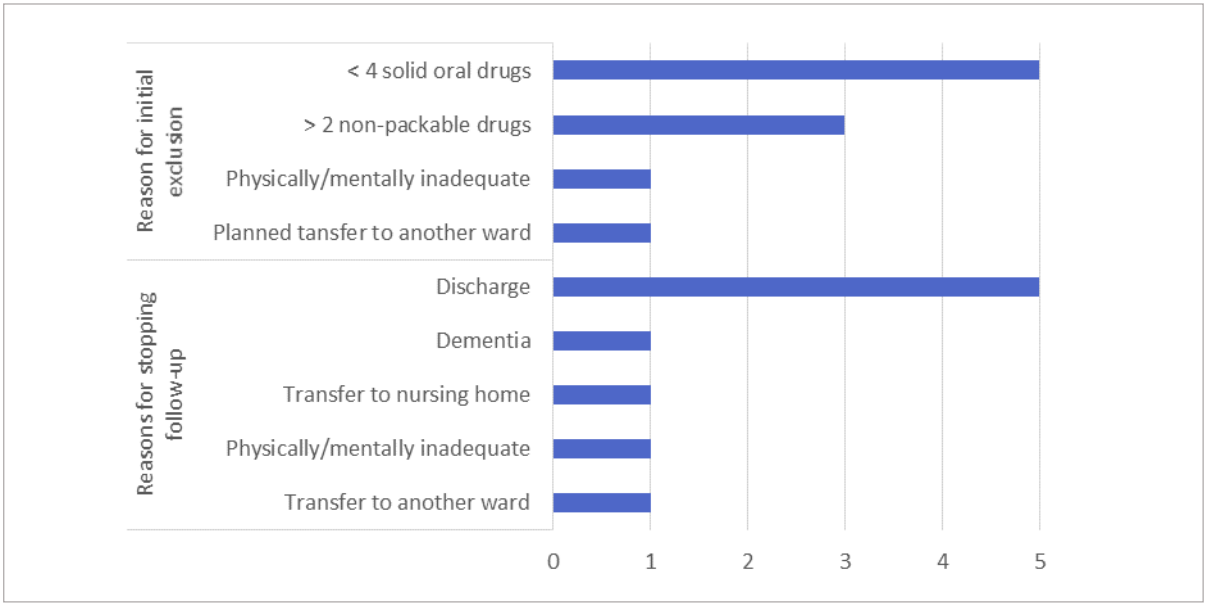

Figure 12: Reasons for initially excluded and followed-up patients (n=10) and reasons for stopping the follow-up (n=9). One patient was still followed-up at the end of the observation phase.

For data entry, a preset MS Access database and a corresponding data dictionary were available. The filling of the database was manageable in adequate time (8.9 ± 3.2 for all data from screening to recruitment).

The communication within the study team was reported to be optimizable. The communication of the study team with employees of the hospital pharmacy, the study pharmacy, and the hospital ward was rated as good. The observations confirmed these statements. Availability of information from nurses and physicians was good.

A summary of the process evaluation of the hospital phase is given in **Table 7**.

Table 7. Summary table of the hospital phase evaluation. The dots indicate the judgment of the evaluator based on the results of the measurements according to the evaluation catalogue performed during the study. Green dots indicate adequate process / improvement unnecessary; orange dots indicate optimizable process / minor improvements recommended; red dots indicate inadequate process / major improvements necessary. The feasibility of the structure was not evaluated herein.
N.e., not evaluated.

Study step	1. Screening	2. Screening	Recruitment	Discharge	Hospital	Documents	Study team	Patients	Software
Structure									
Quality	🔴	🔴	🔴	🟢	🟢	🟢	🔴	🔴	n.e.
Efficiency	🟠	🔴	🟠	🔴	🟢	🟢	🔴	🟢	n.e.
Procedure									
Feasibility	🟢	🟢	🟠	🟢	🟢	🟠	n.e.	🟢	🟢
Quality	🟠	🟢	🟢	🟠	🟢	🔴	🔴	n.e.	🔴
Efficiency	🟠	🟢	🔴	🔴	🟢	🟠	🔴	🟢	🔴

Primary care phase and patient satisfaction

The rest of the evaluation catalogue was answered by the study coordinator's experiences and by analysis of the study databases, and was mainly qualitative. The following paragraph lists, a summary of the inadequate points of study structure and process.

Inadequate points of the study structure:

- Follow-up visits:
  - Problematic understandability of SF12 v.2 and patient satisfaction questionnaires
- Study patients: a drop-out rate of 33% is not acceptable
- Community pharmacies:
  - Complaint from the regional pharmacy association about neglect of informing
  - Complaint from a community pharmacy because of client theft and subsequent implication to stop cooperation (transmission of patient records)
- Study pharmacy:
  - Non-transferable key to the study pharmacy complicated the organization
  - Missing coordination with the study pharmacy team led to a collision of appointments (team event, follow-up visit)
- Multidrug punch card / POEMS
  - We used prototype POEMS films, with which we experienced technical difficulties: false positives because of interference with other chips, false positives and early recordings because of injured circuitries before the actual removal or without removal, complete loss of data of 11 multidrug punch cards and nine additional days because of technical failure.

- Non-availability of RFID-chips resulting in a delay of recruitment and therefore in a loss to follow-up (discharge), and in increased effort for the intervention patient (more frequent visits).

Major inadequate points of the study procedure:

- Questionnaires: Conduction as interviews because of reluctance or inability of patients to fill out questionnaires.
- Multidrug punch cards
  - High time expenditure for production for four weeks (1.5-2h).
  - Difficulty in removing medications from the electronic multidrug punch card by the intervention patient if the cavities were fully loaded.

The summary of the structure and process evaluation of the primary care phase is illustrated in **Table 8**.

Table 8. Summary table of the primary care phase evaluation. The dots indicate the judgment of the evaluator according to the evaluation catalogue, based on the experiences of the study coordinator and database analysis. Green dots indicate adequate process / improvement unnecessary; orange dots indicate optimizable process / minor improvements recommended; red dots indicate inadequate process / major improvements necessary.
Comm. pharm., community pharmacies; Cons., consolidation; MDPC, multidrug punch card; n.e., not evaluated; POEMS, POlypharmacy Electronic Monitoring System

Study step	Cons. phone call	Follow-up visits	Study patients	Comm. pharm.	Study pharmacy	MDPC / POEMS	Resources	Outcomes
Structure								
Feasibility	🟠	n.e.	🟠	🟠	🟢	🟠	🟢	🟢
Quality	🟢	🟢	n.e.	🔴	n.e.	🔴	n.e.	🟠
Efficiency	🟢	n.e.	🔴	🟠	🔴	🔴	🟠	🟠
Procedure								
Feasibility	🟠	n.e.	🟠	n.e.	n.e.	n.e.	n.e.	n.e.
Quality	🟢	🟠	🟢	n.e.	🟠	🟢	n.e.	n.e.
Efficiency	🟢	🟠	🟢	n.e.	n.e.	🔴	n.e.	n.e.

Patient perspective

Patient satisfaction with the study elements was high (**Figure 13**).

In summary, the few and moderate criticisms concerned the high number of questions of the baseline assessment at the hospital, the information about the study, the structure and volume of discharge

counseling, the atmosphere in the study center. The intervention patient criticized the lack of financial compensation.

Detailed results of satisfaction about hospital phase and discharge counseling, consolidation phone call, and follow-up are illustrated in **Figures 14, 15,** and **16**.

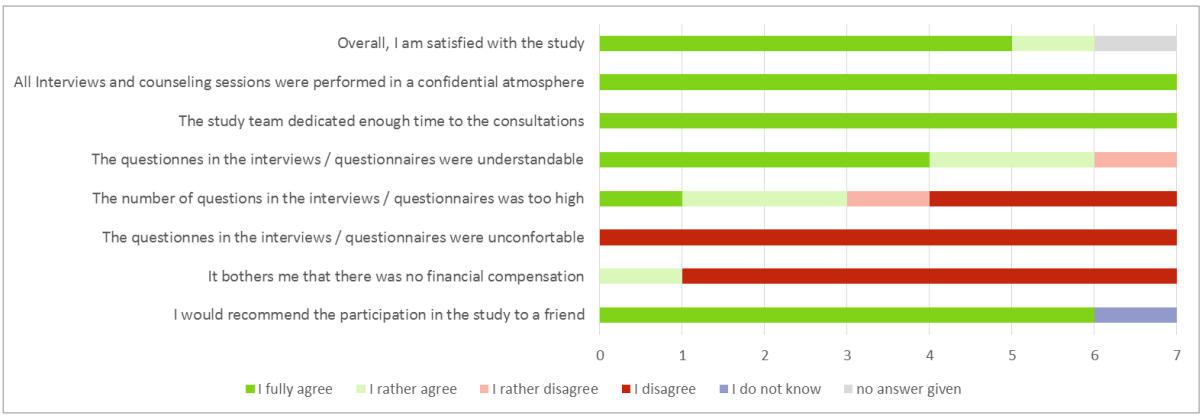

Figure 13: Overall satisfaction of all study patients with the study structures and processes (n=7).

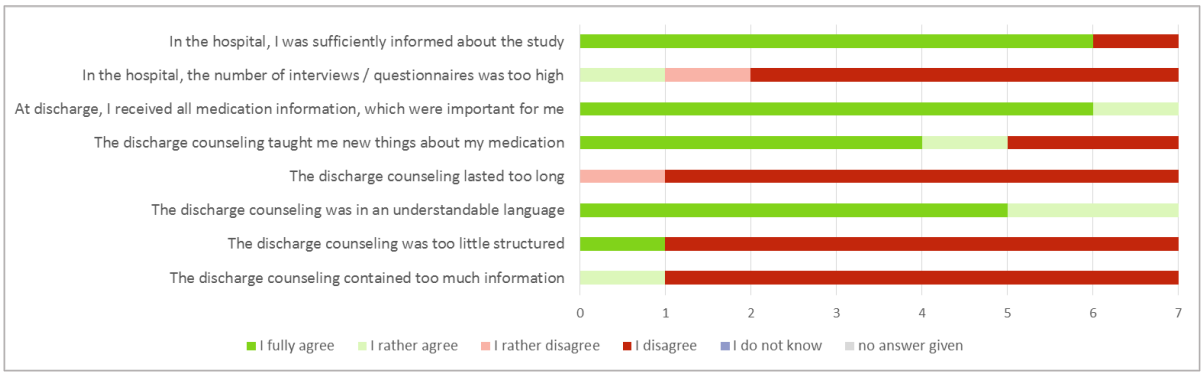

Figure 14: Patient satisfaction with the hospital phase and discharge counseling (n=7).

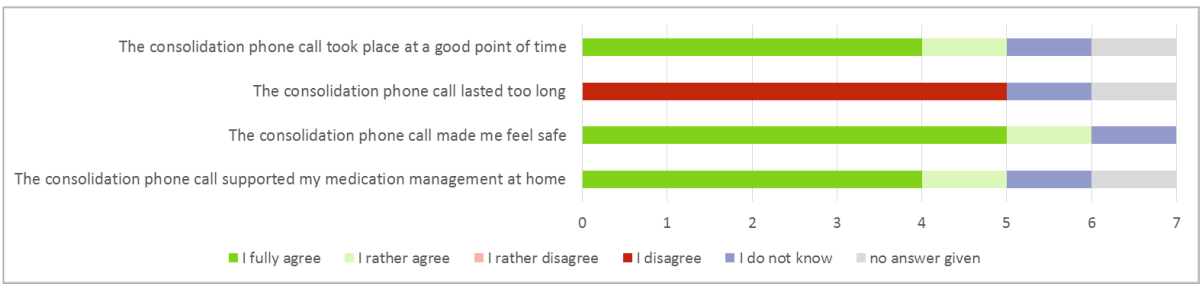

Figure 15: Patient satisfaction with the consolidation phone call (n=7).

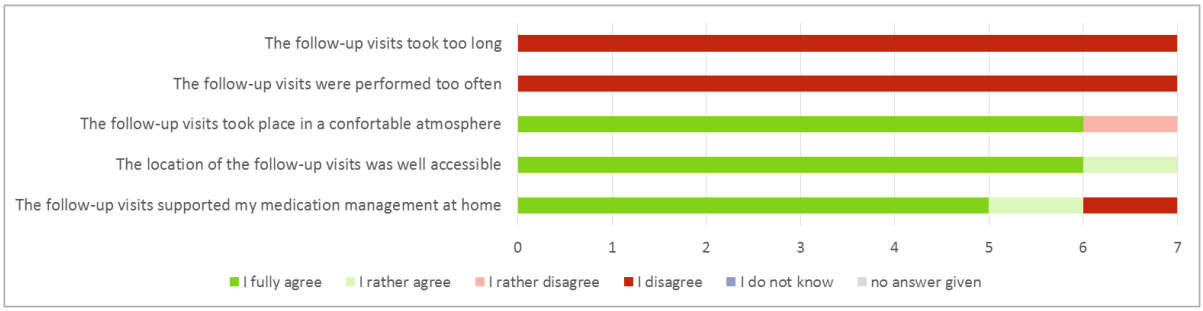

Figure 16: Patient satisfaction with the follow-up visits (n=7).

Discussion

Summary

This pilot study showed adequate feasibility of the study design, but a lack in efficiency and quality. Accordingly, only ten patients could be recruited and only one patient accepted the intervention. Over the whole study duration there was no unplanned hospital readmission and one major adjustment of drug therapy in the intervention patient. However, the intervention patient maintained perfect adherence, and was clinically stable over the whole study year. In the control group, adherence was at a maximum according to self-report and medication possession ratio (MPR) and quality of life was adequate. Major inadequate points of the study procedure and structure concerned the high exclusion and rejection rates, the inadequate time management, the vague task assignment and poor communication within the study team, insufficient communication with the community pharmacies, the induction of a potential bias by medication counseling at the follow-up assessments, and technical difficulties with the POEMS prototypes. The evaluation of the pilot study pointed out important barriers for successful study performance and hence proved beneficial.

C1.1 Pilot study

The intent of this study was to show the effectiveness of electronic multidrug punch cards and feedback on electronic dosing history on adherence and patient-relevant outcomes, independently from clinical condition and age. The results of such a study would be representative for the general population and are highly demanded [62,142,155]. With the small study sample, this question could not be answered.

Overall, the patients participating in the study showed maximal adherence throughout the study period and implied ambivalent and affirmative attitudes towards medication intake. The adherence results of the control group lie over values reported for comparable patient groups [29,300]. Of course, the results of our small study sample cannot be representative. In addition, patients engaging in a study investigating adherence might be interested in health and thus motivated to be adherent. Adherence of patients participating in a study is known to be higher than in real-life [91]. Further, a reporting bias might be assumed, which occurs when the patients try to anticipate the preferred

answer [252]. We performed a discharge counseling with all patients to exclude the interference of variable medication knowledge with our outcomes [108,265-267]. However, the discharge counseling itself could have had an influence on the outcome parameters of the control patients, as this was shown by previous work [301]. Additionally, we actively discussed medication changes at the follow-up meetings with all patients. Under these circumstances, the control patients probably had an unintended intervention and cannot be compared to patients having usual care from the community pharmacy.

Another source for falsification is the insufficient reliability of patient self-report [268]. However, the high values of self-reported adherence were supported by high MPR values in our study. For all control patients the mean MPR was between 0.91 and 1.16. Such MPR values have been reported favorable for health outcomes in various diseases [78,79]. The oversupply, indicated by an MPR of over 1, occurred frequently and is comprehensible for adherent patients because they refill their medication before the use of the last tablet resulting in supply overlaps. However, this also means that the assumption defined for this calculation, i.e., that the patients were out of medication stock at the first supply, has to be doubted and therefore MPR could be underestimated. On the other hand, we did not account for supply gaps and allowed the retrospective filling of these gaps, which of course overestimates adherence. Further information is lost by the exclusion of patients with fewer than two pharmacy claims. For these patients, non-persistence has to be assumed. Finally, the calculation of a mean MPR per patient balances high and low values and hides non-adherence to single medications. In our sample, there were MPR values below 0.9 for some medications. Above all, it is noticeable that MPR values for statins were especially low and that this trend occurred in all patients with prescribed statins. Such trends have also been observed in other studies [87,104]. For patients with polypharmacy, a new method to calculate adherence has been proposed recently, which accounts for the shortcomings discussed above, e.g. retrospective filling of gaps [82]. In the intervention patient, the MPR symbolizes the supplies that registered by the study pharmacist for the multidrug punch card production and does not represent the actual refill of the patient. However, indirectly it implies that the patient collected all multidrug punch cards for a continuous supply.

There was no unplanned readmission to the hospital during one year after the index hospitalization. This could indicate either that all patients were clinically stable due to optimal adherence, or that the observation period for this kind of outcome in that particular population was too short. Available literature rather supports the first assumption [99,105,292,293], however, the small sample size limits such considerations. One major adjustment of therapy occurred 79 days after discharge in the intervention patient (doubling of the bisoprolol dose). Treatment intensification has been associated with poor adherence [95]. The intervention patient suffered from uncontrollable blood pressure, which persisted during index hospitalization and over the whole study period. All other treatments remained

unchanged and adherence was high according to all measurement methods. We therefore do not assume treatment failure as a result of non-adherence. In the control group, a considerable number of treatment changes occurred too. Nevertheless, there was no major therapy adjustment indicating treatment intensification.

Quality of life yielded good results representing average values related to the US population (indicated by the SF12 tool [289]). The initial drop of the physical component at the three-month follow-up might reflect the reason or consequence of the index hospitalization. All control patients had a multicompartment adherence aid and / or a strategy remembering the intake of their medication, which might further explain the good adherence results. The fact that most of them had had the medication and the management system before index hospitalization, made them well used to it and medication was integrated in their daily life, which was shown to be beneficial for adherence [57,264]. Most patients were very satisfied with their own medication management system. One patient indicated handling problems and limitations by her system and reported low adherence rates, indicating that the system did not sufficiently support her. Accordingly, this patient requested a dose-dispensing aid that she could fill by herself at the end of the study. Only one patient of the control group was interested in adopting a multidrug punch card at the end of the study. He was the youngest of all patients in the trial and was hospitalized because of a myocardial infarction without taking any medications before that time point. He had the lowest adherence rate of all control patients according to MPR and suboptimal adherence according to self-report. This could point out that young patients completely integrated in work life receiving multiple newly prescribed medications after a major clinical event could be a target group for multidrug punch cards. This assumption is supported by a qualitative study reporting that younger patients with busy lives encounter similar medication self-management troubles as elderly patients, e.g., forgetting medication intake [255]. The other patients either had compelling strategies for medication management (e.g., one patient kept a log sheet with a self-made medication plan and all medication changes including therapy goals and blood pressure monitoring), rejected the use of multidrug punch cards, or had a reduced number of prescribed medications the end of the study not requiring support for medication management.

Our intervention patient was perfectly adherent according to all adherence measures and clinically stable during the whole study period. The feedback sessions helped him to grow more confident in medication self-management and in adherence reporting. The gain of quality of life might have to do with the stable clinical condition. We suggest that the sustained pharmaceutical care by the multidrug punch card and the repetitive feedback sessions supported the maintenance of the patient's adherent behavior. Increased adherence was reported by five of six studies with multidrug punch cards [49,159,160,176,211], two of them showing improved clinical outcomes[49,160]. These results strengthen our

assumptions. Initial handling difficulties resolved quickly and the patient reported to be very satisfied with the multidrug punch card use. He wished to continue the service after completion of the study.

Due to the easy application and the good acceptance, we suggest POEMS to constitute an instrument for further applications e.g., for diagnosis of therapy resistance, to detect non-adherence or white coat adherence and to improve pharmaco-vigilance (by allowing the timely association of drug-drug interactions and adverse effects). The use within adherence-enhancing programs allows the detection of specific adherence behavior, feedback thereon and tailoring of specific interventions according to the detected behavior. Feedback with electronic dosing history of MEMS® and tailored adherence support were claimed to be most effective in adherence support [126,136]. Therefore, we suggest similar success with POEMS for adherence to polypharmacy.

C1.2 Evaluation

This part of the report extensively discusses the shortcomings that led to the abandonment of the pilot study, exploring reasons and proposing solutions for a more successful future approach.

At the study planning, the hospital phase was expected to be the most critical phase due to anticipated communication difficulties with the ward staff, problems of access to the case notes and loss to follow-up due to missed discharge. However, feasibility proved very well in the hospital phase and information was readily available on request. Apart from this, the unprompted information flow *from* the ward *to* the study team about discharge proceedings did not work well. We instructed the ward staff to inform the study team about the discharge of the study patients by hotline call. This was highlighted during two staff meetings (to physicians, to nurses) and described in a leaflet posted in the physicians' and nurses' room, and in the case notes of every participating patient. However, we received one hotline call during the whole study period. Consequently, discharge proceedings were actively pursued by the study team.

In the follow-up phase, feasibility was worse, with weak points including problematic communication with community pharmacies of the region, technical difficulties with the electronic monitoring technology and the reluctance of the patients to fill the questionnaires.

The communication with the community pharmacies of the region was difficult. Some of them felt competed against, because the intervention patients (10 were intended for the pilot study and 100 for the main study) would have received their medication from the study pharmacy instead from their usual community pharmacy. This could have resulted in loss of costumers for the community pharmacies in the region. This fact was inadequately communicated to the regional professional pharmacy association, which inquired for clarification after the commencement of the study. The individual information of the community pharmacies by fax at the point of discharge of a study patient

belonging to their client base was deemed insufficient. Therefore, projects of this kind and dimension might be worth to be introduced at a regional association meeting, addressing challenges and conflicts of interest. Additionally, the possibility of collaboration could be checked, for example for dispensing of the prepared multidrug punch cards to the intervention patients. In fact, the reluctance to change the usual community pharmacy led to many rejections of the study participation. A closer collaboration might be beneficial for both sites. Most patients were reluctant and one patient was unable to fill questionnaires by their own, which were consequently performed as interviews. This could result in an observer bias where the anticipated answers are filled without confirmation of the patient. Therefore, the suitability of the instruments has to be checked meticulously for suitability for the anticipated study population.

The efficiency in the hospital phase was majorly flawed, resulting in a recruiting rate of 1%. Inadequate points included the high exclusion rate, the time management during the whole hospital phase, the vague task assignment to the study team members, and the poor communication in the study team. The average hospital stay of 7.4 days minus 3.2 days lost due to the out-of-date electronic database minus 2.0 days for the patients to decide over study participation left two days for two screenings, recruitment, baseline assessment, and discharge management. To screen ten new patients and include two of them in the time-intensive second screening usually lasted one hour. In this screening step the, first baseline assessment from paper case notes was included, which was inefficient considering the large rejection rate. Additionally the follow-up of initially excluded patients cost unnecessary time, because all of them were excluded eventually. Due to these time management problems, patients were lost to follow-up because of discharge.

The exclusion rate was exceptionally high and mainly due to domicile and prescription of a vitamin K antagonist in the first screening. We anticipated the first exclusion criteria to be limiting because the recruitments' setting was a competence center and university hospital congregating patients from all over Switzerland and from abroad. The ethics approval was restricted to the patients in the region and the reduced mobility of the multimorbid patients was limiting for the inclusion of patients living further away. In the second screening, the main reasons for exclusion were '< 4 oral medications' and 'transfer to another institution'. The high frequency of the first exclusion reason was unexpected due to the assumption that the patients on the ward of the internal medicine were mainly multimorbid requiring five or more medications. However, there were also acute patients, who had no underlying chronic conditions, e.g., patients with severe infections and patients with stationary oncologic treatment. These patients had no additional long-term medications. The multimorbid and old patients and the patients, who were admitted for severe clinical events, e.g., stroke, myocardial infarction, mostly had over four prescribed medications, but were often transmitted to a rehabilitation center or to a nursing

home, which precluded their participation. The main reasons for rejection reflected the characteristics of the screened population, namely acute and/or severe illness and therefore physically or psychologically not able to engage in a study or, apart from the hospitalization reason, vital and independent, preferring to self-manage their medication. Here came to light, that the use of dose-dispensing aids was somehow stigmatizing and not acceptable for all patients. A predominant statement was that they were not so old or dement as to require such an aid. It was investigated before that the patients accepting multidrug punch cards had to be picked by special characteristics, e.g. retired, living alone, low education grade, preference for daily routines [271]. The experiences of the hospital phase with its high exclusion and rejection rate showed that the location chosen for recruitment did not accommodate this target group.

The number of lost-to-follow-ups was kept within reasonable limits and was mainly due to a shortage of the study team. 'Exclusion from the ward round' was due to the processes of the ward and the limited availability of the study team members. The ward accommodated 35 patients with three responsible physicians. Regular ward rounds took place from 9-11 a.m. in parallel, with each physician visiting approximately 10 patients. Most of the time, only one study team member was available and attended the ward round of one physician, automatically excluding approximately two thirds of the patients. The shortage of the study team resulted out of unclear definition of the study team members' tasks and roles, from high timely demand (e.g., one discharge counseling with preparation and post processing lasted approximately 4-6 hours), the lack of communication within the study team, and a lack of briefing for the task. Although an SOP was available, it was not used as intended, and tasks and roles were not clear for all study team members. This indicated that the formation and continuous information for the study team is of major importance for study efficiency [302]. Organization of time coverage by the study team for the whole study duration should be initiated with defining one responsible investigator and one investigator on picket for each day of the week. The study coordinator additionally being the main investigator seems to be inadequate, also from the perspective of methodological quality (e.g., observer bias). A kick-off meeting, followed by individual briefing and regular information update might be valuable. Additionally regular study team meetings should discuss uncertainties, difficult situations and problems with the study protocol. This would strengthen the feeling of belonging to the team, make the study team members confident and efficient in their work, facilitates the precise definition and delegation of tasks, relieve timely constraints, and make study procedures more efficient.

The efficiency of the primary care phase contained also problematic but mainly optimizable points. The accessibility of all study team members to the study pharmacy and exchange of event dates at the pharmacy (team meetings, follow-up visits) can promote efficient working steps. The production of

multidrug punch cards for a four-week supply of one patient took a considerable amount of time and involved two study team members. Except for the double check of the multidrug punch card content, this work could also be completed by a pharmacy technician, relieving the study team. Instructions were available from an SOP. The material for the POEMS, namely the RFID chips were scarce and did sometimes prevent recruitment of more intervention patients. Additionally the intervention patient could not at all times be provided with the number of multidrug punch cards according to his wishes to reduce refill frequency.

The quality of the hospital phase was mostly evaluated to be inadequate. These shortcomings were mostly technical in nature and could be improved by small changes. For example the emergency hotline did not work properly, which was corrected immediately. Confusion with and availability of the CRFs induced the rethinking about having all-in-one electronic forms.

In the primary care phase, the quality was mostly optimizable. One point concerned the understandability of the questionnaires. It seems important to test them preliminary with real patients instead of students or team members, which was the common practice. It seems questionable if the study follow-up visits should be performed by a pharmacist and if it is suitable to discuss medication changes actively. This could lead to a bias. Almost all patients indicated that their medication management at home improved because of the follow-up visits, which indicates a bias and undermines the effect of the intervention. There were some drawbacks of the prototype POEMS films limiting the results of the electronic adherence measurement. First, the electronic film was sensitive to handling resulting in false positive results and preventing the analysis of timing adherence. Second, there were interferences with other signals, but these could be detected and deleted. Third, due to deficiency of the film or the chip, data of 11 multidrug punch cards was lost. Nevertheless, the data obtained from the electronic monitoring was valuable for analysis and for the patient. Improvement of the functionality and specificity of the technology should be attempted to yield reliable and continuous data.

Finally, there were processes and structures that worked remarkably well. Especially the work on the ward was agreeable and the atmosphere was friendly and open. Information was provided without hesitation or delay. This could be due to the reason that the ward was well organized, that they were used to ongoing studies and that they were informed prior to study commencement. Also the Notfallapotheke Basel was found to be a suitable place as a study center. Collaboration with the teams of all locations went very well. Additionally the satisfaction of the patient with the study was high. The discharge counseling and the medication plan were much appreciated by the patients, however, it seemed that the information of the counseling should be as short as possible and more tailored to the

patient's needs [283].The financial compensation of an intervention patient could be reconsidered because of substantial additional expenses.

The evaluation of the hospital phase led to several changes (connection of first and second screening; allocation to the control group at non-acceptance of the intervention). These changes slowed down the study process, and hence the tasks were better manageable by the study team and the time management improved. The screening was limited to one hour a week and to one to two thirds of the patients of the ward. The rotation from one third to the other enabled to see new patient at every ward round. The physicians and nurses accepted the participation in the ward rounds. Although one to two thirds of the patients were excluded by this proceeding, the recruitment success did not decrease but improved marginally (four patients in four months before and six patients in four months after the changes). However, the majority of the patients had still to be excluded and the recruiting rate was still inadequate. For this reason, the pilot study was abandoned for revision of the study design. Overall, the parallel conduction of the evaluation proved beneficial and indicated key points for amelioration.

Limitations

The study sample was too small to draw conclusions. Further, there were limitations of the outcomes measures, namely reliability of self-report, calculation method of MPR, and functionality of the POEMS prototypes. The discharge counseling and the active discussion on medication change at the follow-up visits could have influenced the good adherence outcomes of the control patients. Inversely, a selection bias could have included patients in the study who were basically adherent, indicated by the high baseline adherence. Due to the slow progress of the study, some points of the evaluation could only be studied insufficiently and precluded a fully systematic approach. Analysis based partly on subjective judgment of the master student or the study coordinator. Although this limits the results, several inadequate points could be detected, which impeded feasibility, efficiency and quality and which should be improved for a resumption of the study.

Challenges

In summary, the major challenges of the pilot study were:

- High exclusion and rejection rate
- Coordination of and communication within the study team
- Communication with the community pharmacies of the region / regional pharmacy association
- Organization and coordination of the study within the real-life setting
- Time management
- Limited availability and functionality of POEMS prototypes

- Inadequate number and storage of study documents
- Reluctance of the study patients to fill questionnaires, inadequate understandability of questionnaires

Outlook

For the revision of the study to yield adequate feasibility, efficiency, and quality, several recommendations can be made:

- A new location for recruitment may provide a population corresponding to the defined inclusion criteria and accepting the multidrug punch card use. In our opinion, a rehabilitation center could accommodate such patients. A further advantage of the rehabilitation center would be the longer stay of the patients, enabling an improved time management. Alternatively, patients could be recruited at the community pharmacy.
- A pre-assessment of the adherence pattern of eligible patients might be considered to select the target population for the multidrug punch card intervention.
- Physicians on the ward may be involved in recruitment. The patients' medication self-management at home could be easily determined during the ward round and at detection of problematic polypharmacy, the physician could refer a patient to discharge counseling, where the suitability and acceptance of study participation could be checked. For this purpose, a tool to check patients at risk could be helpful.
- The regional professional pharmacy association could be involved at an early time in study conceptualization to clarify conflicts of interest and to identify possibilities for collaboration.
- Organization and formation of the study team has to start early, including the clear definition of roles and tasks, maintenance of a study calendar and time coverage (ideally through a responsible investigator and a picket investigator per day), and regular information, e.g., kick-off meeting, briefing, regular follow-up meetings, update e-mails.
- The separation of the study coordinator and the main investigator has to be considered to minimize observation bias, enable blinding of the investigator, and the enable the study coordinator to more adequately fulfill coordinating tasks.
- For calculation of adherence to polypharmacy out of pharmacy claims, Daily Polypharmacy Possession Rate (DPPR) seems more appropriate than MPR.
- Functionality, sensitivity and specificity of POEMS have to be improved in the next generation.

Annex

- A4.1 Final board decision of the Ethikkommission Beider Basel for the Medication Blister Study
- A4.2 Case report form hospital screening, assessment and recruiting (CRF T-1)

- A4.3 Example of a case report form for a follow-up visit (at three month)
- A4.4 Questionnaire Adherence
- A4.5 Short form 12 version 2 (quality of life questionnaire)
- A4.6 Patient satisfaction questionnaire
- A4.7 Analysis of the Believes about Medicines Questionnaire (BMQ)

Supplementary material *(available on CD-R or on request)*

- Administrative material
- Case report forms
- Questionnaires
- Data dictionaries
- Material used at discharge counseling
- Information material for co-workers
- Standard Operation Procedures
- Evaluation method catalogues and assessment forms

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Project C2

Success of a sustained pharmaceutical care service with electronic adherence monitoring in a diabetic patient over 12 months

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Summary

We report of the first polypharmacy adherence monitoring over 371 days, integrated in a pharmaceutical care service (counselling, electronic multidrug punch cards, feedback on recent electronic records) for a 65-year old male diabetic patient after hospital discharge. The initial 4-times daily regimen with 15 daily pills changed after 79 days into a 2-times daily regimen with 9 daily pills for the next 292 days. The patient removed all medication from the multidrug punch cards (taking adherence 100%) and had 96.9% correct dosing intervals (timing adherence). The 57 evening doses showed the least variation in intake times at 17h 45min ± 8min. Over the observation year, the patient was clinically stable. The patient was very satisfied with the multidrug punch card use and the feedbacks on electronic records. In conclusion, long-term monitoring of polypharmacy was associated with the benefit of successful disease management.

***Keywords**: Healthcare improvement and patient safety, medical management, medical education.*

Background

According to its latest definition, "Pharmaceutical Care is the pharmacist's contribution to the care of individuals in order to optimize medicines use and improve health outcomes" [39]. Thus, medication adherence, i.e., the extent of a patient following the recommendations by a health-care professional, represents a central concern in pharmacy practice. With typical adherence rates for oral prescription medication of approximately 50-76% [37,90], non-adherence has been designated as one of the largest health care problems in society [37,65,143], since it impairs clinical outcomes and quality of life, and generates costs [83,103,105,113,269]. Polypharmacy, i.e. the use of multiple drugs administered to the same patient [14], has been described as a factor strongly related to non-adherence [13,303]. However, polypharmacy has become common because of e.g. clinical practice relying on multidrug combinations, increased rates of comorbidities and the aging population. In this context, dose-dispensing aids such as multidrug punch cards are suggested to improve adherence to polypharmacy and clinical outcomes [62,146,258].

Electronic monitoring is considered nearest to gold standard in adherence measurement [272]. Several studies used a pill bottle with a computer chip equipped cap that records each opening of the bottle. Because of the design of this pill bottle, one lead drug can be monitored at one time [274-278]. The recent development of printed electric circuitries and RFID technology made it possible to monitor polypharmacy by using a paper film and a chip collecting real time data (Confrérie Clinique S.A., Lausanne, Switzerland) affixed on the back of a multidrug punch card [273]. The POlypharmacy Electronic Monitoring System (POEMS) records date, time, and location of medication removal of the whole therapy regimen.

We report of the first polypharmacy adherence monitoring over 12 months, integrated in a pharmaceutical care service for a diabetic patient after hospital discharge. The patient was recruited within a pilot study to prove feasibility of a pharmaceutical care service with electronic adherence monitoring (ClinTrials.gov Identifier: NCT01759095).

Case presentation

We report of a 65-year old male patient who was hospitalized for a sepsis by Staphylococcus aureus at a large Swiss university hospital from January 28th to February 18th 2013. His actual diagnoses included late onset autoimmune diabetes in the adult (HbA_{1C}: 8%, 30.01.2013) with manifest complications (diabetic foot with chronic osteomyelitis, non-proliferative retinopathy, polyneuropathy), coronary heart disease with double stenting during the actual hospitalisation (LDL: 2.83 mmol/l, 01.02.2013; TG: 1.82 mmol/l, 01.02.2013), and a beginning heart failure (LVEF 40%, blood pressure: 183/93 mmHg, 18.02.2013). Signs of a beginning dementia were reported but not further investigated. He was retired, lived independently and alone in a middle-sized city, and self-managed his medication by the use of a weekly pillbox. In January 2013, he was newly prescribed basal insulin by the general physician (GP) in addition to rapid-acting insulin that had been initiated years before. Amputation of digits I and II on the left foot had occurred after emergency hospitalisation in October 2010. He had no allergies and was a current smoker (30 pack years). At discharge, the patient was prescribed ten different medications representing 15 pills in a 4-times daily regimen (**Table 1**). Medication reconciliation, i.e. the comparison of pharmacotherapy before and after hospitalisation, showed that three medications were newly introduced, one dosing frequency was reduced, one strength was augmented, and intake times changed from 2-times daily to 4-times daily.

Investigations

Adherence to polypharmacy was measured by POlypharmacy Electronic Monitoring System (POEMS) affixed on a disposable weekly multidrug frame card with 28 unit-of-use doses spread over 7x4 plastic cavities, filled by the community pharmacist with all oral solid medication.

Treatment

During hospitalisation, a clinical pharmacist recommended to refer the patient to a pharmaceutical care service consisting of individualized counselling (knowledge of medication), packaging of solid oral medication into multidrug punch cards (facilitation of polypharmacy management), and electronic adherence monitoring (measurement-guided medication management). Insulin management did not require further instruction. The responsible physician approved the recommendation and the patient provided written informed consent.

Two days prior to discharge, the pharmacist counselled the patient on indication, long-term benefit, adverse effects, and correct use of all discharge medication using standardized information sheets. The sheets were handed out instead of official package inserts upon the patient's request. The pharmacist instructed the use of the multidrug punch card and tested the patient's dexterity to remove tablets.

At discharge, the patient was provided with one multidrug punch card equipped with POEMS, containing all prescribed oral solid medication for one week and his medication plan (**Table 1, Figure 1**).

Table 1: Medication plan handed out to the patient at hospital discharge.
HTC, hydrochlorothiazide; n.p., no picture available.

Medication plan for [patient name] *[year of birth]

Universitätsspital Basel

Physician _____ **Date** dd.mm.yyyy
Ward _____ **Visum** _____

Hotline: xxx xxx xx xx

Medication		Dosage				Picture	Indication	Note
Name	**Dose**	**morning**	**noon**	**evening**	**night**			
Irbesartan / htc	300/12.5 mg	**1**					Blood pressure	
Aspirine®	100mg	**1**					Blood thinning	Before meal
Atorvastatin	40mg			**1**			Blood fat	
Pantoprazol	40mg	**1**					Gastric acid	
Bisoprolol	2.5mg	**1**		**1**		n.p.	Blood pressure	
Clopidogrel	75mg	**1**					Blood thinning	
Metformin	1000mg	**1**		**1**			Sugar	
Clindamycin	300mg	**2**	**2**		**2**		Infection	Stop on 07.05.13
Insulin Lisprum							Sugar	According to scheme
Insulin Glargine							Sugar	According to scheme

Figure 1: Electronic multidrug punch card front (left) and back with affixed POlypharmacy Electronic Monitoring System (POEMS; right).

Five days after discharge, the patient was called to consolidate the safe and correct management of the electronic multidrug punch card. Exchange of empty multidrug punch cards for new filled ones occurred every 2-4 weeks at a predefined community pharmacy. The electronic records of the previous week were discussed following a protocol for measurement-guided medication management (MGMM) [272] and using elements of motivational interviewing [285] like open-ended questions, reflective listening, affirmative style, enhancement of personal motivation, setting goals and obtainment of a change of plan.

Outcome and follow-up

The monitoring period lasted from February 18th 2013 (discharge day) until February 23rd 2014 and covered 371 days. In total, 54 multidrug punch cards with 899 unit-of-use doses were handed out. All returned multidrug punch cards were empty (taking adherence by pill count of 100%). Eleven multidrug punch cards (20.4%) and 9 random days were not readable (technical failure), and 17 event times were not recorded, leading to lost data for 218 doses (24.2%). The patient removed 8 pocket doses in anticipation of intakes away from home, which were excluded from the calculation. The summary of adherence statistics was derived from 673 electronic records.

The first 79 days of treatment comprised 4-times daily intakes (QID) due to antibiotic treatment until 7th May 2013, and covered 21.3% of the observation period. On May 8th 2013, the GP augmented bisoprolol from 2.5mg to 5mg twice daily without influence on the number of pills or the intake times. The next 292 days comprised twice-daily intakes (BID). A total of 278 doses were retrieved in the morning (QID: 63, BID: 215) in average at 7h 34min ± 55min (QID: 7h 24min ± 27min, BID: 7h 36min ± 1h 1min). The antibiotics assigned to be taken at noon (63 doses) and at night (65 doses) were taken in average at 12h 22min ± 2h 6min and at 21h 44min ± 44min, respectively. A total of 267 doses were retrieved in the evening (QID: 57, BID: 210) in average at 17h 39min ± 1h 1min (QID: 17h 45min ± 8min, BID: 17h 37min ± 1h 14min). The electronic records over the whole year are displayed in **Figure 2**.

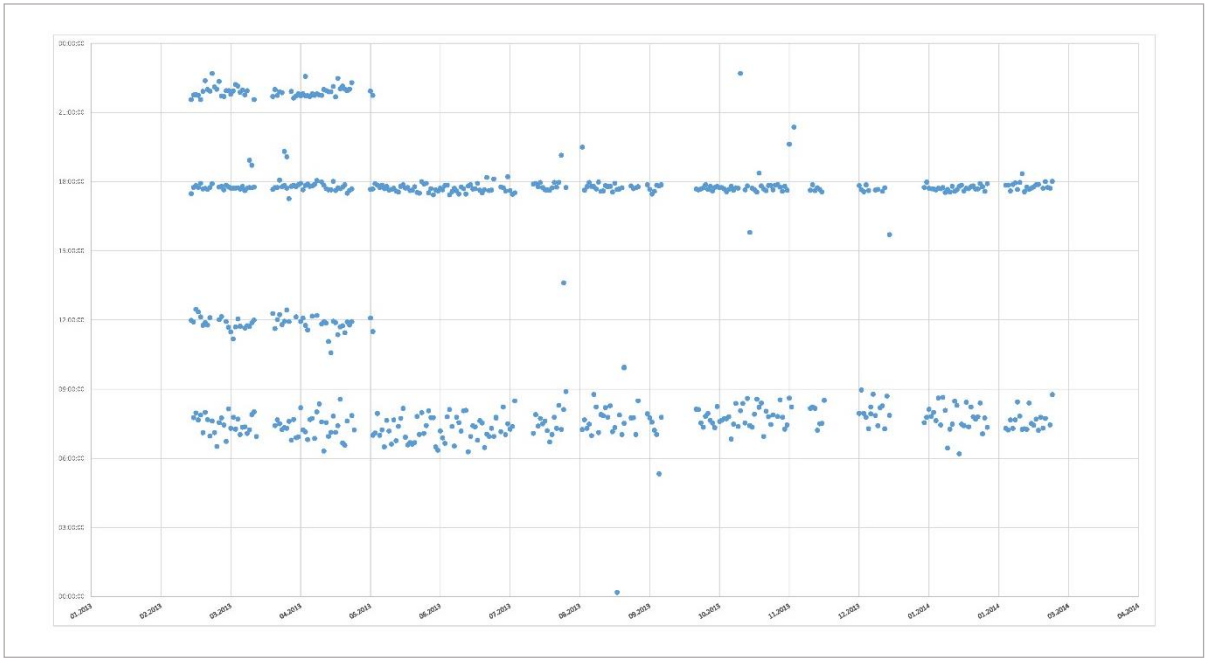

Figure 2: Electronic records over the one-year monitoring period.

A dosing interval was defined as correct if the time between doses was within 25% of the prescribed dosing interval, i.e., ± 3h for a 12-hour period (BID) and ± 1.5h for a 6-hour period (QID). Overall 96.9% of the dosing intervals were correct. All morning and evening doses of the QID regimen were taken in the grace period of 1.5 hrs, while 10/63 doses at noon and 4/65 doses at night were taken earlier or later, representing 5.4% of all QID doses. Of the BID regimen, 2/215 doses in the morning and 5/210 doses in the evening were taken outside the grace period of 3 hrs, representing 1.6% of all BID doses.

The patient kept all 17 planed appointments for multidrug punch card exchange and feedback sessions. He went on vacations thrice for several weeks. During the 9 feedback sessions conducted regularly every 1-2 months, the patient confirmed the safe and correct use of the punch card. He was very satisfied with his electronic records and emphasized his efforts for a highly regular taking and timing adherence. He reported a strong integration of the process of medication taking into his daily routine, i.e. coupled to mealtimes and insulin injection.

During the 12 months of monitoring, the patient had no readmission to hospital and no emergency visit. Laboratory values remained stable (LDL: 2.9 mmol/l, 29.01.2014; TG: 2.2 mmol/l, 29.01.2014; blood pressure: 193/88, 31.01.2014). HbA_{1C} decreased to 7% (31.01.2014).

The patient was satisfied with the intervention and declared a feeling of increased medication safety owing to the multidrug punch card use. The electronic records used during the feedback sessions helped the patient to gain confidence in medication management and to maintain perfect regularity

of the intakes. The electronic monitoring did not bother him. At the beginning, the removal of the medication out of the multidrug punch card caused him trouble because the back layer was hard to push through. However, he got used to it quickly, reported no more problems and wished to keep the punch cards after end of monitoring.

Discussion

We found 3 close case reports in literature. First, a 79-year old Japanese female with type 2 diabetes and mild cognitive impairment took all medication 3-times daily from a sounding and light flashing electronic device [304]. After 6 months, adherence by pill count was one missed dose per week (95%) and HbA_{1C} decreased from 8.0 to 7.1%, demonstrating the efficacy of the electronic reminder device. Second, a 17-year old female treated for Fanconi Anaemia with 8 drugs daily had an estimated adherence of 25% [305]. She received 35 motivational interviewing sessions over 17 months. Adherence to the lead medication levothyroxine measured by electronic pill bottle showed a significant improvement up to 82%, demonstrating the efficacy of motivational interviewing. Third, a 65-year old Swiss male with epilepsy and suspected abuse of sleeping pills was monitored with electronic multidrug punch cards over 3 weeks [76]. Inadequate medication intake behaviour could be corrected with feedback sessions.

Our case with pharmaceutical care service including electronic monitoring of adherence to polypharmacy and regular feedback on electronic records was successful to maintain perfect adherence and clinical stability during one year. A glycosylated haemoglobin (HbA_{1C}) level of 7% was reached during the one-year monitoring period and represents the target level recommended by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) for elderly comorbid patients [306]. The lowering of the HbA_{1C} by 1% is known to improve micro- and macrovascular clinical endpoints significantly and to reduce all-cause mortality by 14% [307]. In our case, the HbA_{1C} reduction probably followed from the adjustment of insulin therapy one month before hospitalisation. However, the impact of multidrug punch cards was demonstrated by a mean HbA_{1C} reduction of 0.95% in 36 diabetic patients with oral antidiabetics after 8 months in a randomized controlled trial [161]. We thus can suppose that for our patient, the multidrug punch card acted as a railing and interrelated the oral therapy with the insulin therapy.

The challenging therapy plan of 4-times daily intake for over a fifth of the observation time and changes in daily routine like vacation had no influence on the patient's adherence. Because frequent dose dispensing and interruption in daily life were reported to negatively affect adherence [89,308,309] we assume that the multidrug punch card (as practical tool) coupled to the continuous feedback sessions (as external motivator) were able to consolidate and maintain perfect adherence. This assumption is

supported by a meta-analysis attributing a large effect to the intervention of feedback on electronic dosing history [136].

We acknowledge some limitations. The substantial loss of data due to technical flaws of our first generation POEMS is inherent in newly developed technologies. The subsequent generation of electronic films will be improved. Electronic monitoring is often criticized to assume rather than prove the patient's actual medication intake. However, we observed that patients usually accept monitoring and thus swallow the removed medication [310]. Finally, the patient's being aware of observation is supposed to have an impact on the outcomes. However, a recent study showed that the use of an electronic device leads to a small, non-significant increase in adherence compared to standard packaging [311]. In conclusion, this case is to our knowledge the first report of long-term monitoring of polypharmacy associated with the benefit of successful disease management.

Learning points/take home messages

- The pharmaceutical care intervention – comprising electronic monitoring of adherence to polypharmacy and recurrent feedback sessions – maintained optimal adherence and stabilized disease management.
- The patient accepted the electronic monitoring of adherence to polypharmacy over one year and was satisfied with the service. He was even willing to continue with this service after study end.
- Electronic monitoring of polypharmacy was feasible over one year and yielded valuable results.

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General discussion and conclusions

In this thesis, we researched the evidence, the present circumstances, and the effectiveness of multidrug punch card use in primary care with the aim to support the patient's medication self-management for optimization of medication use and thus to reach appropriate polypharmacy.

The World Health Organization and other organs urge the development of effective interventions to enhance adherence as a first priority subject. To have an overview of the work done with the focus on dose-dispensing aids, PROJECT A1 was designed to review and map the evidence of dose-dispensing aids to improve adherence and economic, clinical, and humanist outcomes. Previously published reviews with restrictive inclusion criteria were deemed insufficient to have a complete overview [147,155,156]. Evidence mapping stipulates the use of broader inclusion criteria to give an overview on a whole topic area and allows the identification of evidence gaps [168]. With the use of this methodology and of a tool specifically designed to assess the methodological quality of public health studies with variable study designs [163], we were able to include more studies. Further, as health-care professionals rely on both, robust evidence and details of the delivered interventions to integrate them into clinical practice, we developed a list of additional criteria for completeness of information. Just recently, new guidelines were published as an extension to the CONSORT statements, which support this approach [312].

We found that a substantial amount of research has been done, including 10 randomized controlled trials, 19 controlled trials, and 1 cohort study, which involved different dose-dispensing aids in single or combined interventions. These devices offered a broad field of application and were mostly studied in elderly patients with polypharmacy. Dose-dispensing aids had a significant effect on adherence in 17 out of 27 studies, using multicompartment adherence aids (6 studies), multidrug punch cards (5 studies), and unit-of-use packaging (4 studies; 2 without description of device), either as single or as an element of a composite intervention. In direct comparison (i.e., in factorial trials), effects tended to be larger in composite interventions, which is consistent with the reporting of prior studies [126,155]. Ten of fifteen studies reporting clinical outcomes showed significant improvements. However, if focusing on those with strong methodological quality, studies with significant outcomes in adherence reduced to three (in geriatric [177], in chronic mental ill [178], and in cardiovascular patients [49]) and studies with significant clinical improvements reduced to two (in diabetes mellitus type 2 [191] and cardiovascular patients [49]). At the further application of the list of additional criteria for completeness of information, overall only one study with reliable results and a replicable intervention remained [49]. Economic and humanistic outcomes (as defined by Kozma et al. [174]), and safety issues were either missing or

insufficiently addressed. Further, long-term, disease-unspecific, generalizable clinical outcomes like (re-) hospitalization rates were lacking. Clinical effects on multimorbid populations with polypharmacy were not evaluated. Twelve of the included studies only measured adherence, and although improvement in adherence is generally acknowledged to be associated with improved clinical outcomes, it remains widely unclear how much adherence is needed to reach significant health benefits for the patient [59,81]. In this context, our review detected three studies, which reported a significant effect on adherence, but not on clinical outcomes [159,178,182]. Ethical standards for adherence research urge that adherence is 'a means to an end' and should only be measured in connection with clinical outcomes to ensure a positive effect on patient-relevant outcomes (i.e. clinical and humanistic outcomes) [141]. The discussed shortcomings served as a rationale for the development of a randomized controlled trial in a later project (PROJECT C1), on the use of a dose-dispensing aid in primary care patients with polypharmacy, including measures of adherence, clinical, and humanistic outcomes.

In the next step of the thesis (B), we explored the status quo in the Swiss primary care setting. On one hand, we investigated how and how often community pharmacy staff counsels about adherence (PROJECT B1). On the other hand, we studied the integration of multidrug punch card provision in daily pharmacy practice and the characteristics, preferences, and experiences of current multidrug punch card users in primary care in PROJECT B2 and B3, which will be discussed further down.

In PROJECT B1, we observed daily practice of counseling by the pharmacy staff in community pharmacies. The unique position of the community pharmacy in the healthcare chain, with its easy access, regular patient visits, the possibility to monitor medication refill frequency, and the pharmacist's competences, predestines for counseling about adherence. Evidence on successful interventions in improving health outcomes and adherence delivered by community pharmacists has accumulated [44-50,232-235] with the conclusion that the pharmacists' cognitive services were beneficial for safe and effective medication use [51,52]. We found that counseling was provided to half of the patients obtaining any medication, and significantly more often to patients receiving medication on prescription, a new prescription, and if served by a pharmacist. Our observed counseling rates are in line with prior research, reporting limited pharmaceutical care services [218,220,236-240] and predominant product-centered counseling [223-225,240]. Significantly more patients received explicit adherence counseling if served by a pharmacist compared to other staff members. However, on the whole, the group of patients receiving this kind of counseling represented only 6.7% of the patients obtaining any medication. We defined explicit adherence counseling as a direct, patient-centered and implicit adherence counseling as an indirect, product-centered approach. From this perspective, we suggest that implicit adherence counseling insufficiently addresses the problem and may at most influence unintentional non-adherence. In contrary, explicit adherence counseling directly addresses the

problem and can be supposed to facilitate the effective detection, assessment, support, and monitoring of intentional and unintentional non-adherence. Literature supports a considerate and individualized approach to engage the patients into counseling [243] [244] [225], which would include the more direct, explicit adherence counseling.

Discordant to the low rate of observed adherence counseling, almost all pharmacists stated to counsel about adherence every day and named most of the topics on our predefined list of explicit adherence counseling. They were obviously familiar with the topics, though less frequently addressed them during the observed patient contacts. Further, the most frequently named topics by the pharmacists were implicit. Thus, our observations indicated an implementation problem of research and knowledge into daily practice. It seems that changes of structures and processes lagged behind the changing role of the pharmacist [42,244,245]. Correspondingly, pharmacists named barriers to adherence counseling concerning structures (e.g., lack of public acknowledgement of the pharmacist's competences) and procedures (e.g., time constraints).

Revisiting the numbers of PROJECT B1, we can quantify that out of 1'476 patients receiving medications, 99 were counseled about adherence topics and only 11 of them specifically on the adherence topic 'organization', i.e. with potential sale of a dose-dispensing aid. PROJECT B2 revealed that only 51 of 1'743 community pharmacies in Switzerland produced multidrug punch cards in 2011, predominantly for patients in nursing homes and only for 269 (14%) primary care patients. Active recommendation of multidrug punch card use to primary care patients was performed in 75% of the pharmacies with a rather low success rate of 31%. These pharmacies indicated that they targeted a population for the service, which seems adequate, namely people with polypharmacy, suspected non-adherence, increased age, inability for medication self-management, and at hospital discharge. The dose-dispensing service fitted well in the community pharmacies' daily practice with the multidrug punch card production being easy and cost-covering and by adding additional values to the pharmacy (e.g., the profiling of the pharmacy in advanced pharmaceutical care service or enhanced interdisciplinary cooperation). Pharmacies mostly assumed their primary care patients to be very satisfied with the use of multidrug punch cards and estimated a very high adherence rate of 93.3% for its users. A qualitative study from England also reported a positive attitude of health-care professionals towards dose-dispensing aids, which they recommended to elderly patients with medication self-management problems [32].

The 269 primary care patients detected to use multidrug punch cards represented the basic target group for the subsequent PROJECT B3. We combined quantitative and qualitative interviews in an explanatory way to investigate the acceptance, preferences, experiences, and impact on adherence of

current multidrug punch card use by primary care patients. We thus responded to a call from prior publications, to clarify the characteristics of the primary care patients benefitting most from dose-dispensing aids and hence to facilitate targeted adherence interventions [32,152,255]. We found that an independent primary care patient accepting the use of multidrug punch cards is over 70 years old, has a low education grade, is retired, lives alone, favors tidiness, rituals, and daily routines, and is unable or reluctant to leave home. She/he trusts the health-care professionals, is a regular customer of the same community pharmacy, is motivated to conduct a healthy life, and has a feeling of high necessity for medication. In consequence, it was not surprising that the patients of our study reported perfect adherence. Emerging key variables for their adherent behavior were trust in health-care professionals and personal experiences (i.e. either experience of an adverse health outcome in case of non-adherence, or clinical well-being in case of adherence). Both variables have been reported before to be associated with adherent behavior [262,313]. Our patients stated an improved adherence of +37% after the initiation of multidrug punch card service. In connection with their strong intent for being adherent, this indicates that they might have been unintentionally non-adherent prior to multidrug punch card use, and thus our results support the assumption that unintentionally non-adherent patients might represent a target population for dose-dispensing aids [62,145]. The support that multidrug punch cards offer to such patients encompasses a reminder function, visual control of intake (i.e. adherence self-monitoring), and simplification of daily life. We additionally identified habits and routines, which have in fact long been described to be beneficial for adherence [57,255,264], to replace reminders because they promoted an 'automatism' of medication intake.

We addressed two major issues of concern about the multidrug punch card use: difficulties with handling of multidrug punch cards [32,146,151] and reduction of knowledge about medication [32,152,153]. Both were reported to constitute a risk of decreased medication safety for patients with dose-dispensing aids. This could not be confirmed by our study. In contrary, the patients were very satisfied with the handling of the multidrug punch card, highlighting the clear design, which contributed vastly to their feeling of medication safety. The majority of the patients did not need or want more information on their medication. Although medication knowledge is generally known to improve adherence [108,265-267], patients with dose-dispensing service seem to be exempted from this association [154], which could result from the minimization of potential administration errors by the packaging.

Overall, PROJECT B3 proved that a considerable group of patients benefitted from multidrug punch card use, initiating our next step: to investigate the effectiveness of multidrug punch cards to improve clinical and humanistic outcomes through enhanced adherence.

PROJECT C1 was the development and pilot of a randomized controlled trial, which aimed at answering this question within a population of various ages and different clinical conditions. To assess the feasibility, efficiency, and quality of the study structures and procedures we ran an evaluation in parallel to the start of the pilot study. Within nine months, we were able to recruit ten patients from the internal medicine's ward of a university hospital and only one patient accepted the use of a multidrug punch card. In the following, the results of these patients and further down the findings from the evaluation will be discussed.

Overall, the patients participating in the study showed maximal adherence rates by self-report and medication possession ratio (MPR) through the whole study period, which is not representative for comparable patient groups [29,300]. Of course, our small sample cannot picture the general situation. Other possible explanations are the occurrence of a reporting bias [252], overestimation of adherence due to the chosen adherence measurement method of self-report [268] and MPR [82], and higher adherence rates in patients participating in a study compared to real-life conditions [91]. The discharge counseling and the active discussion of medication changes at the follow-up visits could have biased the outcomes by supporting adherence [301]. The only primary outcome was registered in the intervention patient and could not be explained with non-adherence. In the control group, a considerable number of treatment changes occurred too, however, no major therapy adjustment. The low number of registered primary clinical outcomes indicates either that optimal adherence induced clinical stability, or that the observation period was too short. Available literature rather supports the first assumption [99,105,292,293], however, the small sample size limits such considerations. Quality of life remained relatively stable in both treatment groups. In the control group, almost all patients had had polypharmacy before hospital admission and a system or strategy to cope with it. They were very satisfied with their own medication self-management system. Feedback from one patient of the control group at the end of the study indicated that patients integrated fully in working life might represent an alternative target group for multidrug punch card use, which was also reported in a previous qualitative study [255]. Recruiting pharmacists of PROJECT B3 provided further clues for this suggestion by mentioning rejection of study participation because of a busy life-style. This patient group was probably missed in the characterization of multidrug punch card users.

Our intervention patient, whose results were explored in detail in PROJECT C2, was to our knowledge the first case of long-term adherence monitoring of polypharmacy integrated in a pharmaceutical care service over one year. The patient maintained perfect adherence according to all adherence measures and clinical stability through the whole study period. The stability in quality of life and the gain of confidence with medication self-management might have been the result of successful disease management with the support of the intervention. Similar studies performed with MEMS® devices

combined with feedback on electronic dosing histories [274-278] and with multidrug punch cards as interventions [49,159,160,176,211] showed improved adherence and clinical outcomes and let us assume similar results in a successfully performed randomized controlled trial with electronic multidrug punch cards. No harms or adverse events could be associated with the intervention.

The evaluation showed that the study design was feasible, but lacked in quality and efficiency. The University Hospital Basel provided excellent infrastructure and working atmosphere and the Notfallapotheke Basel was a suitable place serving as study pharmacy. Collaboration with the teams of all locations exceeded our expectations. Additionally, patient satisfaction with the study was high. As opposed to the low acceptability of the multidrug punch cards, the patients much appreciated the discharge counseling.

The efficiency of the pilot study was mostly flawed in the hospital phase leading to the poor recruiting rate. Major inadequate points were the high exclusion rate, the inadequate time management, the vague task assignment for the study team members, and the poor communication within the study team. Similar issues were pointed out as being crucial for the successful conduction of a randomized controlled trial [302]. Both, the exclusion rate and the rejection rate were high, predominantly because of the characteristics and preferences of the eligible patients. The location seemed inadequate for recruitment of the target population of multidrug punch cards service as determined in PROJECT B3. A tool to assess the characteristics of patients accepting the multidrug punch cards would be helpful in the identification of eligible patients. Going even further, adherence could be thought of as a medical diagnosis, though this has been discussed controversially [314,315]. Under these assumptions, it would make sense that patients are treated only, i.e. included only into a corresponding study, if they had an indication, similarly to any other clinical condition, e.g. hypertension or diabetes mellitus. Several authors highlighted that the inclusion of adherent patients into trials testing the effectiveness of an adherence-enhancing intervention might be inefficient and costly, dilute the effect of the intervention, and impair the patient-centered approach [62,314,316]. These considerations strengthen the approach to specifically select non-adherent patients for such studies and require a tool with adequate sensitivity and specificity to differentiate between different types of (non-)adherence (e.g. intentional and unintentional) [314]. Such tools have been developed and proposed for similar research questions [14,314,317]. The classification of interventions according to dimensions and factors of adherence (e.g., health system, condition-related, patient-related) could additionally facilitate the attribution of proper interventions for specific patterns of non-adherence. Translated to our study, the application of such a tool would be beneficial because intentionally non-adherent patients will not change their adherence behavior with the intervention of a multidrug punch card and thus diminish the intervention's effect. All these thoughts congregate in the approach of tailored adherence-enhancing interventions

according to the patients' needs and necessities, which have been deemed most promising [37,62,142]. In fact, tailored adherence interventions per se should exclude adherent patients from adherence-enhancing interventions.

The poor quality of the study in the hospital phase resulted from the low quality of available data, complexity of the case report forms, and technical difficulties with the hotline. All of these shortcomings could be adjusted easily. For the primary care phase, the cooperation with the community pharmacies of the region has to be reconsidered by effective communication and by involving them more into the study proceedings. The induction of a potential bias by the assignment of a pharmacist for the follow-up assessments has to be assumed and eliminated. We used prototypes of the POEMS technology disclosing technical flaws, which have to be solved for a subsequent generation in order to yield continuous, reliable results of electronic adherence measurement.

The evaluation of the hospital phase led to several changes, which improved time management and efficiency, hence the parallel conduction of the evaluation proved beneficial. Further change of study elements are necessary to yield an adequate recruitment rate and to improve the quality of the study structures and procedures.

Major challenges during this thesis were:

- Finding an adequate method to appropriately perform a comprehensive literature review
- Development and validation of questionnaires for different target groups, i.e. patients and health-care professionals
- Motivating community pharmacists for patient recruitment
- Performing telephone interviews with elderly patients
- Becoming familiar with qualitative research methods and integrating them in the frame of a mixed methods study
- Development, preparation, conduction, and analysis of a randomized controlled trial
- Organization and coordination of a randomized clinical trial in a real-life setting with multiple locations and collaborators
- Recruiting an adequate number of patients for a randomized controlled trial

Limitations

The overall limitation of this thesis was the constant low recruitment rate. In PROJECT B3, we relied on the cooperation of the community pharmacies, who were not always that motivated due to time constraints. However, the initial small number of primary care patients using multidrug punch cards without external help was already limiting. This results from the fact that in Switzerland multidrug

punch cards were originally intended for the supply of nursing homes and recommended only in the last few years to primary care patients. We further observed that the community pharmacists targeted a narrow group of primary care patients for multidrug punch card provision. This might also have an association with the limited adherence counseling provided, which we observed in PROJECT B1. In consequence, the omission of addressing adherence topics by the pharmacists could lead to a small rate of multidrug punch card recommendation. Further, the patient populations found at the locations defined for recruitment did not match our predefined inclusion and exclusion criteria in both, PROJECT B3 and C1. The resulting small study populations precluded comparative statistical analysis. Old patients have trouble to perform a telephone interview for several reasons, e.g. impaired hearing and reduced cognitive capacity. The duration of the qualitative interviews of 45 minutes could have been a barrier for younger multimorbid patients with busy life-styles, who could represent an additional target group for multidrug punch card provision. Further biases could be assumed to have influenced our results, e.g., selection bias, observation bias and Hawthrone effect [252]. Our own experience and the feedback of the recruiting pharmacists let us assume that the patients most in need for it, decline corresponding interventions.

Within PROJECT B3, we also attempted the collection of the physicians' opinion about multidrug punch cards. However, the response rate to a survey was too low to analyze. Due to the slow progress of the pilot study in PROJECT C1, some points could not be studied sufficiently, limiting the results. However, identified inadequate points were altered and led to an improvement. Finally, technological shortcomings of the POEMS prototypes limited the results of the electronic adherence measurement. Steps have to be taken to augment its functionality and specificity for a next generation. However, despite the missing data, the electronic measurement of polypharmacy proved feasible and yielded valuable results for our research experience and for the intervention patient.

Our studies are constricted to one region in Switzerland and cannot be generalized to other European countries, where the dispensing of dose-dispensing aids occurs more frequently, e.g. the Netherlands [154].

Conclusions

This thesis adds findings on the existing evidence of dose-dispensing aids, on current practice of adherence counseling and multidrug punch card service in community pharmacies, on the experiences and preferences of multidrug punch card users in primary care, on the impact of the devices on adherence of multidrug punch card users, and on experiences of a pilot study with the aim of improving adherence and patient-relevant outcomes through electronic multidrug punch card use in primary care patients after hospital discharge.

The following conclusions could be drawn:

- Several research gaps exist throughout the literature about dose-dispensing aids (e.g. economic and humanistic outcomes), which in combination with poor methodological and reporting quality precluded a firm conclusion about the evidence of dose-dispensing aids in improving adherence and economic, clinical, and humanistic outcomes. For reviews aiming at giving recommendations for clinical practice, the assessment of completeness of information seems inevitable. The identification of evidence gaps provided a rationale for future research.
- Provision of adherence counseling in contemporary practice in Swiss community pharmacies is poor and delivered more frequently by pharmacists than by other staff members. Structural and procedural barriers hinder pharmacists to adequately deliver explicit adherence counseling (e.g. lack of public acknowledgement of the pharmacists' competences, time mismanagement).
- Multidrug punch card service by community pharmacies is limited in Switzerland, but well integrated in daily practice. Few primary care patients are provided with the service. Pharmacies estimate them to be satisfied and to benefit from improved adherence with multidrug punch card use. We suggest that many more primary care patients could be approached for multidrug punch card use.
- A specific group of primary care patients reports to benefit from multidrug punch card use, i.e., patients of the age of over 70 years, low education grade, living alone, appreciation for tidiness and daily routines, trust in health-care professionals, fidelity to pharmacy, and motivation for a healthy lifestyle and medication adherence. Multidrug punch cards constitute a simplification for the patients' lives, make them feel safe and promote their adherent behavior. Emerging key variables for accepting multidrug punch card use and for perfect medication adherence were trust in health-care professionals and the patient's experiences.
- A pilot study investigating the effect of electronic multidrug punch cards in primary care patients failed in recruitment of an adequate number of patients because of poor efficiency and quality of the study structures and procedures. A parallel evaluation enabled the detection of the key points for study improvement. Further changes are necessary to yield an adequate recruitment rate and study quality.
- Six patients discharged from the internal medicines' ward without any further intervention than a discharge counseling maintained perfect adherence, stability of clinical condition and quality of life over one year.
- One patient receiving the intervention of the electronic multidrug punch card combined with recurrent feedback on his adherence behavior showed maintenance of perfect adherence, stability of clinical condition and quality of life, gain in confidence of medication self-management, and

satisfaction with the device. No harms could be associated with the use of electronic multidrug punch cards.

- Prototypes of the POlypharmacy Electronic Monitoring System were easy to apply and well accepted by the intervention patient. However, drawbacks in the technology's functionality and specificity weakened the quality of our results and have to be addressed in the future development of the device.

Outlook

According to the conclusions and experiences of this thesis, the recommendations for practice are:

- In order to empower pharmacists to assume their responsibility in patient-centered counseling, structural and procedural barriers have to be overcome by e.g.:
  - Promotion of the pharmacist's role by public information and advertisement
  - Consideration of new remuneration models for cognitive services for pharmacists
  - Intensification of clinical pharmacy education and training in adherence counseling
  - Reorganization of pharmacy accommodations and staffing.
- Medication self-management and non-adherence should be addressed actively at patient contacts. The patient's experiences and believes have to be included into counseling, as they can have a strong impact on adherence. The embedment of medication taking into daily routine should be attempted. Adherence counseling should respect the patient's preferences and life-style.
- It must be considered that adherence interventions have the goal of nothing less than a behavior change, which is a difficult and private matter. Accordingly, prior to recommending an adherence-enhancing intervention, trust has to be established between the patient and the provider and the patient's active involvement in decision making seems inevitable for an accepted and successful intervention. Fidelity to one community pharmacy should be supported, because this may lead to trust towards health-care professionals, which in turn leads to acceptance of interventions and improved adherence and medication safety.
- Multidrug punch cards should be recommended actively to primary care patients with polypharmacy with regard to their capabilities, needs, and necessities. While recommending them, pharmacists should emphasize the advantages of facilitation of medication self-management and increased medication safety reached through multidrug punch card use.
- In order to ensure continuous care, dose-dispensing service should be embedded in a pharmaceutical care framework, involving, e.g.:
  - Giving instruction on multidrug punch cards if necessary (anticipation of handling difficulties, integration into life-style, reminder strategies)
  - Detailed instruction of separate medication

  - Inclusion of short term medication into the packaging
  - Regular medication review of the packaged medication by a pharmacist
  - Regular contact between pharmacy and patient.
- Tailored interventions for non-adherent patients should be attempted. Steps of tailoring might include *a. screening* to assess the patient's individual pattern of adherence; *b. selection* of an appropriate intervention out of prepared toolbox of evidence based adherence-enhancing interventions in consideration of the patient's preferences and capacities; and *c. monitoring* of satisfaction, adherence and clinical outcomes.
- We suggest that POEMS might constitute an instrument for applications in clinical practice, e.g., to diagnose therapy resistance, to 'diagnose' and characterize non-adherence, and to address pharmaco-vigilance questions (by allowing the timely association of drug-drug interactions and adverse effects).

Our recommendations for future research encompass:

- To identify further patient groups who accept multidrug punch cards and benefit from their use, e.g. younger multimorbid patients with busy life-styles.
- To develop guidelines for the delivery of tailored adherence support, including an assessment tool, which enables the detection of adherence patterns. A classification system for adherence-enhancing interventions analogue to the classification of factors for non-adherence could support this approach.
- Under the assumptions that adherence is an individual behavior influenced by 771 variable, interrelating factors [13], it seems inappropriate to investigate mono-interventions without stratifying the patients' individual factors of non-adherence. At the development of clinical trials investigating the effectiveness of an adherence-enhancing intervention, the exclusion of adherent patients should be reconsidered to enable the estimation of the real, undiluted effect of an intervention.
- A subsequent randomized controlled study on the effectiveness of multidrug punch cards could be optimized by
  - A well-instructed, adequately sized study team
  - Sufficient communication between all collaborators
  - Integration into clinical practice (e.g. physicians assisting recruitment at the ward and community pharmacies assisting in delivering the intervention)
  - Availability of sufficient, functioning electronic measurement material

- Locations enabling the recruitment of an adequate number of the target population (e.g., a rehabilitation center, community pharmacies).

- To develop studies focusing on adherence-enhancing strategies with larger, multimorbid populations, measuring patient-relevant outcomes, and use of standardized adherence measures to enable comparison and generalization.

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Annex

Index

A1.1 Assessment of pharmacy characteristics

Departement Pharmazie Universität Basel
Pharmaceutical Care Research Group
Irene Rüfenacht

Basler Apothekenbeobachtungsstudie 2010

Angabe zur Apotheke: Code ☐

Wochentag der Beobachtung

Mo	Di	Mi	Do	Fr	Sa

Öffnungszeiten der Apotheke

Vormittags	
Nachmittags	
Durchgehend	

Erfasste Zeiten

Vormittags	
Nachmittags	

Ort

BS	
BL	

Lage

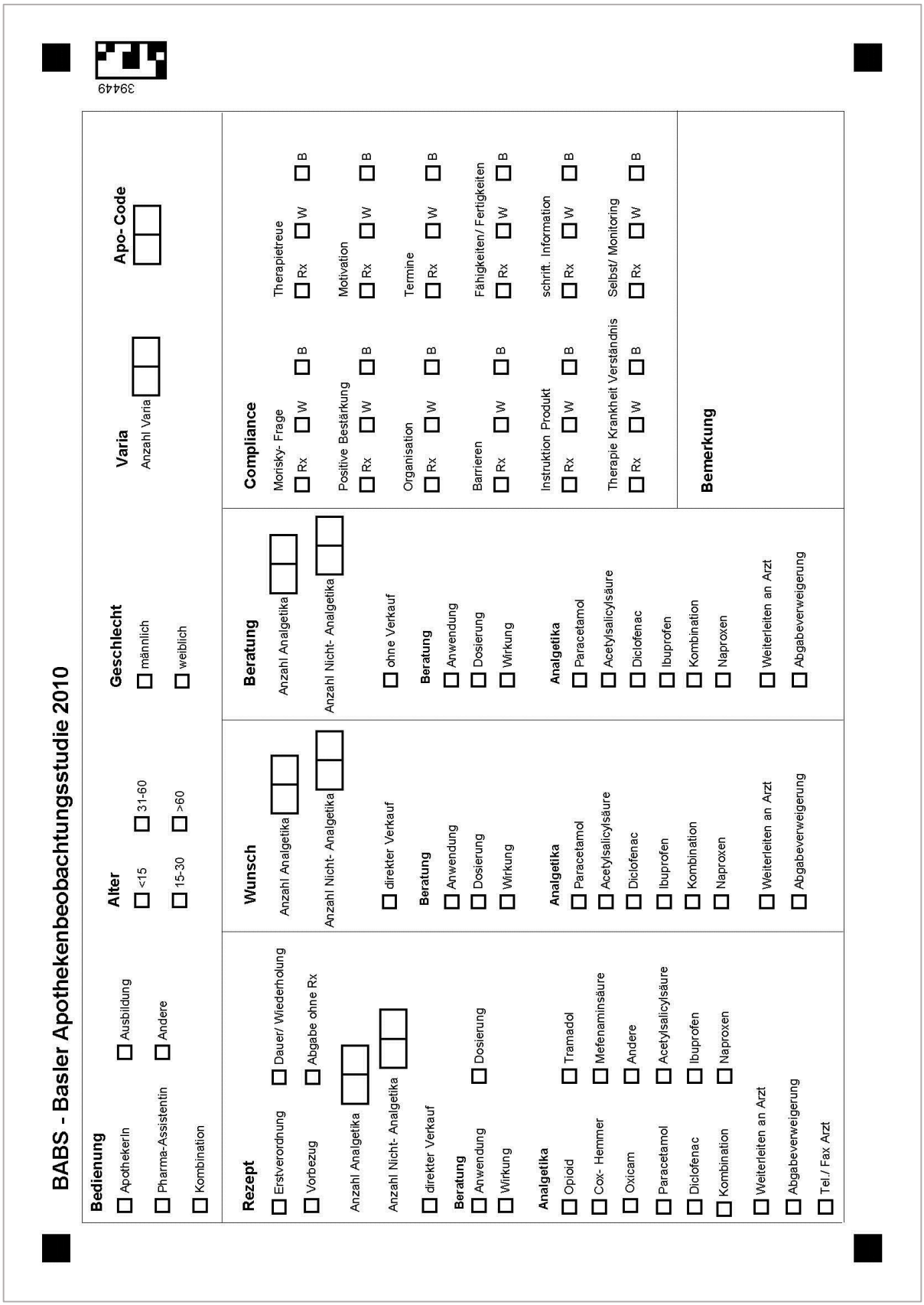
City/ Passantenlage	
Wohngebiet/ Quartier	
Einkaufszentrum	

 # Mitarbeitende am Studientag

ApothekerInnen	
Pharma- AssistentInnen	
Ausbildung	
Andere	

 # Verkaufsinseln ☐

A1.2 Checklist for recording of counseling



A1.3 Pharmacist interview

Apothekencode ……
Geschlecht …… Jahrgang ……

Apotheken - Interview

Wir möchten Ihnen einige Fragen bezüglich Compliance/ Adherence stellen. Die Definition lautet: „Unter Adherence verstehen wir nicht nur die „Therapietreue" des Patienten, sondern die Einhaltung der gemeinsam von Patient und Arzt gesetzten Therapieziele".

1) Wie viele Prozente arbeiten Sie in der Apotheke? …… Prozent 1.1

2) Sprechen Sie Ihre Kunden aktiv auf Ihre Compliance an?

Ja	2.1	Nein	2.2

3) Wie oft pro Monat? …… pro Monat 3.1

4) Sie führen also ein Gespräch über Compliance. Welche Themen sprechen Sie konkret an?

Anwendung	4.1	Dosierung	4.2
Wirkung	4.3	Morisky- Frage	4.4
Therapietreue	4.5	Positive Bestärkung	4.6
Motivation	4.7	Organisation	4.8
Barrieren	4.9	Fähigkeiten/ Fertigkeiten	4.10
Instruktion Produkt	4.11	Schriftliche Information	4.12
Therapie/ Krankheit Verständnis	4.13	Termine	4.14
Selbst-/ Monitoring	4.15		

Anderes: 4.16 ……

5) Welche Kriterien sind für Sie ausschlaggebend für ein solches Gespräch?

DauerRx/ Wiederholung	5.1	Erstverordnung	5.2
Polymedikation	5.3	Halbe Tabletten	5.4
Alter	5.5	Demenz	5.6
Fähigkeiten/ Fertigkeiten	5.7	Spezielles Krankheitsbild	5.8
Spezielles Medikament, Name 5.9			

Anderes: 5.10 ……

6) Welche Faktoren würden die Durchführung eines solchen Gesprächs begünstigen?

Mehr Zeit	6.1	Fakturierung	6.2

Anderes: 6.3 ……

BABS- Studie 2010 Irene Rüfenacht, Pharmazentrum, Klingelbergstr. 50, 4056 Basel

A2.1 Pharmacy survey on multidrug punch card provision

UNIVERSITÄT BASEL

Pharmaceutical Care Research Group
Departement Pharmazeutische Wissenschaften

Klingelbergstrasse 50
CH-4056 Basel

Tel.+41 (0)61 267 14 26
Fax+41 (0)61 267 14 28
www.pharmacare.unibas.ch

Apothekenfragebogen: Evaluation des Pharmis® Medikamenten Blisters

Besten Dank im Voraus für Ihre Teilnahme. Im ersten Abschnitt bitten wir Sie um allgemeine Angaben gefolgt von Fragen zu Erfahrungen, Bedienung/Umgang und Compliance. Das Ausfüllen des Fragebogens dauert ca. 20 Minuten. Ihre Angaben werden anonymisiert behandelt.

Die Fragen sollten bevorzugt durch eine/n Mitarbeitende/n beantwortet werden, welche/r regelmässig Pharmis® Medikamenten Blister herstellt. Falls Sie bei gewissen Fragen nicht sofort antworten können, bitten wir Sie in geeigneten Unterlagen zu recherchieren und/oder die Antwort unter Mithilfe einer informierten Person zu beantworten.

Kontaktdaten (rechts Platz für Stempel)

- Name der Apotheke:.....
- Adresse:.....
- Postleitzahl / Ort:.....

Geben Sie bitte bei einer Nichtteilnahme trotzdem Ihre Kontaktdaten an und schicken Sie uns den Fragebogen zurück. Wir sind dankbar für eine kurze Begründung:

.....
.....
.....

Code (*bitte leer lassen*): definitive Version 18.11.2014

Apothekenfragebogen: Evaluation des Pharmis® Medikamenten Blisters 2011

Allgemeine Informationen zur Apotheke

Typ der Apotheke ☐ Unabhängig ☐ Apotheke als Teil einer Kette ☐ Mitglied einer Gruppierung (unabhängig)	Welche Form der Arzneimittelabgabe überwiegt in Ihrem Einzugsgebiet? ☐ Keine Selbstdispensation ☐ Eingeschränkte Selbstdispensation (Erstabgabe durch Arzt erlaubt) ☐ Mischform (Distanzregelung) ☐ Selbstdispensation
Lage der Apotheke (*nur eine Antwort möglich*) ☐ Zentrumslage: City, Passantenlage, Bahnhof, Ladenpassage ☐ Periphere Lage: Quartier, Aussenquartier, Nebenstrasse ☐ Dorf- oder Landapotheke ☐ Apotheke in Einkaufszentrum ☐ Spitalapotheke	Apotheke in Ärztehaus bzw. in Gesundheitszentrum (*oder direkt angrenzend*) ☐ Ja ☐ Nein

Angaben zur Person

Dieser Fragebogen wird ausgefüllt durch eine/n:

☐ Eidg. dipl. Apotheker/in
☐ Pharmaassistent/in

Geschlecht: ☐ männlich ☐ weiblich

Geburtsjahr:_____ Anzahl Jahre Berufserfahrung:_____

Allgemeine Fragen zu Pharmis® Medikamenten Blister

1. Seit wann arbeitet Ihre Apotheke mit Pharmis® Medikamenten Blister?

☐ Mehr als ein Jahr. Jahr der Einführung:_____
☐ Weniger als ein Jahr. Monat der Einführung:_____

2. Für wen bereiten Sie die Pharmis® Medikamenten Blister vor? *Bei den angekreuzten Feldern bitte genaue **Anzahl Patienten** angeben.*

☐ Alters/Krankenheim: _____ Patienten
☐ Spitex: _____ Patienten
☐ ambulante Patienten: _____ Patienten
☐ andere: …….. _____ Patienten

3. Empfiehlt Ihre Apotheke den ambulanten Patienten aktiv Pharmis® Medikamenten Blister? Falls *Ja*, schätzen Sie Ihre Erfolgsrate in Prozent. (*Erfolgsrate: Patient willigt ein, Pharmis® Medikamenten Blister zu verwenden.*)

☐ Ja, Erfolgsrate ca._____%
☐ Nein (*weiter mit Frage 5*)

UNI BASEL

Code (*bitte leer lassen*): definitive Version: 01.03.2011 1

4. Für welche Patienten und in welchen Situationen empfehlen Sie aktiv Pharmis® Medikamenten Blister?

.....

.....

.....

5. Empfiehlt Ihre Apotheke den Ärzten aktiv Pharmis® Medikamenten Blister?

☐ Ja
☐ Nein

6. Wie verrechnen Sie der Spitex / den Altersheimen die Dienstleistung der Verblisterung?

☐ Keine Verrechnung
☐ Verrechnung gemäss Vertrag

Herstellung

Die Herstellung des Pharmis® Medikamenten Blisters umfasst die **Administration** (z.B. Abrechnung, Patientenerfassung), das **Richten** und die **Kontrollen**. Diese Teilschritte werden meistens von verschiedenen Mitarbeitenden ausgeführt.

7. Schätzen Sie den Aufwand in Prozent.

Administration		Richten		Kontrollen	
Eidg. dipl. Apotheker/in:	____%	Eidg. dipl. Apotheker/in:	____%	Eidg. dipl. Apotheker/in:	____%
Pharmaassistent/in:	____%	Pharmaassistent/in:	____%	Pharmaassistent/in:	____%
Andere:	____%	Andere:	____%	Andere:	____%
Total:	**100%**	**Total:**	**100%**	**Total:**	**100%**

8. Schätzen Sie den Zeitbedarf für die Herstellung eines einzelnen Blisters in Minuten.

Administration: _____min.	Richten: _____min.	Kontrollen: _____min.

9. Wie beurteilen Sie die Kosten für Blistermaterial und Software? (*in Relation zur Abgeltung der Dienstleistung*)

günstig	gerade richtig	eher zu teuer	viel zu teuer
☐	☐	☐	☐

Apothekenfragebogen: Evaluation des Pharmis® Medikamenten Blisters 2011

10. Der Pharmis® Medikamenten Blister wird entweder durch Heissversiegelung oder durch Zusammenkleben der Boden- und Deckkartons verschlossen. Welche Methode verwenden Sie in Ihrer Apotheke?

☐ Heissversiegelung, aus folgenden Gründen:	☐ Zusammenkleben, aus folgenden Gründen:

11. Wie beurteilen Sie den Platzbedarf für Blistermaterial, Arbeitsstationen und Medikamentenlager?

sehr niedriger Platzbedarf	niedriger Platzbedarf	angemessener Platzbedarf	grosser Platzbedarf	sehr grosser Platzbedarf
☐	☐	☐	☐	☐

12. Für die Inbetriebnahme und einen reibungslosen Ablauf der Blisterherstellung waren / sind möglicherweise zusätzliche Anschaffungen wie z.B. Computer, Drucker oder Verbrauchsmaterial (Handschuhe etc.) notwendig. Wie hoch schätzen Sie diese Zusatzkosten?

☐ keine Zusatzkosten
☐ <1'000 CHF
☐ 1'000-2'500 CHF
☐ 2'500-5'000 CHF
☐ 5'000-7'500 CHF
☐ 7'500-10'000 CHF
☐ >10'000 CHF

Erfahrungswerte aus Apotheken- und Patientenperspektive

13. Nennen Sie je zwei Stichpunkte, bei denen Sie zufrieden bzw. unzufrieden sind mit dem Pharmis® Medikamenten Blister und geben Sie zwei Verbesserungsvorschläge an:

zufrieden	unzufrieden	Verbesserungsvorschläge

14. Welche Auswirkungen hatte die Einführung des Pharmis® Medikamenten Blisters für Ihre Apotheke? Welche der folgenden Aussagen treffen zu?

	trifft voll und ganz zu	trifft eher zu	trifft eher nicht zu	trifft über-haupt nicht zu	weiss nicht
	1	2	3	4	5
Gewinn von neuen Patienten	☐	☐	☐	☐	☐
Gewinn von neuen Kunden (Spitex / Altersheime)	☐	☐	☐	☐	☐
Intensivere interdisziplinäre Zusammenarbeit	☐	☐	☐	☐	☐
Neue Möglichkeit, den Patienten besser pharmazeutisch zu betreuen	☐	☐	☐	☐	☐
Bessere Möglichkeit zur Kontrolle der Compliance	☐	☐	☐	☐	☐
Umsatzsteigerung	☐	☐	☐	☐	☐
Profilierung der Apotheke	☐	☐	☐	☐	☐

15. Durch eine gute Compliance und damit verbundenem Therapieerfolg können Kosteneinsparungen erzielt werden. Schätzen Sie ein, welche Auswirkungen die Einführung von Pharmis® Medikamenten Blister auf Kosteneinsparungen hat. Welche der folgenden Aussagen treffen zu?

	trifft voll und ganz zu	trifft eher zu	trifft eher nicht zu	trifft über-haupt nicht zu	weiss nicht
	1	2	3	4	5
Abfallvermeidung bei Medikamentenwechsel	☐	☐	☐	☐	☐
Ökonomische Verrechnung der Medikamente	☐	☐	☐	☐	☐
Weniger Arztbesuche	☐	☐	☐	☐	☐
Weniger Spitalaufenthalte	☐	☐	☐	☐	☐
Geringerer Bedarf an Spitex	☐	☐	☐	☐	☐
Vermeidung von Übertritten ins Altersheim	☐	☐	☐	☐	☐

16. Gemäss Ihren Erfahrungen seit der Einführung von Pharmis®: Sind die Patienten zufrieden mit dem Pharmis® Medikamenten Blister?

Sehr unzufrieden	Eher unzufrieden	Weder noch	eher zufrieden	sehr zufrieden
☐	☐	☐	☐	☐

17. Notieren Sie stichwortartig Begriffe, die Zufriedenheit bzw. Unzufriedenheit der Patienten ausdrücken (*z.B. praktisch, bessere Kontrolle bei Einnahme*):

.....

.....

.....

.....

.....

.....

Bedienung / Umgang

18. Wie beurteilen Sie folgende Aspekte der Herstellung eines Pharmis® Medikamenten Blisters? Bitte kommentieren Sie ihre Beurteilung:

	sehr einfach	eher einfach	eher kompliziert	sehr kompliziert	weiss nicht
	1	2	3	4	5
Bedienung der Pharmis® Software	☐	☐	☐	☐	☐
Kommentar:					
Administration	☐	☐	☐	☐	☐
Kommentar:					
Richten	☐	☐	☐	☐	☐
Kommentar:					
Versiegeln	☐	☐	☐	☐	☐
Kommentar:					

19. Welche Vorteile bzw. Nachteile sehen Sie im Vergleich zu herkömmlichen Wochendispensern wie z.B. Dosett®? Bitte in Stichworten auflisten:

Vorteile:	Nachteile:

Apothekenfragebogen: Evaluation des Pharmis® Medikamenten Blisters 2011

20. Welche weiteren Compliance-Hilfssysteme kennen / verwenden Sie?

Kennen wir:	Verwenden wir:

Bei der **Administration** und dem **Richten** des Pharmis® Medikamenten Blister können möglicherweise Fehler passieren. Diese Fehler werden vermieden durch Kontrollen **während** der Herstellung und durch eine Nachkontrolle durch eine Zweitperson. Beantworten Sie folgende Fragen hinsichtlich der letzten **zwei Monate**.

21. Wann führen Sie Kontrollen durch?

	Ja	Nein
Nach der Eingabe der Verordnung	☐	☐
Vor dem Abfüllen der Medikamente in den Blister	☐	☐
Nach dem Abfüllen der Medikamente in den Blister	☐	☐
Nach dem Versiegeln des Blisters (Nachkontrolle)	☐	☐

22. Schätzen Sie in Prozent, wie oft in diesen Kontrollen durch Zweitpersonen Fehler entdeckt werden.

Bei ca. _____% der Blister in den letzten **zwei Monaten**.

23. Wie verteilen sich die Fehlerarten bei diesen Kontrollen? Schätzen Sie in Prozent.

Verordnung falsch eingegeben:	____%
Falsches Medikament bereitgestellt:	____%
Falsches Medikament abgepackt:	____%
Richtiges Medikament am falschen Ort verpackt:	____%
Medikament vergessen abzupacken:	____%
Medikament zu wenig abgepackt:	____%
Medikament zu oft abgepackt:	____%
Für falsche Patienten abgepackt:	____%
Total:	**100%**

24. Gab es schon Patientenverwechslungen bei der Abgabe (*Ein Patient erhielt den Wochenblister eines anderen Patienten*)?

☐ Ja, in den letzten **6 Monaten** ca. _____ mal
☐ Nein

Apothekenfragebogen: Evaluation des Pharmis® Medikamenten Blisters 2011

Instruktion / Beratung zu Compliance

25. Die Instruktion des Pharmis® Medikamenten Blisters kann bei verschiedenen Patienten unterschiedlich intensiv sein:

A) Den Patienten wird die Anwendung des Pharmis® Medikamenten Blisters erklärt.
B) Den Patienten wird die Anwendung und kurz das Ziel der Compliancеverbesserung erläutert.
C) Den Patienten wird die Anwendung und das Ziel der Compliancеverbesserung ausführlich erklärt. Auf die Patienten wird aktiv eingegangen *(z.B. mittels Hilfsmittel / Beratungsraum)*.

Welche Pharmis® Patienten (*Patienten, welche den Pharmis® Medikamenten Blister anwenden*) instruieren Sie auf der betreffenden Stufe? *Bitte füllen Sie alle Antwortoptionen aus.*

A) Anwendung:	**Ja**	**Nein**
Alle Patienten	☐	☐
Betagte Patienten (> 70 Jahre)	☐	☐
Patienten nach Spitalaustritt	☐	☐
Patienten, welche Compliancеprobleme haben	☐	☐
Patienten mit bestimmten Krankheiten, bei welchen eine gute Compliance wichtig ist	☐	☐
Patienten mit einer gewissen Anzahl Medikamenten	☐	☐
B) Anwendung und Compliancеverbesserung kurz:		
Alle Patienten	☐	☐
Betagte Patienten (> 70 Jahre)	☐	☐
Patienten nach Spitalaustritt	☐	☐
Patienten, welche Compliancеprobleme haben	☐	☐
Patienten mit bestimmten Krankheiten, bei welchen eine gute Compliance wichtig ist	☐	☐
Patienten mit einer gewissen Anzahl Medikamenten	☐	☐
C) Anwendung und Compliancеverbesserung ausführlich:		
Alle Patienten	☐	☐
Betagte Patienten (> 70 Jahre)	☐	☐
Patienten nach Spitalaustritt	☐	☐
Patienten, welche Compliancеprobleme haben	☐	☐
Patienten mit bestimmten Krankheiten, bei welchen eine gute Compliance wichtig ist	☐	☐
Patienten mit einer gewissen Anzahl Medikamenten	☐	☐

26. Kontrollieren Sie, ob Pharmis® Patienten compliant sind? (*Einsammeln und Kontrolle der gebrauchten Blister*).

	Ja	**Nein**
Das haben wir noch nie gemacht	☐	☐
Falls die Patienten den Blister zurückbringen	☐	☐
Ja, immer. Die Patienten werden aktiv aufgefordert, den Blister zurückzubringen	☐	☐
Patienten mit bestimmten Krankheiten, bei welchen eine gute Compliance wichtig ist	☐	☐
Patienten mit einer gewissen Anzahl Medikamenten	☐	☐
Andere Methode *(bitte konkretisieren Sie)*:.....	☐	☐

Apothekenfragebogen: Evaluation des Pharmis® Medikamenten Blisters 2011

27. Fragen Sie Pharmis® Patienten direkt, um Informationen zu ihrer Compliance zu erhalten?				
nie ☐	eher selten ☐	manchmal ☐	häufig ☐	immer ☐

28. Schätzen sie die Compliance von Pharmis® Patienten in Prozent.

Anteil an Dosen, welche eingenommen werden („Taking Compliance"): _____%

29. Schätzen Sie, um wieviel Prozent sich die Compliance bei Patienten verbessert, welche aufgrund von Compliance-Problemen auf Pharmis® Medikamenten wechseln.

Die „Taking Compliance" hat sich um _____% verbessert.

☐ weiss nicht

Wünsche, Anregungen, Kommentare:

.....

.....

.....

.....

.....

.....

.....

.....

.....

.....

Vielen Dank für Ihre Antworten!

A3.1 Final board decision of the Ethikkommission beider Basel for the quantitative patient interviews

Ethikkommission beider Basel EKBB

Präsident
Prof. André P. Perruchoud
Vizepräsidenten
Prof. Thomas Kühne
Prof. Marius Kränzlin

Herrn
Prof. Dr. K. Hersberger
Pharmazentrum
Klingelbergstrasse 50
4056 Basel

Basel, 28. März 2011

55/11:
Use of Pharmis® drug blister in Switzerland - an evaluation at pharmacist's, physician's and patient's level

Sehr geehrter Herr Prof. Hersberger, sehr geehrter Herr Dr. Zeller

Besten Dank für Ihr Schreiben datiert vom 04. März 2011 (erhalten am 22. März 2011) samt Beilagen. Die Ethikkommission beider Basel hat die nachfolgend erwähnten Dokumente zur oben genannten Studie, zustimmend zur Kenntnis genommen und genehmigt:

- Protokoll - Version 3 vom 21. März 2011
- Patienteninformation - Version 3 vom 21. März 2011
- Einverständniserklärung zur Kontaktaufnahme - Version 3 vom 21. März 2011
- Einverständniserklärung zur Studienteilnahme - Version 3 vom 21. März 2011.

→ Die letzten Auflagen der EKBB wurden somit erfüllt.

Wir hoffen, Ihnen mit dieser Bestätigung zu dienen und wünschen Ihnen für die Durchführung der Studie viel Erfolg.

Mit freundlichen Grüssen

Vis: Prof. M. Kränzlin
Vizepräsident der Ethikkommission
beider Basel / EKBB

Prof. A. P. Perruchoud
Präsident der Ethikkommission
beider Basel / EKBB

A3.2 Final board decision of the Kantonale Ethikkommission Aargau/Solothurn for the quantitative patient interviews

KANTON AARGAU

Departement
Gesundheit und Soziales
Kantonale Ethikkommission

Formular für die
Beschlussmitteilung der Kantonalen Ethikkommission

Die **Kantonale Ethikkommission** des Departementes Gesundheit und Soziales vertreten durch den Präsidenten hat am **14. April 2011** das folgende Forschungsprojekt eingehend begutachtet.

Forschungsprojekt Ref.Nr. EK: 2011/026

Use of pharmis drug blister in Switzerland - an evaluation at pharmacist's, physician's and patient's level.

Prüfer/in (verantwortliche Studienleiter/in am Versuchsstandort)

Name, Vorname, Titel:	Prof. Dr. sc. nat. K. Hersberger
Funktion:	Universitätsspital Basel - Pharmazentrum
Adresse:	Klingelbergstrasse 50 - 4056 Basel

Die Ethikkommission stützt ihre Beurteilung auf die Unterlagen, wie sie dem beiliegenden „Basisformular zur Einreichung eines biomedizinischen Forschungsprojektes" vom 4. April 2011 beigefügt sind.

☐ normales Verfahren ☒ vereinfachtes Verfahren ☐ Nachbegutachtung

Die Ethikkommission kommt zu folgendem Beschluss, Präsidialentscheid basierend auf dem positiven Votum der Ethikkommission beider Basel vom 28. März 2011:

☒ **Positiv** [1]

☐ **Auflagen** [2] **(** sind vor der Genehmigung zu erfüllen)

- ☐ Die revidierten Dokumente werden im ordentlichen Verfahren geprüft (Anzahl Kopien: …)
- ☐ Die revidierten Dokumente werden im vereinfachten Verfahren geprüft (Anzahl Kopien:)

☐ **Negativ** [3] (mit Begründung)

☐ **Nicht zuständig** [4] (mit Begründung)

[1] Bedeutet:
- Die Studie kann bei der zuständigen eidg. Notifikationsbehörde (Swissmedic/BAG/BUWAL) eingereicht werden.
- Die Studie kann gestartet werden (Studien, die nicht unter das Heilmittelgesetz, Transplantationsgesetz, Stammzellforschungsgesetz oder die Strahlenschutzverordung fallen)

[2] Bedeutet:
- Die betroffenen Dokumente müssen revidiert der Ethikkommission eingereicht werden,
- Der Versuch kann bis zum Erhalt eines positiven Votums weder notifiziert noch begonnen werden

[3] Bedeutet:
- Die Studie kann in der vorliegenden Form nicht durchgeführt werden. Eine Neueinreichung ist möglich.

[4] Bedeutet:
- Die Ethikkommission ist für die Beurteilung rechtlich nicht zuständig. Entweder ist eine andere Stelle für die Bewilligung zuständig, oder sie kann ohne Bewilligung durchgeführt werden.

Der Beschluss gilt auch für die im "Basisformular" gemeldeten weiteren Prüfer/innen im Zuständigkeitsbereich der Ethikkommission.

Bemerkungen:
Die Kantonale Ethikkommission bestätigt, dass sie nach ICH-GCP-Richtlinien arbeitet.

A3.3 Quantitative patient interview

Patientenbefragung: Evaluation des Pharmis® Medikamenten Blisters 2011

EVALUATION DES PHARMIS® MEDIKAMENTEN BLISTERS – EKBB 55/11

Patientenbefragung (telefonisches Interview)		
Einschlusskriterien für ambulante Patienten: Vor Befragung auszufüllen		
	Ja	**Nein**
Alter: ≥ 18 Jahre	☐	☐
Lebt Zuhause ohne externe Unterstützung	☐	☐
Deutschkundig	☐	☐
Fähig, selbstständig eine Einverständniserklärung abzugeben	☐	☐
Verwendung Pharmis® Medikamenten Blister: ≥ 3 Monate	☐	☐
Zugang zu Patientendaten der Apotheken: ≥ 12 Monate	☐	☐

Datum:	Zeit:
Geschlecht: ☐ männlich ☐ weiblich	Geburtsjahr:
Patienten-Code:	Apotheken-Code:

Introsatz

Guten Tag Frau / Herr X, Hier ist Philipp Braun am Apparat. Ich freue und bedanke mich, dass Sie sich nach unserem letzten Gespräch einverstanden erklärt haben an der Patientenbefragung teilzunehmen. Ich kontaktiere Sie nun an unserem vereinbarten Termin um die Befragung durchzuführen. Können Sie sich an unser letztes Gespräch erinnern? Sind während dieser Zeit noch Fragen aufgetaucht? Ich möchte Sie nochmals daran erinnern, dass die Befragung ca. 30 min. dauert und Ihre Angaben anonym bleiben. Sie sind nicht gezwungen, alle Fragen zu beantworten. Falls Sie Fragen aus verschiedenen Gründen nicht beantworten wollen, dürfen Sie jederzeit eine Antwort verweigern. Auch können Sie jederzeit die Befragung für beendet erklären oder gar nicht teilnehmen.

Einstiegsfragen

1. Sind Sie **erwerbstätig?**

☐ Ja
☐ Nein

2. Welchen höchsten **Bildungsgrad** haben Sie? Ich gebe Ihnen 5 Antwortmöglichkeiten:

☐ keinen Abschluss
☐ Hauptschulabschluss
☐ Matur
☐ Hochschulabschluss
☐ Promotion

3. ***Wohnsituation***: Leben Sie alleine oder mit anderen Personen im gleichen Haushalt?

☐ alleine
☐ mit anderen Personen im gleichen Haushalt

Patientenbefragung: Evaluation des Pharmis® Medikamenten Blisters 2011

4. Denken Sie an die letzten 2 Wochen. Beschreiben Sie ihren gegenwärtigen Gesundheitszustand. Ich gebe Ihnen 5 Antwortmöglichkeiten:

☐ sehr gut ☐ gut ☐ mässig ☐ schlecht ☐ sehr schlecht

5. Wie stark **achten** Sie im Allgemeinen auf Ihre Gesundheit? Ich gebe Ihnen 5 Antwortmöglichkeiten:

☐ sehr stark ☐ stark ☐ mittelmässig ☐ weniger stark ☐ gar nicht

6. Ich lese Ihnen nun **5 Aussagen** vor. Sie können mit Ja oder Nein antworten:

	Ja	Nein
6.1 Ich bin Brillen- oder Linsenträger / in, inkl. Lesebrille	☐	☐
6.2 Ich habe zittrige Hände	☐	☐
6.3 Ich bin eingeschränkt in meinen Fingerfertigkeiten (z.B. zittrige Hände)	☐	☐
6.4 Meine Hände machen weh (*Rheuma, Arthrose*)	☐	☐
6.5 Ich nehme alle Medikamente selbstständig ein	☐	☐
6.6 Ich bekomme Hilfe von Angehörigen bei der Medikamenteneinnahme	☐	☐

7. ***Falls Ja bei 6.5***: Wie helfen Ihnen die Angehörigen? ***Offene Antwort***

8. Verwenden Sie neben den Medikamenten im Pharmis® Medikamenten Blister noch **andere Medikamente** wie z.B. Flüssigkeiten, Spritzen, Salben, Reservemedikamente?

☐ Nein
☐ Ja. **Welche**:

Allgemeine Fragen zum Pharmis® Medikamenten Blister

Nun folgen einige **allgemeine Fragen** zum Pharmis® Medikamenten Blister.

9. Durch **wen oder was** sind Sie auf den Pharmis® Medikamenten Blister **aufmerksam** geworden? Ich gebe Ihnen 4 Antwortmöglichkeiten:

☐ Arzt / Ärztin ☐ Apotheke ☐ Verwandte, Freunde ☐ Andere:

10. ***Falls Sie durch einen Arzt / eine Ärztin oder Apotheke auf den Pharmis® Medikamenten Blister aufmerksam gemacht wurden***: Falls Sie sich no daran erinnern können: Aus welchen **Gründen** wurden Sie informiert? Sie dürfen frei antworten. ***Semi-strukturiert:***

	Ja	Nein
10.1 Weiss ich nicht mehr	☐	☐
10.2 Aufgrund meines Alters	☐	☐
10.3 Ich hatte Mühe, meine Therapie einzuhalten	☐	☐
10.4 Ich muss viele verschiedene Medikamente zu unterschiedlichen Zeitpunkten einnehmen	☐	☐
10.5 Ich hatte vorher ein anderes Wochendosierungssystem, mit welchem ich nicht zurecht kam	☐	☐
10.6 Spitalaustritt	☐	☐
10.7 Andere Gründe, nämlich:	☐	☐

Patientenbefragung: Evaluation des Pharmis® Medikamenten Blisters 2011

11. Inwiefern **hilft** Ihnen der Pharmis® Medikamenten Blister im täglichen Gebrauch? Nennen Sie **Vorteile**. Nennen Sie **Nachteile**. Sie können frei antworten. ***Offene Antwort:***

Vorteile:	Nachteile:
☐ Reminderfunktion ☐ abgepackt	☐ Bevormundung, eingeschränkte Autonomie ☐ Grösse
andere Vorteile:	andere Nachteile:

12. Wie kommt der Pharmis® Medikamenten Blister zu Ihnen nach Hause? Ich gebe Ihnen 3 Antwortmöglichkeiten:

☐ Die Apotheke bringt / liefert mir den Pharmis® Medikamenten Blister nach Hause (weiter mit A.)
☐ Ich hole den Pharmis® Medikamenten Blister selber bei der Apotheke ab (weiter mit B)
☐ Angehörige / Freunde bringen mir den Pharmis® Medikamenten Blister nach Hause. (weiter mit C)

13. ***A. Fragestellung hängt von Antwort in Frage 12 ab***. Denken Sie an die letzten 3 Monate: Hat Ihre Apotheke vergessen, den Pharmis® Medikamenten Blister vorbeizubringen?
☐ Ja
☐ Nein. ***Weiter mit Frage 15***

B. Haben Sie vergessen, den Pharmis® Medikamenten Blister zu holen?
☐ Ja
☐ Nein. ***Weiter mit Frage 15***

C. Hat Ihr Angehöriger vergessen, den Pharmis® Medikamentenblister zu holen?
☐ Ja
☐ Nein. ***Weiter mit Frage 15***

14. ***Fragestellung hängt von Antwort in Frage 12 ab***:
A. Wie oft ist es vorgekommen in den letzen 3 Monaten, dass Ihre Apotheke vergessen hat den Pharmis® Medikamenten Blister vorbeizubringen?
_____ mal
B. dass Sie vergessen haben, den Pharmis® Medikamenten Blister abzuholen?
_____ mal
C. dass Ihr Angehöriger vergessen hat den Pharmis® Medikamentenblister abzuholen?
_____ mal

15. Ist es in den letzten 3 Monaten vorgekommen, dass Sie nicht den richtigen Pharmis® Medikamenten Blister erhalten haben?

☐ Ja
☐ Nein

16. Wie **zufrieden** sind Sie im Allgemeinen mit dem Pharmis® Medikamenten Blister? Ich gebe Ihnen 4 Antwortmöglichkeiten

sehr zufrieden	eher zufrieden	eher unzufrieden	sehr unzufrieden
☐	☐	☐	☐

Patientenbefragung: Evaluation des Pharmis® Medikamenten Blisters 2011

Handhabung

Bei den folgenden Fragen geht es um die **Handhabung** des Pharmis® Medikamenten Blister.

17. Es folgen Fragen zum Herausdrücken. Beantworten Sie die folgenden Aussagen mit Ja oder Nein:

	Ja	Nein
17.1 Ich drücke die Medikamente selber aus dem Pharmis® Medikamenten Blister. ***Falls Ja, weiter mit 17.3***	☐	☐
17.2 Angehörige drücken mir die Medikamente aus dem Pharmis® Medikamenten Blister raus. ***Falls Ja, weiter mit Frage 21***	☐	☐
17.3 Ich drücke die Medikamente mit den Fingern aus dem Pharmis® Medikamenten Blister raus	☐	☐
17.4 Die Medikamente drücke ich direkt in ein Auffanggefäss wie z.B. ein Glas oder Teller	☐	☐
17.5 Ich schneide mit einem Messer die Alufolie hinten auf, um die Medikamente einfach rauszubekommen.	☐	☐
17.6 ***Falls 17.1 bis 17.5 mit Nein beantwortet werden***: Ich habe eine andere Methode. Beschreiben Sie die Methode:	☐	☐

18. Haben Sie Mühe, die Medikamente aus dem Pharmis® Medikamenten Blister rauszudrücken? Beantworten Sie mit „immer", „oft" (bei mehr als der Hälfte der Blisterfächlein), „selten" (bei weniger als der Hälfte der Blisterfächlein), „nie".

immer	oft (mehr als Hälfte)	selten (weniger als Hälfte)	nie
☐	☐	☐	☐

19. ***Nur falls Frage 18 nicht mit „nie" beantwortet wird***: Warum haben Sie Mühe beim Herausdrücken? ***Semi-strukturiert***

	Ja	Nein
19.1 Zu dicke Alufolie	☐	☐
19.2 Die Blisterfächlein in der Mitte sind schwierig erreichbar	☐	☐
19.3 Medikamente spicken weg	☐	☐
19.4 Volle Blisterfächlein	☐	☐
19.5 Kleine Tabletten sind schwierig rauszubekommen	☐	☐
19.6 Anderer Grund:	☐	☐

20. ***Nur falls Frage 18nicht mit „nie" beantwortet wird***: Kam es in den letzten 4 Wochen vor, dass Sie Medikamente nicht aus dem Pharmis® Medikamenten Blister herausbekommen haben?

☐ Ja, wie oft:
☐ Nein

21. ***Pharmis® Medikamenten Blister für unterwegs***: Was machen Sie, wenn Sie kurzfristig einen Tag oder länger unterwegs sind? Antworten Sie mit Ja oder Nein:

	Ja	Nein
21.1 Ich nehme den ganzen Pharmis® Medikamenten Blister mit	☐	☐
21.2 Ich fülle die Medikamente um	☐	☐
21.3 Ich habe eine andere Methode:	☐	☐

22. Ging Ihnen der Pharmis® Medikamenten Blister **kaputt** in den letzen **3 Monaten**, das heisst er war nicht mehr brauchbar?

☐ Ja
☐ Nein

23. War der Pharmis® Medikamenten Blister beschädigt in den letzten 3 Monaten, das heisst er war nicht mehr im Ausgangszustand, eine korrekte Einnahme war aber trotzdem noch möglich?

☐ Ja
☐ Nein

24. Wo bewahren Sie den Pharmis® Medikamenten Blister prinzipiell auf? ***Semi-strukturiert***

☐ Küche ☐ Badezimmer ☐ Wohnzimmer ☐ Schlafzimmer ☐ Auto ☐ anderer Ort:

25. ***Aufbewahrung***: Es geht immer noch um die Aufbewahrung. Beantworten sie die folgenden Aussagen mit Ja oder Nein:

	Ja	Nein
25.1 Ich bewahre den Blister in einer Schublade / einem „Chäschtli“ auf	☐	☐
25.2 Ich bewahre den Blister in einem verschlossenen Fach auf	☐	☐
25.3 Es stört mich, wenn andere Personen den Blister bei mir zu Hause sehen	☐	☐

26. Wie beurteilen Sie den Pharmis® Medikamenten Blister. Sie können antworten mit „trifft voll und ganz zu“, „trifft eher zu“, „trifft eher nicht zu“ oder „trifft überhaupt nicht zu“

	trifft voll und ganz zu	trifft eher zu	trifft eher nicht zu	trifft über-haupt nicht zu
	1	2	3	4
26.1 Ich empfinde den Pharmis® Medikamenten Blister für mich als notwendig	☐	☐	☐	☐
26.2 Ich fühle mich mit dem Pharmis® Medikamenten Blister sicherer in der Therapie	☐	☐	☐	☐
26.3 Der Pharmis® Medikamenten Blister verwirrt mich	☐	☐	☐	☐
26.4 Ich fühle mich gut betreut durch die Apotheke	☐	☐	☐	☐
26.5 Ich würde lieber selber meine Medikamente richten	☐	☐	☐	☐
26.6 Allgemein bin ich sehr zufrieden mit der Handhabung des Pharmis® Medikamenten Blister	☐	☐	☐	☐
26.7 Der Pharmis® Medikamenten Blister ist praktisch in den Ferien	☐	☐	☐	☐
26.8 Der Pharmis® Medikamenten Blister ist praktisch, wenn ich einen Tag oder länger unterwegs bin	☐	☐	☐	☐

Gestaltung

Die folgenden Fragen beziehen sich auf die **Gestaltung** des Pharmis® Medikamenten Blisters.

Patientenbefragung: Evaluation des Pharmis® Medikamenten Blisters 2011

27. Sie können antworten mit „trifft voll und ganz zu“, „trifft eher zu“, „trifft eher nicht zu“ oder „trifft überhaupt nicht zu“.

	Trifft voll und ganz zu	trifft eher zu	trifft eher nicht zu	trifft überhaupt nicht zu
	1	2	3	4
27.1 Der Pharmis® Medikamenten Blister ist robust	☐	☐	☐	☐
27.2 Der Pharmis® Medikamenten Blister ist praktisch	☐	☐	☐	☐
27.3 Ganz allgemein gefällt mir die Gestaltung des Pharmis® Medikamenten Blisters	☐	☐	☐	☐
27.4 Der Pharmis® Medikamenten Blister ist übersichtlich.	☐	☐	☐	☐
27.5 Die Orientierung mit Hilfe der Tage und Uhrzeiten fällt mir leicht	☐	☐	☐	☐
27.6 Der Pharmis® Medikamenten Blister ist zu gross und sperrig	☐	☐	☐	☐
27.7 Die Gestaltung des Pharmis® Medikamenten Blister spielt mir keine grosse Rolle weil die Funktion mir wichtiger ist	☐	☐	☐	☐
27.8 Ich kann den Text auf der Rückseite (Therapiebeschreibung) ohne Probleme lesen	☐	☐	☐	☐
27.9 Ich beachte den Text auf der Rückseite nie	☐	☐	☐	☐
27.10 Ich wünsche mir eine Hülle oder einen Deckel	☐	☐	☐	☐

Therapietreue

Wir kommen zum letzten Abschnitt der Befragung. Die folgenden Fragen beziehen sich auf die **Therapietreue**. Therapietreue bedeutet, dass Sie die richtigen Medikamente zum richtigen Zeitpunkt nehmen.

28. Wer erklärte Ihnen den **Aspekt der Therapietreue** bei der Einführung des Pharmis® Medikamenten Blister? Beantworten Sie mit Ja oder Nein:

	Ja	Nein
28.1 Arzt / Ärztin	☐	☐
28.2 Apotheke	☐	☐
28.3 Weiss ich nicht mehr	☐	☐

29. Sie verwenden momentan den Pharmis® Medikamenten Blister.
Wie hoch schätzen Sie Ihre Therapietreue in Bezug auf die Einnahme? 0% heisst, Sie nehmen keine Medikamente. 100% heisst, Sie nehmen alle Medikamente.
Wie hoch schätzen Sie Ihre Therapietreue in Bezug auf den Zeitpunkt der Einnhame. 0% heisst, Sie nehmen die Medikamente nie zum richtigen Zeitpunkt. 100% heisst, Sie nehmen alle Medikamente zum richtigen Zeitpunkt.
Überlegen Sie sich nun noch einmal , wie Ihre Therapietreue ohne den Pharmis® Medikamenten Blister wäre bzw wie es vorher ohne Blister war.
Wie hoch schätzen Sie Ihre Therapietreue in Bezug auf die Einnahme? 0% heisst, Sie nehmen keine Medikamente. 100% heisst, Sie nehmen alle Medikamente.
Wie hoch schätzen Sie Ihre Therapietreue in Bezug auf den Zeitpunkt der Einnhame. 0% heisst, Sie nehmen die Medikamente nie zum richtigen Zeitpunkt. 100% heisst, Sie nehmen alle Medikamente zum richtigen Zeitpunkt.

Einnahmetherapietreue mit Blister:_____%	Einnahmetherapietreue ohne Blister:_____%
Zeitliche Therapietreue mit Blister:_____%	Zeitliche Therapietreue ohne Blister:_____%

30. Wie würden Sie sich gesundheitlich ohne den Pharmis® Medikamenten Blister fühlen? Ich gebe Ihnen 6 Antwortmöglichkeiten:

viel besser	eher besser	gleich	Eher schlechter	Viel schlechter	Weiss ich nicht
☐	☐	☐	☐	☐	☐

31. Die Patientenbefragung ist hiermit beendet. Haben Sie noch zusätzliche Vorteile, Nachteile oder Kommentare zum Pharmis® Medikamenten Blister, welche Sie gerne anbringen möchten?

Ich möchte mich ganz herzlich bei Ihnen für die Teilnahme **bedanken**.

A3.4 Final board decision of the Ethikkommission Beider Basel for the qualitative patient interviews

Ethikkommission beider Basel EKBB

Präsident
Prof. André P. Perruchoud
Vizepräsidenten
Prof. Thomas Kühne
Prof. Marius Kränzlin

Herrn
Prof. Dr. K. Hersberger
Pharmazentrum
Klingelbergstrasse 50
4056 Basel

Basel, 26. Dezember 2013

55/11:
Use of Pharmis® drug blister in Switzerland - an evaluation at pharmacist's, physician's and patient's level

Sehr geehrter Herr Prof. Hersberger

Besten Dank für Ihr Schreiben datiert vom 12. Dezember 2013 samt Beilagen. Die Ethikkommission beider Basel ist mit der Verlängerung der obgenannten Studie bis zum 30. Juni 2014 sowie mit der Erweiterung auf die Kantone Aargau/Solothurn einverstanden.

Wir hoffen, Ihnen mit dieser Bestätigung zu dienen und verbleiben

mit freundlichen Grüssen

Prof. M. Kränzlin
im Namen der Ethikkommission
beider Basel / EKBB

Prof. A. P. Perruchoud
Präsident der Ethikkommission
beider Basel / EKBB

Geschäftsführerin: Frau Irene Oberli, Hebelstrasse 53, 4056 Basel, Telefon 061 268 13 50, Fax 061 268 13 51, ekbb@bs.ch, www.ekbb.ch

A3.5 Topic guide for the qualitative interviews

Qualitatives Interview zum Pharmis® Blister 2013 Nathalie Spalinger

Demographische Daten				
Datum / Zeit				
Geschlecht	☐ m	☐ w	**Geburtsjahr**	
erwerbstätig	☐ Ja	☐ nein		
andere Medis	☐ Ja	☐ nein		
Wohnsituation	☐ alleine	☐ mit anderen Personen im gleichen Haushalt		
Ausbildung	☐ Keinen Abschluss ☐ Hauptschulabschluss	☐ Matur ☐ Hochschulabschluss ☐ Promotion		
Code	Patienten-Code:	Apotheken-Code:		

Wir sind von der Uni Basel und arbeiten an einer Studie zum Pharmis® Medikamenten-Blister. Da Sie den Blister schon länger gebrauchen, würden wir Ihnen gerne ein paar Fragen stellen und von Ihren Erfahrungen profitieren. Sie dürfen frei antworten. Damit wir keine Antworten verlieren, nehmen wir das Interview auf Tonband auf.

Einstieg	- Wie sind sie zum Blister gekommen?
Akzeptanz	- Wie war das am Anfang, als Ihnen der Blister empfohlen wurde? - Wer hat Ihnen den Blister empfohlen

Management/Handhabung	
- Welche Erfahrungen haben Sie bezüglich der Handhabung mit dem Blister gemacht?	
Medikamenten-entnahme	- Denken Sie mal an das Herausnehmen der Medikamente. Wie machen Sie das? (vorführen) - Manche Patienten haben Schwierigkeiten beim Herausdrücken der Medikamente, wie ist dies bei Ihnen?
Funktionalität	- Was ist Ihnen wichtig bezüglich der Medikamenteneinnahme im Alltag? - Was bringt Ihnen der Blister?
Organisation	- Denken Sie daran, dass sie wöchentlich einen neuen Blister brauchen, wie haben Sie sich organisiert?
Mobilität	- Wie mobil sind Sie mit dem Blister? - Wie machen Sie das, wenn Sie einen Tag verreisen/in die Ferien gehen?

Pharmaceutical Care Research Group

Qualitatives Interview zum Pharmis® Blister 2013 Nathalie Spalinger

Kommunikation / Instruktion	- Wie gestaltet sich der Kontakt zur Apotheke? - Wie wurde Ihnen die Handhabung des Blisters erklärt? - Wie werden Sie bei einer Therapieänderung informiert?
Sicherheit	- In welcher Weise gibt Ihnen der Blister ein Gefühl von Sicherheit? - Wie kontrollieren Sie, ob Sie ihre Medikamente eingenommen haben?

Design	
- Was gefällt Ihnen am Blister und was nicht? (Demo-Modell zeigen)	
Grösse	- Wie finden Sie die Grösse des Blisters?
Kalender	- Wie finden Sie die Kalenderfunktion des Blisters?
Identifikation	- Wie finden Sie den Umfang der Informationen auf dem Blister? (Tablettenbeschreibung) - Wie gut wissen Sie über die einzelnen Tabletten Bescheid?

Therapietreue
- Was sagt Ihnen der Begriff Therapietreue? / Was stellen Sie sich darunter vor? *Definition:* so wie verschrieben/ an jedem Tag/ zur richtigen Zeit
- Wer hat Ihnen den Aspekt Therapietreue erklärt? - Wie wichtig ist Ihnen die Therapietreue? - Wie würden Sie Ihre eigene Therapietreue einschätzen? (auf einer Skala von 0-10)

0	1	2	3	4	5	6	7	8	9	10

- Fällt Ihnen gerade noch was ein? / Möchten Sie noch etwas sagen?

Notizen
□ Patientenhistory

Pharmaceutical Care Research Group

A4.1 Final board decision of the Ethikkommission Beider Basel for the Medication Blister Study

Beschlussmitteilung der Ethikkommission beider Basel

Die Ethikkommission beider Basel hat an ihrer Sitzung vom 21. Februar 2012 (in der Zusammensetzung, wie sie auf Seite 2 wiedergegeben ist) sowie an der Ausschuss-Sitzung vom 18. Juni 2012 das nachstehende Forschungsprojekt eingehend begutachtet.

Titel des Forschungsprojektes Ref.Nr. EK: **54/12**

Electronic multidrug blister packs to improve clinical and humanistic outcomes in patients after hospital discharge

Prüfer/in

Name, Vorname, Titel:	Hersberger, Kurt, Prof. Dr. sc. nat. & Hug, Balthasar, PD Dr. med.
Funktion:	Head Pharmaceutical Care, Uni Basel & LA Innere Medizin
Adresse:	Pharmazentr., Klingelbergstr. 50, 4056 Basel & Universitätsspital, 4031 Basel

Die Ethikkommission stützt ihre Beurteilung auf die Unterlagen, wie sie im beiliegenden "Antrag auf Begutachtung" vom 06. Februar 2012 (korr.: 04. Juni 2012) abschliessend aufgezählt sind.

X normales Verfahren ☐ vereinfachtes Verfahren ☐ Nachbegutachtung

Die Ethikkommission kommt zu folgendem **Beschluss**:

X **A positiv**
☐ **B positiv mit Bemerkungen** (siehe Seite 2ff)
☐ **C mit Auflage** (siehe Seite 2ff)
Nachbegutachtung durch Ethikkommission notwendig ☐
schriftliche Mitteilung an Ethikkommission ausreichend ☐
☐ **D negativ (mit Begründung und Erläuterung für die Neubeurteilung)** (siehe Seite 2ff)
☐ **E Nicht-Eintreten (mit Begründung)** (siehe Seite 2ff)

Der Beschluss gilt auch für die im "Antrag auf Begutachtung" gemeldeten weiteren Prüfer/innen im Zuständigkeitsbereich der Ethikkommission.

Pro Memoria: **Pflichten des/der verantwortlichen Prüfers/in**
- Geprüfte Produkte und Vergleichsprodukte (Arzneimittel und Medizinalprodukte) müssen - zur Sicherstellung der Qualität und der Sicherheit - fachgerecht hergestellt, evaluiert und eingesetzt werden.
- Meldepflicht bei:
  a) schwerwiegenden unerwünschten Ereignissen (serious adverse events) unverzüglich
  b) neuen Erkenntnissen, die während des Versuchs verfügbar werden und die Sicherheit der Versuchspersonen sowie die Weiterführung des Versuchs beeinflussen können
  c) Änderung des Protokolls (Versuchsplans)
  d) Ende oder Abbruch der Studie
- Zwischenbericht: einmal pro Jahr
- Meldungs- oder Bewilligungspflicht von Studien bei Swissmedic bzw. anderen Bundes- oder kantonalen Behörden - sofern erforderlich (bei sponsorisierten Studien ist dies die Pflicht des Sponsors)
- Schlussbericht

Für die Ethikkommission:

Ort, Datum: Basel, 12. Juli 2012 Name(n): Prof. A. P. Perruchoud
Prof. M. Kränzlin

Unterschrift(en):

A4.2 Case report form hospital screening, assessment and recruiting (CRF T-1)

UNIVERSITÄT BASEL

Dep Pharm Wiss
Pharmaceutical Care

Fabienne Böni
Studienkoordination

Klingelbergstrasse 50
CH-4056 Basel

Tel. 061 267 15 29 / 077 442 85 23
Fax 061 267 14 28
E-Mail: fabienne.boeni@unibas.ch

Datum:_____

Visum: _____

PatCode:

T-1 – CRF HOSP

Fallnr./Randomisierungsnr.		PatientenCode	
Indexhospitalisation	__/__/_____	Station / Zimmer	
Randomisierung	☐I ☐K	*nach Einverständnis des Patienten einfügen*	

Screening

ISMed

Einschlusskriterien			**Ja**	**Nein**
Geburtsdatum (tt.mm.jjjj):	___/___/_____	Patient ≥ 18 Jahre	☐	☐
Versichert durch eine CH Grundversicherung			☐	☐
Wohnhaft im Kanton BS/BL			☐	☐
Patient ist der deutschen Sprache mächtig			☐	☐
Ausschlusskriterien			**Nein**	**Ja**
Geschlecht	☐m ☐w	Schwangerschaft?	☐	☐
Transplantierte/r Patient/in			☐	☐
Diagnostizierte Demenz			☐	☐
Blindheit			☐	☐
Polytoxomanie			☐	☐

Visite/Kardex

Einschlusskriterien	**Ja**	**Nein**
Verschreibung von ≥ 4 verschiedenen oralen festen Medikamenten	☐	☐
Ausschlusskriterien	**Nein**	**Ja**
> 2 Medikamente nicht für Pharmis geeignet (z.B. Flüssigkeiten, Inhalatoren, Externa etc.)	☐	☐
Orale Antikoagulation mit Vitamin K Antagonisten: ☐ Marcoumar® ☐ Sintrom®	☐	☐
durch die verantwortliche Pflegefachfrau als „kognitive beeinträchtigt“ evaluiert	☐	☐
ist in andere Studie mit klinischen Prüfpräparaten involivert	☐	☐
PatientIn wird in ein Heim / in ein Spital übertreten	☐	☐

Case Management		
Hat Case Management:	☐ Ja	☐ Nein
Abklärung Case Management:		

Ausschluss während CRF T-1					
Datum: ___/___/_____					
Stufe:	☐ Screening 1	☐ Screening 2	☐ Visit 1	☐ Visit 2	☐ BD Interview
Grund:					

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T-1 – CRF HOSP

Rekrutierung und Interview zur Erfassung von demographischen Parametern

Vorbereitung: Couvert Patienteninformation/Einverständniserklärung

Visit 1

„Guten Tag Frau/Herr <...>.
Ich bin <...> von der Pharmazie.
Wir untersuchen in einer Studie eine Strategie für das Medikamentenmanagement zu Hause. Wir haben Sie ausgewählt, weil Sie viele Medikamente haben und weil Sie nach dem Spital Sie wieder nach Hause gehen werden. Durch die Teilnahme haben Sie die Möglichkeit ein innovatives System auszuprobieren und gratis von den verbundenen Dienstleistungen von der Apotheke zu profitieren.

Ich lasse Ihnen die Information für die Studie da, dann können Sie mal reinschauen, wenn Sie mögen. Ich oder ein Kollege/eine Kollegin komme/t heute Nachmittag noch einmal vorbei.
Patienteninformation und informed consent zeigen und abgeben.

Falls Ablehnung: „Darf ich Sie nach Ihrem Ablehnungsgrund fragen?“
Grund für Nichtteilnahme an Studie: _____
(ev. als Einwand „Sie dürfen auch danach noch entscheiden ob sie mitmachen wollen oder nicht.“)

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Visit 2

Vorbereitung: Schema Studienablauf auf A4, Schema Medikamentenanwendung A4, Randomisierungsliste, Randomisierungcouvert, Kalender, 1 Packung ASS cardio, 1 Packung verblisterte Tabletten, Fragebogen SF12, Studienverordnungsblatt

„Guten Tag Frau/Herr <...>. Wie geht es Ihnen?
Ich bin <...> von der Pharmazie. Wir haben uns vorher bei der Visite kennengelernt, können Sie sich erinnern?“

„Ich habe Ihnen heute Morgen die Information zu der Studie schon abgegeben. Konnten Sie sie schon anschauen? Ich werde Ihnen jetzt die wichtigsten Punkte der Studie noch einmal kurz mit Ihnen durchgehen, ist das so für Sie ok?“

Falls nein: „Darf ich Sie nach Ihrem Ablehnungsgrund fragen?“
Grund für Nichtteilnahme an Studie: _____
(ev. als Einwand „Sie dürfen auch danach noch entscheiden ob sie mitmachen wollen oder nicht.“)
„Unterbrechen Sie mich, wenn Sie etwas nicht verstehen oder etwas fragen wollen, jederzeit.“

Studie anhand Patienteninformation erklären. Wichtigste Punkte:

- Zufällige Einteilung in 2 Gruppen; Gruppe 1: Pharmis Blister, Gruppe 2: normal, wie bisher
- Studienstart ab Austritt
- Studiendauer 12 Monate oder bis zur Rehosp
- Keine Blutproben
- Keine Umstellung der Medikamente
- Anonyme Auswertung
- Auf medizinische Behandlung oder Arztwahl keinen Einfluss
- Sie sind jederzeit berechtigt, ohne die Angabe von Gründen, aus der Studie auszutreten. Dadurch entsteht Ihnen in keinster Weise ein medizinischer Nachteil

Danach, aus dem Gespräch hinaus: „wie ist das denn bei Ihnen zu Hause...“

Ein- /Ausschlusskriterien	**Ja**	**Nein**
Organisieren Sie die Einnahme Ihrer Medikamente selber? ☐ Wird die Einnahme Ihrer Medikamente durch eine/n Angehörige/n organisiert? ☐ Erstverordnung (bisher keine Medikamente)? ☐ ***Kriterium für Ein-/Ausschluss: mind. 1 der oberen 3 trifft zu* = Ja**	☐	☐
Wer hilft Ihnen?		
Wie wird Ihnen geholfen?		
Beziehen Sie Ihre Medikamente in einer Apotheke?	☐	☐
Benutzten Sie bereits eine Hilfestellung oder ein Ritual um sich an die Einnahme Ihrer Medikamente	☐	☐

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zu erinnern?“		
Falls Ja: was benutzen Sie als Hilfestellung um sich an Ihre Medikamente zu erinnern? ☐ einen Wochendispenser Welchen: _____ ☐ Natel ☐ Wecker ☐ Sonstige: _____		
Benutzen Sie einen Medikamentenblister von Pharmis oder Medifilm als Hilfestellung?	☐	☐
Zeigen Sie mir doch einmal, wie Sie eine Tablette aus diesem Blister rauszudrücken? *Fremdbeurteilung: Ok?*	☐	☐

„Vielen Dank“

„Haben Sie jetzt gerade noch Fragen zum Studienablauf oder sonstigem?“

Studienteilnahme	**Ja**	**Nein**
„Würden Sie an der Studie teilnehmen?“	☐	☐
PatientIn ist unentschlossen	☐	☐
Falls nein: „Das finde ich sehr schade. Können Sie mir sagen warum Sie nicht teilnehmen möchten?“ *Grund für Ablehnung der Studienteilnahme*: _____		

➔ ***Falls Studienteilnahme:*** „Das freut mich sehr!“

„Dann können wir gleich die Einverständniserklärung zusammen ausfüllen (*auspacken und zeigen*).

Informed consent zeigen und gemeinsam mit Patient ausfüllen.

➔ ***Falls zögerlich***: „Ich gebe Ihnen gerne noch etwas Zeit zum Entscheiden. Sie haben ja hier die ausführliche Information, die Sie noch einmal in Ruhe durchlesen können. Es ist auch das Formular zum Einverständnis der Studienteilnahme dabei, das Sie ausfüllen und unterschreiben können, wenn Sie sich entschieden haben an der Studie teilzunehmen. Ich werde später wieder kommen und alle Ihre Fragen beantworten. Wenn Sie wünschen kann ich Ihnen die Studie auch noch detaillierter erklären“. → *falls ja, weiter mit Zusatzinfos.*

„Wann darf ich wieder vorbei kommen?“

Inkl. Abklärung Austritt (wann?)!

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Visit 2: Informed Consent unterschrieben

Ein- /Ausschlusskriterien	Ja	Nein
Hat der Patient die Einverständniserklärung verstanden und unterschrieben?	☐	☐
Falls nein: „Das finde ich sehr schade aber ich respektiere Ihre Entscheidung voll und ganz. Können Sie mir sagen warum Sie nicht teilnehmen möchten?“ *Grund für Ablehnung der Studienteilnahme*: _____		

➔ Falls ja: „Vielen Dank dass Sie sich bereit erklären, an dieser Studie teilzunehmen.“

„Ok, dann können wir ja jetzt loslegen. Ich werde Ihnen jetzt erklären welche weiteren Schritte wir zusammen machen.

1. Wir werden jetzt Ihre Gruppeneinteilung herausfinden. Danach mache ich ein Interview mit Ihnen, um Ihre Grunddaten, wie wir das nennen, zu erfassen. Das geht ca. 15 Minuten. Wenn wir mit dem Teil durch sind, werde ich Ihnen einen Fragebogen geben, den Sie selber ausfüllen können.
2. Vor Ihrem Austritt aus dem Spital werde ich mit Ihnen die Medikamente genauer anschauen, die Sie nach dem Austritt nach Hause einnehmen sollen. Dann erkläre ich Ihnen auch, wie der weitere Ablauf aussieht.

Wenn Sie mögen, werden wir den ersten Schritt gerade jetzt anhängen, oder ich komme morgen noch einmal vorbei.“

➔ *Weiterführung sofort* ☐

➔ *Weiterführung morgen* ☐: „Kein Problem. Dann werde ich oder einE StudienmitarbeiterIn morgen kommen um mit Ihnen das Interview zu machen.“

Gruppenzuteilung: Randomisierungcouvert öffnen und Pat zeigen/mitteilen.

Falls Interventionsgruppe Abklärung wg

- *Medikamentenbezug (Notfall-Apo ok?)*
- *Krankenkasse*
- *Einstellung zu Generika*

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Basisdateninterview

Falls am nächsten Tag: Begrüssung, Vorstellung, Erklärung, was jetzt gemacht wird, Abklärung ob Fragen von Seiten des Patienten vorhanden sind, Beantwortung.

„Gut, dann fangen wir die Befragung mit ein paar kurzen Aufgaben an. Ich möchte Sie nochmals erwähnen, dass die Befragung ca. 30 min. dauert und Ihre Angaben anonym bleiben. Falls Sie Fragen aus verschiedenen Gründen nicht beantworten wollen, dürfen Sie jederzeit eine Antwort verweigern. Sie können auch jederzeit die Befragung für beendet erklären."

Aufgaben

1. **Haben Sie eine Lesehilfe?**
   ☐ Ja → bitte anziehen
   ☐ Nein

2. **Nun gebe ich Ihnen eine Packung Aspirin Cardio® und bitte Sie diesen Text laut vorzulesen. („Aufbewahrungstemperatur")**
   ☐ ok ohne Zögern ☐ ok mit wenig Zögern ☐ ok mit vielen Fehlern ☐ nicht ok
   Falls Pat nicht vorlesen kann, selber laut vorlesen, damit man Aufgabe 6 ausführen kann

3. **Nehmen Sie bitte einen Streifen mit Medikamenten aus der Verpackung heraus.**
   ☐ ok ohne Zögern ☐ ok mit wenig Zögern ☐ ok mit vielen Problemen ☐ nicht ok

4. **Heute ist _____(Wochentag), bitte geben Sie mir die Tablette für heute _____**
   ☐ ok ohne Zögern ☐ ok mit wenig Zögern ☐ ok mit vielen Problemen ☐ nicht ok

5. **Wie einfach empfanden Sie das Herausdrücken der Tablette? So können Sie Ihre Antwort geben: 0 heisst „nicht einfach" und 100 heisst „sehr einfach".**
   _____ VAS

6. **Sie haben vor wenigen Minuten einen Text auf der Packung vorgelesen. Können Sie mir sagen, bei welcher Temperatur Sie das Medikament aufbewahren sollten?**
   _____°C ☐ Richtig ☐ Falsch

Patientencharakteristiken

Nun kommen ein paar allgemeinen Fragen zu Ihrer Lebenssituation. Diese Fragen sind alle auf die Zeit vor Ihrem Spitalaufenthalt bezogen.

1. **Wie lange brauchen Sie von zu Hause bis zum nächsten Spital?**
   _____ [min]
   ☐ keine Angabe (=0)

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2. Welches ist der höchste Ausbildungsgrad den Sie abgeschlossen haben oder jetzt absolvieren?

- ☐ obligatorische Schulzeit
- ☐ Berufslehre / Berufsschule
- ☐ Höhere Berufsausbildung (z.B. Meister, eidg. Diplom)
- ☐ Matura
- ☐ Fachhochschule
- ☐ Universität
- ☐ keine Angabe

3. Sind Sie berufstätig?

☐ Ja
3.1 Was ist Ihr Beruf? _____
3.2 Als was sind Sie momentan tätig? _____
3.3 In welchem Pensum sind Sie tätig? _____%
3.4 Sind Sie in Ausbildung? ☐Ja ☐Nein

☐ Nein 3.5 Sind Sie
- ☐ Hausfrau/-mann
- ☐ pensioniert
- ☐ arbeitsunfähig/IV
- ☐ arbeitslos

☐ keine Angabe

4. Leben Sie alleine oder mit anderen Personen im gleichen Haushalt?

- ☐ mit dem / der LebenspartnerIn?
- ☐ mit anderen Personen im gleichen Haushalt
- ☐ alleine
- ☐ keine Angabe

5. Sie müssen nächste Woche z.B. einkaufen gehen. Wie einfach wird es für Sie sein, wie mobil werden Sie sein auf einer Skala von 0-100? Ich gebe Ihnen ein Bsp.: 0=komme nicht aus dem Haus; 100= erreiche problemlos Geschäfte

_____ VAS

☐ keine Angabe

6. Haben Sie zittrige Hände?

- ☐ Ja
- ☐ Nein
- ☐ keine Angabe

7. Sind Sie eingeschränkt in Ihren Fingerfertigkeiten (Bsp: Schuhbändel binden)

- ☐ Ja
- ☐ Nein
- ☐ keine Angabe

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8. Tun Ihnen Ihre Hände weh?

☐ Ja
☐ Nein
☐ keine Angabe

9. Wenn Sie an die Zeit denken bevor Sie ins Spital gekommen sind, empfinden Sie Ihr Leben als stressig? Ich gebe Ihnen 5 Antwortmöglichkeiten:

☐ immer ☐ oft ☐ manchmal ☐ selten ☐ nie
☐ keine Angabe

10. Wenn Sie an die Zeit denken bevor Sie in das Spital gekommen sind, fühlten Sie sich in Ihrer Lebenssituation überfordert?

☐ immer ☐ oft ☐ manchmal ☐ selten ☐ nie
☐ keine Angabe

Wir kommen jetzt zu Gesundheitsthemen

11. Denken Sie an die letzten 2 Wochen vor der Hospitalisation. Beschreiben Sie ihren gegenwärtigen Gesundheitszustand. Ich gebe Ihnen 5 Antwortmöglichkeiten:

☐ sehr gut ☐ gut ☐ mässig ☐ schlecht ☐ sehr schlecht
☐ keine Angabe

12. Wie stark achten Sie im Allgemeinen auf Ihre Gesundheit? Ich gebe Ihnen 5 Antwortmöglichkeiten:

☐ sehr stark ☐ stark ☐ mittelmässig ☐ weniger stark ☐ gar nicht
☐ keine Angabe

13. Waren Sie in den letzten 3 Monaten im Spital? (stationär)

☐ Ja
☐ Ja, als Notfall
☐ Nein
☐ keine Angabe

14. Wie oft gingen Sie in den letzten 12 Monaten in die Apotheke?

☐ < 1x im Jahr ☐ 1-2x im Jahr ☐ 3-6x im Jahr ☐ 1-3x im Monat ☐ ≥ 1x pro Woche
☐ keine Angabe

15. Fühlen Sie sich gut betreut durch Ihre Apotheke?

☐ Ja
☐ Nein
☐ keine Angabe

16. Wie oft gingen Sie in den letzten 12 Monaten zum Hausarzt?

☐ < 1x im Jahr ☐ 1-2x im Jahr ☐ 3-6x im Jahr ☐ 1-3x im Monat ☐ ≥ 1x pro Woche
☐ keine Angabe

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17. Fühlen Sie sich gut betreut durch Ihren Hausarzt?

☐ Ja
☐ Nein
☐ keine Angabe

18. Benutzen Sie momentan, d.h. bevor, während und/oder nachdem Sie in das Spital gekommen sind ein Medikament, welches Sie selber in der Apotheke / Drogerie gekauft haben?

☐ Ja

Medikament	Stärke	Dosis				Bemerkung

Möglichst Wortgetreu dokumentieren, ev. genauere Infos verlangen. In Medikamentenliste eintragen → CRF ML

☐ Nein
☐ keine Angabe

19. Haben Sie früher einmal eine Nebenwirkung eines Medikamentes erlitten?

☐ Ja Welche? _____
Durch welche(s) Medikament(e)? _____
☐ bisher keine Medikamenteneinnahme
☐ Nein
☐ keine Angabe

20. Manchmal überlegen Patienten, ihre rezeptpflichtigen Medikamente aus Kostengründen nicht einzulösen. Trifft das für Sie zu?

☐ Ja
☐ Nein
☐ keine Angabe

„Vielen Dank für die Beantwortung der Fragen. Nun habe ich hier einen Fragbogen für Sie, welchen Sie bitte ausfüllen / wir gemeinsam ausfüllen. Beachten Sie, dass sich sämtliche Frage auf Ihre Situation vor dem Spitaleintritt beziehen. Ich bin hier. Fragen Sie, wenn etwas unklar sein sollte."

Beim Entgegennehmen des Fragebogens

„Vielen Dank für das Ausfüllen des Fragebogens. Wir sehen uns vor Ihrem Austritt wieder, wo ich mit Ihnen Ihre Medikamente besprechen werde und Ihnen erkläre, wie die Studie weitergeht. Ich wünsche Ihnen bis dahin gute Besserung. Auf Wiedersehen Frau/Herr <...>.

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T-1 – CRF HOSP

Erfassung im ISMed

Wohnort/Kanton:

Krankenkasse:

Eintrittsgrund:

- ☐ OP
- ☐ via Notfallstation
- ☐ elektiv
- ☐ Überweisung
- ☐ keine Angabe

Medikamente bei Eintritt

- ☐ Ja
- ☐ Nein

Hospitalisation in den letzten 3 Monaten vor der Indexhospitalisation?

- ☐ Ja
  - ☐ via Notfallstation
  - ☐ elektiv
  - ☐ keine Angabe
- ☐ Nein

Diagnoseliste

aus ISMed ausdrucken/exportieren!?

Anamnese	**ICD 10**	**Datum Erstdiagnose**	**Bemerkung**
☐ Allergie			
☐ Depression			
☐ Nikotinabusus			
☐ Alkoholabusus			
☐ Substanzenabusus/Polytoxomanie			
☐ Verdacht auf Non-Compliance			

Erfassung auf Station

Kognition		
UT: _____	Datum der Messung: __/__/_____	☐ nicht gemessen
DOS: _____	Datum der Messung: __/__/_____	☐ nicht gemessen
CAM: _____	Datum der Messung: __/__/_____	☐ nicht gemessen

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EintrittsV: Datum:_____ Visum: _____

AustrittsV: Datum:_____ Visum: _____

PatCode:

T-1 – CRF HOSP

Medikamentenliste

SPITALVERORDNUNG							AUSTRITTSVERORDNUNG						
Medikament (Form)	Stärke	Dosierschema				Bemerk./Änderung/Neu	Medikament (Form)	Stärke	Dosierschema				Bemerkung

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Nachbearbeitung (bis und mit T0)

Fremdbeurteilung

Ethnie: ☐ Kaukasier ☐ Asiate ☐ Schwarzafrikaner

Klinische Daten (letzter dokumentierter Wert vor Austritt mit Datum aus ISMed)

K	Na	Krea	BZ	HbA_{1c}	LDL	HDL	TG	BD	KG
__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__

+ Austrittsmedikation S.4 ausfüllen

Rücksprache Arzt

☐ Ja

Name des Arztes: _____

Betreff: _____

Art der Kontaktaufnahme: ☐ mündlich ☐ Telefon ☐ E-Mail Datum der Kontaktaufnahme: ___/___/____

☐ Nein

Rücksprache Pflege

☐ Ja

Name der Ansprechsperson: _____

Betreff: _____

Art der Kontaktaufnahme: ☐ mündlich ☐ Telefon ☐ E-Mail Datum der Kontaktaufnahme: ___/___/____

☐ Nein

Notiz:

Scores

SF-12	
MMAS-8	
BMQ	

Stammapotheke

Name _____

Adresse _____

PLZ/Ort _____

Telefon _____

Fax _____

Hausarzt

Name _____

Adresse _____

PLZ/Ort _____

Telefon _____

Fax

A4.3 Example of a case report form for a follow-up visit (at three month)

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T3 Follow-up *Kontrolle*

PatientenCode			
Indexhospitalisation	__/__/_____		
T0	__/__/_____		
Datum Interview	__/__/_____	Anfangszeit:	Endzeit:
InterviewerIn			
Randomisierung	☐I ☒K		

Vorbereitung: Kalender, Mediplan vom Austritt (für Änderungen!), Laptop, Drucker, Fragebögen QoL und Adherence, CRF Rehosp

Erinnerung erwünscht?

☐Nein
☐Ja

Per ☐E-Mail/ ☐Telefon/ ☐SMS

1. Versuch: __/__/_____ um ___.___Uhr
2. Versuch: __/__/_____ um ___.___Uhr
3. Versuch: __/__/_____ um ___.___Uhr
4. Erinnerungsbrief abgeschickt am __/__/_____

Sagen: Änderungen im Therapieplan notieren und zum Treffen mitbringen

 Bei bestätigter Rehospitalisation → „Ende“ (Dokumentationsblatt S.2 unten)!

Termin verpasst?

☐ Nein
☐ Ja

Erinnerungstelefon:

1. Versuch: __/__/_____ um ___.___Uhr
2. Versuch: __/__/_____ um ___.___Uhr
3. Versuch: __/__/_____ um ___.___Uhr
4. Erinnerungsbrief abgeschickt am __/__/_____

 Bei bestätigter Rehospitalisation → „Ende“ (Dokumentationsblatt S.2 unten)!

Notizen

	Datum	Visum

Medikamentenblister Studie EKBB 54/12 CRF T3 FU **K** / Version 3 vom 08.07.2013 / S. 1

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Interview

Guten Tag Herr / Frau _____
Schön, dass Sie kommen konnten. (0) Wie geht es Ihnen heute?

☐ sehr gut ☐ gut ☐ mittelmässig ☐ schlecht ☐ sehr schlecht
☐ keine Angabe

Wir werden nun eine Befragung von ca. 10 Minuten zusammen durchführen und dann gebe ich Ihnen 2 Fragebögen, die Sie hier selbstständig ausfüllen können. Wollen wir gleich anfangen, oder möchten Sie noch etwas fragen, bemerken?

_____

_____

Ich möchte gerne noch einmal betonen, dass alle Ihre Antworten anonym sind und Sie auch Antworten verweigern oder das Interview abbrechen dürfen.
Sie sind nun schon 3 Monate mit uns unterwegs, und wir sind neugierig zu erfahren, wie es Ihnen ergangen ist und welche Änderungen es in Ihrem Alltag rund um Ihre Medikamente gegeben hat.

Als erstes kommen Fragen zu Ihren Besuchen in der Apotheke.

1. Wann haben Sie das Spitalaustrittsrezept eingelöst?

Datum: ___/___/_____
☐ keine Angabe

2. Wie oft waren Sie seither in der Apotheke?

_____
☐ keine Angabe

3. Hatten Sie seit dem Spitalaustritt gemeinsam mit Ihrem Apotheker / Ihrer Apothekerin eine ausführliche Beratung zu der Organisation Ihrer Medikamente? (Polymedikations-Check)

☐ Ja (Datum aus History: ___/___/_____)
☐ Nein
☐ keine Angabe

Jetzt würden wir gerne ein paar Dinge über Ihre Arztbesuche erfahren.

4. Waren Sie seit dem Spitalaustritt bei Ihrem Hausarzt?

☐ Ja 4.1 Wie oft? ___
4.2 Wie viele davon waren Notfälle? ___
☐ Nein
☐ keine Angabe

5. Waren Sie seit dem Spitalaustritt bei (einem) Spezialisten (Spezialarzt)?

☐ Ja 5.1 bei (einem) Spezialisten für: _____
5.2 Wie oft? ___
5.3 Wie viele davon waren Notfälle? ___

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Visum:_____

PatCode:

☐ Nein
☐ keine Angabe

---

6. Sind Sie seit dem Spitalaustritt wieder ins Spital gekommen, nicht für einen Arztbesuch, sondern so, dass Sie auf Station übernachten mussten? (stationär)

☐ ja 6.1 War das geplant oder ein Notfall? ☐ Notfall → **weiter mit CRF REHOSP**
☐ geplant

☐ Nein

---

7. Haben Sie seit dem Spitalaustritt einen Termin beim HA, Spezialarzt, in der Apotheke gehabt den Sie nicht wahrnehmen konnten?

☐ ja beim 7.1 ☐ HA 7.1.1 Wie oft? ___
7.2 ☐ Spezialarzt 7.2.1 Wie oft? ___
7.3 ☐ in der Apotheke 7.3.1 Wie oft? ___

☐ Nein
☐ keine Angabe

Die nächsten Fragen befassen sich mit Ihrem Medikamentenmanagement zu Hause.

---

8. Wer holt Ihre Medikamente in der Apotheke?

☐ Patient selber ☐ Ehemann/Ehefrau ☐ Verwandte/r ☐ Bekannte/r ☐ die Apotheke bringts
☐ keine Angabe

---

9. Wo bewahren Sie bei Ihnen zu Hause die Medikamente auf?

☐ Küche ☐ Wohnzimmer ☐ Schlafzimmer ☐ Bad ☐ anderes:
☐ keine Angabe

---

10. Wer richtet bei Ihnen zu Hause die Medikamente?

☐ Patient selber ☐ Ehemann/Ehefrau ☐ Verwandte/r ☐ Bekannte/r ☐ Spitex
☐ keine Angabe

---

11. Benutzen Sie jetzt ein Dosett oder eine andere Einnahme bzw. Erinnerungshilfe für die Medikamente?

☐ Ja 10.1 Was benutzen Sie?
☐ Dosett gerichtet durch Apotheke / Drittperson
☐ Dosett gerichtet durch Patient
☐ Pharmis
☐ Medifilm
☐ SMS
☐ anderes: _____

10.2 Wer hat Ihnen die Einnahmehilfe empfohlen?
☐ Apotheke
☐ Arzt
☐ Bekannte / Verwandte
☐ eigene Erfindung des Patienten

10.3 Seit wann benutzen Sie diese Hilfe? _____
(Datum aus History falls vorhanden: ___/___/_____)

☐ Nein
☐ keine Angabe

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12. Wie erinnern Sie sich an die Einnahme Ihrer Medikamente?

☐ visuell ☐ Alarm ☐ durch eine Person ☐ anders:
☐ keine Angabe

13. Verbinden Sie einen bestimmten Tagesablauf mit der Einnahme Ihrer Medikamente?

☐ Mahlzeiten ☐ Zähneputzen ☐ Arbeit ☐ anderes:
☐ keine Angabe

Jetzt wollen wir einmal auf Ihren Medikamentenplan schauen.

14. Haben Sie von Ihrem Arzt ein neues Medikament bekommen oder wurde etwas in Ihrem alten Plan geändert?

Austrittsplan vorlegen

☐ Ja

Medikament	Stärke	neu	stopp	Dosis	Bemerkung
		☐	☐		
		☐	☐		
		☐	☐		
		☐	☐		
		☐	☐		

☐ Nein
☐ keine Angabe

Änderungen direkt ins Excelfile machen oder in den vorgelegten Austrittsplan. Bei Bedarf Counselling mit Hilfe der Karteikarten wiederholen.

15. Haben Sie in Ihrer ☐Apotheke / ☐Drogerie / ☐im Internet ein neues Medikament gekauft?

☐ Ja

Medikament	Stärke	neu	stopp	Dosis	Bemerkung
		☐	☐		
		☐	☐		
		☐	☐		
		☐	☐		
		☐	☐		

☐ Nein
☐ keine Angabe

16. Leiden Sie jetzt unter einer Nebenwirkung Ihrer Medikamente?

☐ ja 13.1 Welche? _____
13.2 Medikament(e)? _____
☐ Nein
☐ keine Angabe

So, das wärs schon gewesen mit dem Interview. Ich schlage vor, wir machen nun noch ein Datum für unseren nächsten Nachfolgetermin ab und danach können Sie noch die 2 Fragebögen selbstständig ausfüllen.

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17. Unser nächster Nachfolgetermin T6 ist in 3 Monaten, in der Woche vom___. Wann geht es Ihnen am besten? Es wird wieder ca. gleich lange dauern wie heute.

Datum: ___/___/_____ ___.___ Uhr

☐ Anruf zu einem späteren Zeitpunkt um den Termin abzumachen Woche: _____

Sie sind einverstanden, ca. 2 Tage vorher einen telefonischen Erinnerungsanruf zu bekommen?

☐ Ja Wann passt es Ihnen am besten? Erwünschte Tageszeit: _____

☐ Nein

Abgabe Fragebögen Adherence und SF-12

Vielen Dank für Ihre Angaben. Hier sind Ihre Fragebögen. Bitte nehmen Sie sich die Zeit, die Sie brauchen. Es gibt keine falschen Antworten. Falls Sie Fragen haben bin ich in der Nähe und Sie können mich rufen.

Die Fragebögen mitzugeben ist eine Option, aber eher nicht wünschenswert. Falls vom Patienten angesprochen: „Wir wären froh, wenn Sie die Fragebögen hier ausfüllen können, aber wenn Sie jetzt dringend gehen müssen gebe ich Ihnen die Fragebögen gerne mit einem Rückantwortcouvert mit. Ich bitte Sie jedoch sie schnellst möglich auszufüllen und zurückzuschicken, weil dies ja eine zeitnahe Erhebung sein soll. Es ist wichtig, dass wir sagen können, dass das was Sie uns hier angeben, nach 3 Monaten geschehen ist."

Abschluss

Ich danke Ihnen vielmals, dass Sie heute da waren und Auskunft gegeben haben. Die Informationen sind für uns sehr wertvoll. Wir sehen uns in 3 Monaten wieder. Sie dürfen mich jederzeit anrufen, wenn Fragen oder Probleme auftauchen, welche die Medikamente betreffen. Sie haben ja meine Nummer (*falls nicht, Natelnr. der Studienhotline auf Visitenkärtli notieren*). Ich wünsche Ihnen eine gute Zeit. Auf Wiedersehen Herr/Frau _____.

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Datum:_____

Visum:_____

PatCode:

Nachbearbeitung

Bedarf Kontaktaufnahme Arzt

☐ Ja Betreff: _____

Art der Kontaktaufnahme: ☐ Telefon ☐ Fax ☐ E-Mail Datum der Kontaktaufnahme: ___/___/_____

☐ Nein

Überweisung an den Arzt

☐ Ja Betreff: _____

Dringlichkeit: ☐ sofort ☐ in den nächsten Wochen ☐ Bespr. beim nächsten regulären Termin

☐ Nein

Pharmaceutical Care:

Notiz:

Scores

MPR	
SF-12	
MMAS-8	
Taking Comp	
Timing Comp	
B&C	

Bedarf Kontaktaufnahme Apotheke

☐ Ja ☐ Betreff: _____

Art der Kontaktaufnahme: ☐ Telefon ☐ Fax ☐ E-Mail Datum der Kontaktaufnahme: ___/___/_____

☐ History anfordern Bezug nehmen auf das Infofax Spez: Datum Bezug, Spezialitätenname, Stärke, Packungsgrösse, Anzahl Packungen, Rx und OTC Verkäufe

Art der Kontaktaufnahme: ☐ Telefon ☐ Fax ☐ E-Mail Datum der Kontaktaufnahme: ___/___/_____

☐ Nein

Major therapeutic change? ☐ Ja Datum: ___/___/_____ Anzahl: ___
Datum: ___/___/_____ Anzahl: ___
Datum: ___/___/_____ Anzahl: ___

☐ Nein

Datum:	Visum:

A4.4 Questionnaire Adherence

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Fragebogen zur Therapietreue

Auszufüllen durch PrüferIn			
PatientenCode			
Randomisierung	☐I ☐K		
Datum	___/___/_____	Anfangszeit:	Endzeit:
Visum PrüferIn		Follow-up T	

Sie nehmen Medikamente täglich für Ihre Krankheit ein. Patienten haben einige Probleme oder Verhaltensgewohnheiten bei der Medikamenten-Einnahme entdeckt und es interessiert uns, was Ihre Erfahrungen sind. Es gibt keine richtige oder falsche Antwort. Bitte beantworten Sie jede Frage gemäss Ihrer persönlichen Erfahrung im Umgang mit Ihren Medikamenten. Vielen Dank!

1. **Vergessen Sie manchmal, Ihre Medikamente zu nehmen?**
   ☐ nein ☐ ja → Wie oft in den letzten 4 Wochen?
   ☐ täglich ☐ mehr als 1x pro Woche ☐ 1x pro Woche ☐ jede zweite Woche ☐ 1x pro Monat
2. **Manchmal wird ein Medikament nicht genommen, und zwar aus einem anderen Grund, als Vergesslichkeit. Wenn Sie an die letzten 2 Wochen denken, gab es Tage, an welchen Sie Ihre Medikamente nicht genommen haben?**
   ☐ nein ☐ ja → Was war der Grund? _____
3. **Haben Sie jemals die Einnahme Ihrer Medikamente verringert oder gestoppt ohne Ihren Arzt/Ihre Ärztin zu informieren, weil Sie sich schlechter fühlten nach der Einnahme?**
   ☐ nein ☐ ja → Wie oft in den letzten 4 Wochen?
   ☐ täglich ☐ mehr als 1x pro Woche ☐ 1x pro Woche ☐ jede zweite Woche ☐ 1x pro Monat
4. **Wenn Sie reisen oder Ihr Zuhause verlassen, vergessen Sie manchmal Ihre Medikamente mitzunehmen?**
   ☐ nein ☐ ja → Wie oft in den letzten 4 Wochen?
   ☐ täglich ☐ mehr als 1x pro Woche ☐ 1x pro Woche ☐ jede zweite Woche ☐ 1x pro Monat
5. **Haben Sie Ihre Medikamente gestern genommen?**
   ☐ ja ☐ nein → Was war der Grund? _____
6. **Wenn Sie das Gefühl haben, dass Ihre Krankheit unter Kontrolle ist, hören Sie manchmal mit der Einnahme Ihrer Medikamente auf?**
   ☐ nein ☐ ja → Für welche Medikamente trifft das zu? _____
   _____
7. **Jeden Tag Medikamente zu nehmen, empfinden viele Personen als lästig. Fühlen Sie sich manchmal schikaniert, wenn Sie den Therapieplan für Ihre Krankheit genauestens einhalten müssen?**
   ☐ nein ☐ ja →
   Gar nicht schikaniert — Extrem stark schikaniert
8. **Wie oft haben Sie Mühe, sich an die Einnahme aller Ihrer Medikamente zu erinnern?**
   ☐ nie / selten ☐ hin und wieder ☐ manchmal ☐ fast immer ☐ immer

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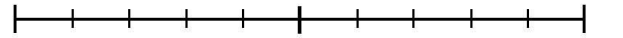
9. Haben Sie ein System benutzt, das Sie in der regelmässigen Entnahme unterstützt hat?

☐ nein ☐ ja →
- ☐ einen akustischen Alarm (Wecker, Natel usw.)
- ☐ ein visuelles Hilfsmittel (Aufbewahrung an speziell sichtbarem Ort, usw.)
- ☐ einen spezifischen Tagesablauf (Zähneputzen, nach dem Essen, vor dem zu Bett gehen)
- ☐ jemand erinnert mich daran
- ☐ andere: _____

10. Denken Sie an alle Medikamente, die Sie in den letzten 4 Wochen täglich nehmen mussten. Schätzen Sie mit einem Kreuz in die Skala, wie viele Einnahmen bzw. Anwendungen in Prozent Sie gemacht haben.



0: keine Einnahme / Anwendung gemacht
100: alle Einnahmen / Anwendungen gemacht

11. Nun schätzen Sie mit einem Kreuz in die Skala, wie genau Sie die Einnahmen / Anwendungen in Prozent in den letzten 4 Wochen mit einem Zeitfenster von +/- 1,5 Stunden gemacht haben.
Beispiel: alle Entnahmen morgens um 7 Uhr → 5.30-8.30, abends um 20 Uhr → 18.30-21.30 usw.

0: nie zum gleichen Zeitpunkt gemacht
100: immer zum gleichen Zeitpunkt gemacht

Gerne würden wir nun Ihre persönliche Überzeugung in Bezug auf Medikamente, die Sie aufgrund Ihrer Krankheit einnehmen, wissen. Dabei präsentieren wir Ihnen 4 Meinungsäusserungen von verschiedenen Patienten. Bitte kreuzen Sie jenes Kästchen an, welches Ihrer Meinung am ehesten entspricht. Es existieren keine richtigen/falschen Antworten. Herzlichen Dank!

	5 ++	4 +	3 +-	2 -	1 --
12. Meine derzeitige Gesundheit hängt von meinen Medikamenten ab.	☐	☐	☐	☐	☐
13. Manchmal mache ich mir Sorgen wegen der langfristigen Auswirkungen meiner Medikamente.	☐	☐	☐	☐	☐
14. Es bereitet mir Sorgen, Medikamente nehmen zu müssen.	☐	☐	☐	☐	☐
15. Meine Medikamente schützen mich davor, dass es mir schlechter geht.	☐	☐	☐	☐	☐

5 ich stimme voll und ganz zu
4 ich stimme eher zu
3 weder noch
2 ich stimme eher nicht zu
1 ich stimme überhaupt nicht zu

Vielen Dank!

A4.5 Short form 12 version 2 (quality of life questionnaire)

PatCode: _____

Ihre Gesundheit und Ihr Wohlbefinden

In diesem Fragebogen geht es um die Beurteilung Ihres Gesundheitszustandes. Der Bogen ermöglicht es, im Zeitverlauf nachzuvollziehen, wie Sie sich fühlen und wie Sie im Alltag zurechtkommen. ***Vielen Dank für die Beantwortung dieses Fragebogens!***

Bitte kreuzen Sie für jede der folgenden Fragen das Kästchen ☒ der Antwortmöglichkeit an, die am besten auf Sie zutrifft.

1. **Wie würden Sie Ihren Gesundheitszustand im Allgemeinen beschreiben?**

Ausgezeichnet	Sehr gut	Gut	Weniger gut	Schlecht
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. **Die folgenden Fragen beschreiben Tätigkeiten, die Sie vielleicht an einem normalen Tag ausüben. Sind Sie durch Ihren derzeitigen Gesundheitszustand bei diesen Tätigkeiten eingeschränkt? Wenn ja, wie stark?**

	Ja, stark eingeschränkt	Ja, etwas eingeschränkt	Nein, überhaupt nicht eingeschränkt
a Mittelschwere Tätigkeiten, z. B. einen Tisch verschieben, staubsaugen, kegeln, Golf spielen	☐ 1	☐ 2	☐ 3
b Mehrere Treppenabsätze steigen	☐ 1	☐ 2	☐ 3

PatCode: _____

3. Wie oft hatten Sie in den vergangenen 4 Wochen aufgrund Ihrer körperlichen Gesundheit folgende Schwierigkeiten bei der Arbeit oder anderen alltäglichen Tätigkeiten im Beruf bzw. zu Hause?

	Immer	Meistens	Manchmal	Selten	Nie
a Ich habe weniger geschafft als ich wollte	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Ich konnte nur bestimmte Dinge tun	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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

	Immer	Meistens	Manchmal	Selten	Nie
a Ich habe weniger geschafft als ich wollte	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Ich konnte Dinge nicht so sorgfältig wie üblich tun	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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

Überhaupt nicht	Etwas	Mäßig	Ziemlich	Sehr
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

PatCode: _____

6. In diesen Fragen geht es darum, wie Sie sich fühlen und wie es Ihnen in den vergangenen 4 Wochen gegangen ist. Bitte kreuzen Sie in jeder Zeile die Zahl an, die Ihrem Befinden am ehesten entspricht. Wie oft waren Sie in den vergangenen 4 Wochen…

		Immer	Meistens	Manchmal	Selten	Nie
a	ruhig und gelassen?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b	voller Energie?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c	entmutigt und traurig?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. 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
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Vielen Dank für die Beantwortung dieser Fragen!

Auszufüllen durch PrüferIn			
PatientenCode			
Randomisierung	☐I ☐K		
Datum	___/___/_____	Anfangszeit:	Endzeit:
Visum PrüferIn		Follow-up T	

A4.6 Patient satisfaction questionnaire

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Visum: _____

PatCode:

Fragebogen zur Patientenzufriedenheit

Auszufüllen durch PrüferIn			
PatientenCode			
Randomisierung	☐I ☐K		
Datum	___/___/_____	Anfangszeit:	Endzeit:
Visum PrüferIn		Follow-up T12	

Sie haben 12 Monate in der Medikamentenstudie mitgemacht. Herzliche Gratulation! Uns interessiert, welche Erfahrungen Sie gemacht haben und wie Sie mit Ihrer Medikamentenorganisation und mit unseren Dienstleistungen zufrieden sind. Der Fragebogen besteht aus 2 Teilen, Medikamentenorganisation und Studie. Es gibt kein „richtig" oder „falsch", bitte kreuzen Sie an, ob die Aussagen für Sie zutreffen.

Fragen		**Antwortskala**				
Damit wir diesen Fragebogen korrekt auswerten können, prüfen wir zuerst die Antwortskala: Meine Lieblingsfarbe ist: _____ (bitte ausfüllen und bei 0 ergänzen).		1 **trifft voll zu**	2 **trifft eher zu**	3 **trifft eher nicht zu**	4 **trifft gar nicht zu**	0 weiss nicht
0	_____ ist eine wunderschöne Farbe	☐	☐	☐	☐	☐
TEIL 1 SYSTEM FÜR DIE MEDIKAMENTENORGANISATION IM ALLTAG Unter „**System** für die Medikamentenorganisation im Alltag" verstehen wir die Strategie, die Sie zu Hause verwenden, um Ihre Medikamente zu richten, vorzubereiten und/oder sich an die Einnahme zu erinnern, z.B. Benutzung einer Medikamentenbox, stellen eines Weckers, Aufbewahrung in einem speziellen Kasten.		1 **trifft voll zu**	2 **trifft eher zu**	3 **trifft eher nicht zu**	4 **trifft gar nicht zu**	0 weiss nicht
1	Mein **System** für die Medikamentenorganisation im Alltag: _____ (bitte beschreiben und bei Bedarf und Kommentar aufzeichnen)					
2	Ich bin mit meinem System zufrieden	☐	☐	☐	☐	☐
3	Ich habe Mühe mit der Handhabung meines Systems	☐	☐	☐	☐	☐
4	Mein System verwirrt mich	☐	☐	☐	☐	☐
5	Mein System schränkt mich ein	☐	☐	☐	☐	☐
6	Mein System hilft mir, dass ich die Medikamente korrekt nehme (= wie vorgesehen/wie verordnet)	☐	☐	☐	☐	☐
7	Mein System gibt mir Sicherheit, meine Medikamente korrekt anzuwenden	☐	☐	☐	☐	☐
8	Ich würde einem Freund/einer Freundin mein System weiterempfehlen	☐	☐	☐	☐	☐

Weiter auf der nächsten Seite →

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Datum: _____

Visum: _____

PatCode:

TEIL 2 STUDIE Als zweites möchten wir gerne erfahren, wie Sie die Studie erlebt haben.		1 **Trifft voll zu**	2 **trifft eher zu**	3 **trifft eher nicht zu**	4 **trifft gar nicht zu**	0 weiss nicht
9	Insgesamt bin ich mit der Studie zufrieden	☐	☐	☐	☐	☐
10	Alle Interviews und Beratungen wurden mit angemessener Diskretion durchgeführt	☐	☐	☐	☐	☐
11	Das Studienpersonal hat sich für die Gespräche ausreichend Zeit genommen	☐	☐	☐	☐	☐
12	Die Fragen in den Interviews/Fragebögen waren verständlich formuliert	☐	☐	☐	☐	☐
13	Die Anzahl der Fragen in den Interviews/Fragebögen war zu hoch	☐	☐	☐	☐	☐
14	Die Fragen in den Interviews/Fragebögen waren unangenehm	☐	☐	☐	☐	☐
15	Es stört mich, dass es in der Studie keine finanzielle Entschädigung gibt	☐	☐	☐	☐	☐
16	Ich würde einem Freund/einer Freundin empfehlen, an der Studie teilzunehmen	☐	☐	☐	☐	☐
Im Spital…						
17	… wurde ich genügend informiert, sodass ich verstanden habe, worum es in der Studie geht	☐	☐	☐	☐	☐
18	… war mir die Anzahl der Interviews/Fragebögen zu viel	☐	☐	☐	☐	☐
Das Austrittsgespräch über meine Medikamente…						
19	… enthielt alle Informationen über meine Medikamente, die wichtig für mich sind	☐	☐	☐	☐	☐
20	… hat mich Neues über meine Medikamente gelehrt	☐	☐	☐	☐	☐
21	… hat zu lange gedauert	☐	☐	☐	☐	☐
22	… war in einer gut verständlichen Sprache	☐	☐	☐	☐	☐
23	… war zu wenig strukturiert	☐	☐	☐	☐	☐
24	… enthielt zu viele Informationen	☐	☐	☐	☐	☐
25	… hätte ich lieber als schriftliche Information gehabt	☐	☐	☐	☐	☐
26	… hat mir Sicherheit gegeben, meine Medikamente korrekt anzuwenden	☐	☐	☐	☐	☐
27	… hat mir Vertrauen in meine Medikamente gegeben	☐	☐	☐	☐	☐
28	… hat meine Medikamentenorganisation zu Hause unterstützt	☐	☐	☐	☐	☐

Weiter auf der nächsten Seite →

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Das Telefoninterview…		1 Trifft voll zu	2 trifft eher zu	3 trifft eher nicht zu	4 trifft gar nicht zu	0 weiss nicht
29	… hat zu einem guten Zeitpunkt stattgefunden	☐	☐	☐	☐	☐
30	… hat zu lange gedauert	☐	☐	☐	☐	☐
31	… hat mir das Gefühl gegeben, gut aufgehoben zu sein	☐	☐	☐	☐	☐
32	… hat meine Medikamentenorganisation zu Hause unterstützt	☐	☐	☐	☐	☐
Die Nachfolgetermine…						
33	… haben zu lange gedauert	☐	☐	☐	☐	☐
34	… haben zu häufig stattgefunden	☐	☐	☐	☐	☐
35	… wurden in einer angenehmen Atmosphäre durchgeführt (Studienzentrum)	☐	☐	☐	☐	☐
36	… waren örtlich gut erreichbar (Studienzentrum)	☐	☐	☐	☐	☐
37	… haben meine Medikamentenorganisation zu Hause unterstützt	☐	☐	☐	☐	☐
Allgemein						
38	Das hat mir in der Studie besonders gut gefallen:					
39	Das könnte man in der Studie verbessern:					
40	Hier dürfen Sie allgemeine Kommentare zur Studie oder Ihrer Medikamentenorganisation abgeben:					

Der Fragebogen ist hier beendet. Bitte geben Sie ihn ab und beantworten Sie noch ein paar zusätzliche Fragen mündlich. **Vielen Dank!**

UNIVERSITÄT BASEL

Dep Pharm Wiss
Pharmaceutical Care

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TEIL 3 VOR-/NACHTEILE

Durch PrüferIn

A) Fragen oben durchgehen und bei weniger als optimaler Antwort, spezifisch nachfragen, was gestört hat und unter „Kommentare" die Antworten notieren (unter Angabe der Fragennummer).

B) Die untenstehenden Fragen mündlich stellen, Antworten notieren.

41	Weshalb sind Sie zufrieden mit Ihrer Medikamentenorganisation / mit ihrem System?
42	Weshalb sind Sie unzufrieden mit Ihrer Medikamentenorganisation / mit ihrem System?
43	Welche Eigenschaften bräuchte ein neues System, das Sie benutzen würden?
44	*Nur Kontrollgruppe: Medikamentenblister zeigen*: Wie finden Sie diesen Medikamentenblister?
45	*Nur Interventionsgruppe:* Wie fanden Sie die Elektronik am Medikamentenblister?

THE END

A4.7 Analysis of the Believes about Medicines Questionnaire (BMQ)

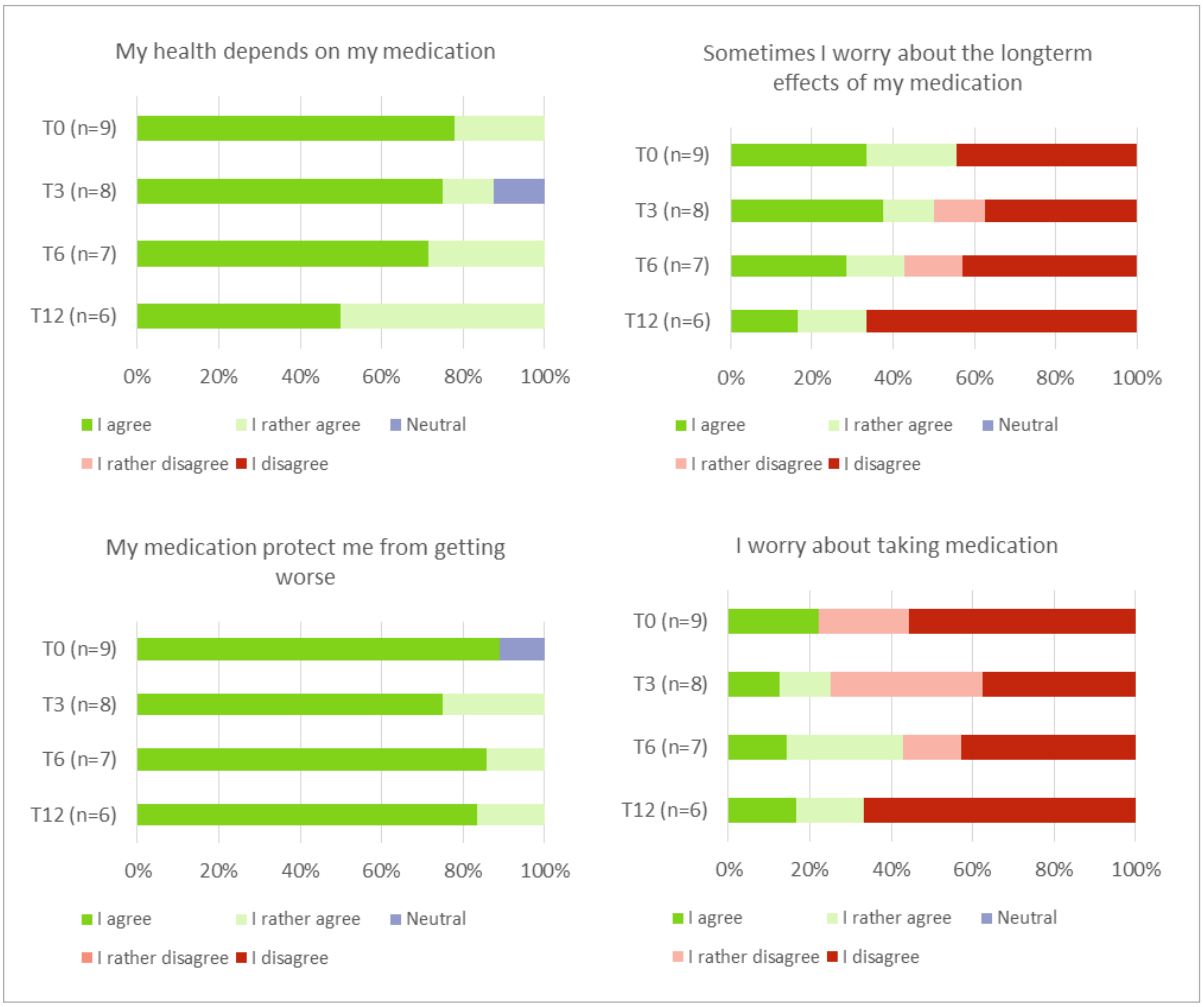

Figure A1: Answers of the control group to BMQ questions over the study period. T0, at discharge; T3,T6,T12, at follow-up at 3,6, and 12 months.

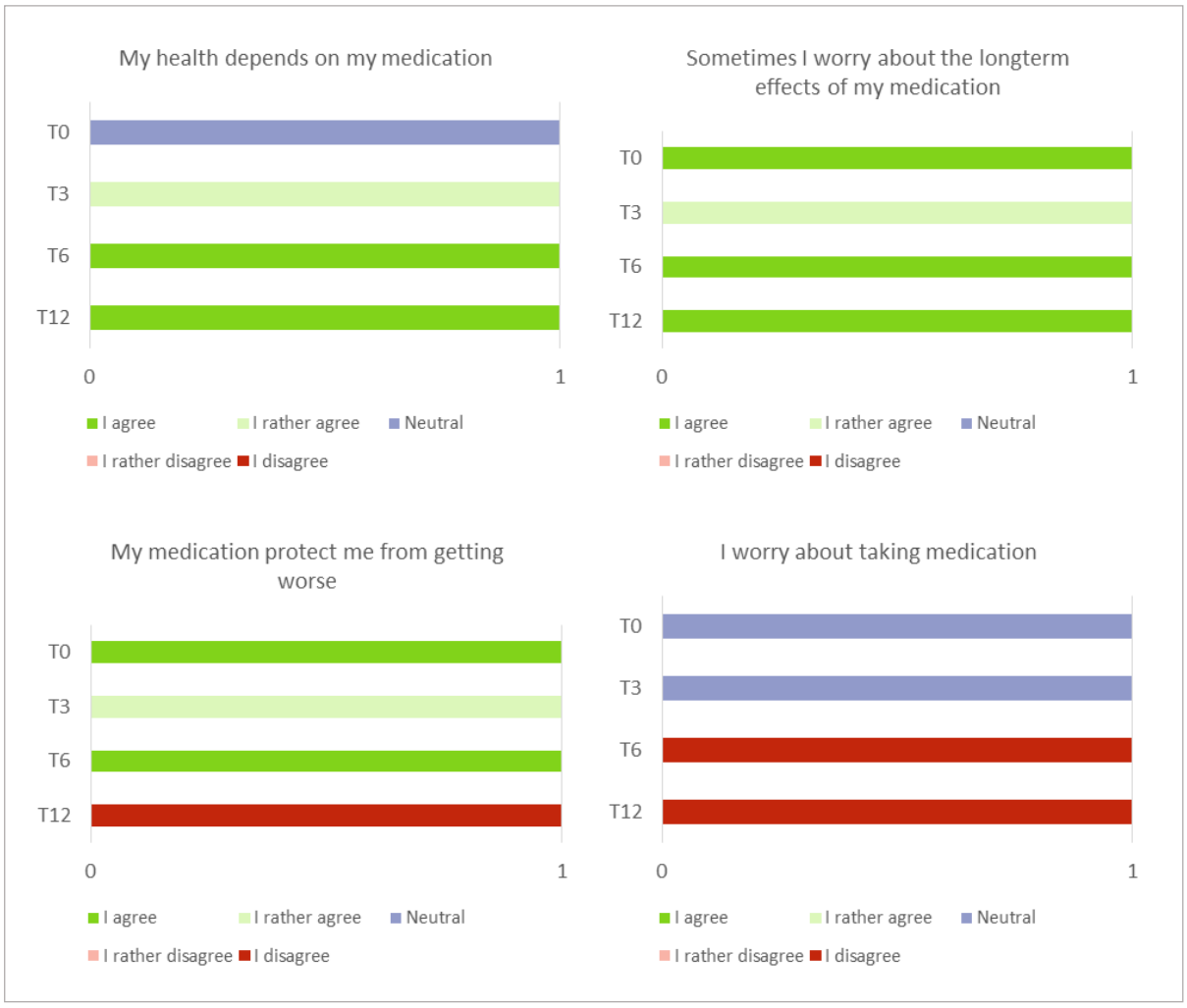

Figure A2: Trend of answers to the BMQ questions during the study by the intervention patient. T0, at discharge; T3,T6,T12, at follow-up at 3,6, and 12 months.

Curriculum Vitae

- On request -