PHARM-CHF

Pharmacy-based Interdisciplinary Program for Patients with Chronic Heart Failure (PHARM-CHF):
A Randomized Controlled Trial

Apothekenbasiertes interdisziplinäres Programm für Patienten mit chronischer Herzinsuffizienz (PHARM-CHF):
eine randomisierte kontrollierte Studie

PROTOCOL

Scientific Heads of the Study:

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Sponsor*:

ABDA - Bundesvereinigung Deutscher Apothekerverbände, Berlin

*) Investigator Initiated Study: The term “Sponsor” is used although this study is not a clinical trial according to German Drug Law or Medical Device Law.

I. Table of Contents

II. Glossary of Abbreviations

ABDA	ABDA – Bundesvereinigung Deutscher Apothekerverbände e.V. (Federal Union of German Associations of Pharmacists)
ACEi	Angiotensin-converting enzyme inhibitors
AMK	Arzneimittelkommission der Deutschen Apotheker (Drug Commission of German Pharmacists)
AMTS	Arzneimitteltherapiesicherheit (Drug Safety)
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
ARB	Angiotensin receptor blockers
BAK	Bundesapothekerkammer (Federal Chamber of Pharmacists)
BB	ß-blockers
BMG	Bundesministerium für Gesundheit (Federal Ministry of Health)
BNP	Brain Natriuretic Peptide (B-type natriuretic peptide)
CEC	Clinical Event Committee
CHF	Chronic Heart Failure
CV	Cardiovascular
DMP	Disease Management Program
DRP	Drug-related Problem
DPC	Committee for Data Protection
EC	Ethics Committee
eCRF	Electronic Case Report Form
EF	Ejection Fraction
HF	Heart Failure
HFmEF	Heart Failure with Mid-range Ejection Fraction
HFpEF	Heart Failure with Preserved Ejection Fraction
HFrEF	Heart Failure with Reduced Ejection Fraction
ITT	Intention-to-Treat
IZKS Mainz	Interdisziplinäres Zentrum Klinische Studien Mainz (Interdisciplinary Center Clinical Trials Mainz)
KV	Kassenärztliche Vereinigung (Associations of Statutory Health Insurance Physicians
LVEF	Left Ventricular Ejection Fraction
MLHFQ	Minnesota Living with Heart Failure Questionnaire
MRA	Mineralocorticoid receptor antagonists
NT-proBNP	N-terminal fragment of BNP
NYHA	New York Heart Association Functional Classification
OTC drug	Over-the-Counter drug
QoL	Quality of Life
PCNE	Pharmaceutical Care Network Europe
PDC	Proportion of Days covered
PGA	Self-reported Patient Global Assessment
PHQ-9	Patient Health Questionnaire (depression module)
PMV	PMV forschungsgruppe an der Universität zu Köln
PP	Per Protocol
RDE	Remote Data Entry
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SOP	Standard Operating Procedure
UdS	Universität des Saarlandes
V	Visit

1 Title

Pharmacy-based Interdisciplinary Program for Patients with Chronic Heart Failure (PHARM-CHF): A Randomized Controlled Trial.

Apothekenbasiertes interdisziplinäres Programm für Patienten mit chronischer Herzinsuffizienz (PHARM-CHF): eine randomisierte kontrollierte Studie.

2 Responsibilities and Contact Details

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SPONSOR	ABDA - Bundesvereinigung Deutscher Apothekerverbände e.V. Unter den Linden 19 - 23, 10117 Berlin
STEERING COMMITTEE (EXECUTIVE BOARD):	Prof. Dr. med. Ulrich Laufs (co-chair) Prof. Dr. rer. nat. Martin Schulz (co-chair) Prof. Dr. med. Stefan Anker, PhD Prof. Dr. med. Michael Böhm Dr. rer. nat. Nina Griese-Mammen Prof. Dr. rer. nat. Charlotte Kloft Prof. Dr. med. Friedrich Köhler Prof. Dr. rer. nat. Dietmar Trenk
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DATA MANAGEMENT/ BIOMETRY/ MONITORING	Interdisziplinäres Zentrum Klinische Studien Mainz (IZKS) Langenbeckstraße 1, 55131 Mainz
CLINICAL EVENT COMMITTEE	A Clinical Event Committee (CEC) has been implemented.

3 Synopsis

AIM OF THE STUDY	The aim of the study is to investigate, whether a continuous interdisciplinary intervention improves medication adherence (primary efficacy variable of interest) and leads to a reduction of hospitalizations and mortality (primary safety variable of interest) in elderly patients with chronic heart failure (CHF). The intervention, consisting of regular contacts with the local pharmacy and weekly dosing aids, aims to improve medication management.
STUDY DESIGN	PHARM-CHF is a prospective, multicentre, randomized controlled study.
PRIMARY VARIABLES	**Primary efficacy variable:** Medication adherence during the 365 days following randomization, pre-specified as a significant difference of the proportion of days covered (PDC) between the intervention and control group using pharmacy claims data for three CHF medications (angiotensin-converting enzyme inhibitors or angiotensin receptor blockers [ACEi/ARB], ß-blockers [BB], and mineralocorticoid receptor antagonists [MRA]) prescribed at baseline **Primary safety variable**: All-cause mortality or unplanned cardiovascular hospitalizations as days lost due to unplanned cardiovascular hospitalizations or death of any cause
SECONDARY VARIABLES	**Secondary efficacy variables** - PDC for each drug class (ACEi/ARB, BB, MRA), percentage of patients with a mean PDC ≥80% (=adherent), and percentage of patients with a PDC ≥80% for each drug class (sensitivity analyses for a cutpoint ≥88%) - Quality of life (Minnesota Living with Heart Failure Questionnaire) after 1 and 2 years - Self-reported patient global assessment (PGA) after 1 and 2 years (scale) - Patient Health Questionnaire (PHQ-9) after 1 year - Self-estimated medication adherence (Scale 0-100%) after 1 year **Secondary safety variables** - All-cause mortality or unplanned cardiovascular hospitalizations as recurrent event (number) - Unplanned cardiovascular hospitalizations (recurrent event, number) - Unplanned hospitalizations for heart failure (recurrent event, number) - Days lost due to hospitalizations of any cause or death - Unplanned all-cause hospitalizations - All-cause mortality
STUDY POPULATION	**Inclusion Criteria** - Age: 60 years and older - Diagnosis of chronic heart failure (CHF) - Stable CHF medication including a diuretic - Hospitalization for decompensated heart failure within past 12 months OR a value of ≥ 350 pg/mL for BNP or ≥ 1400 pg/mL for NT-proBNP - Written informed consent

	Exclusion Criteria - Regular/assisted use of a weekly dosing aid - Unwillingness or inability to visit a participating pharmacy once a week - Planned cardiac surgery - Life-expectancy < 6 months - Unwillingness or inability to comply with the study protocol (including drug abuse or alcohol dependency) - Participation in other studies (currently or in the last 4 weeks)
DURATION OF THE STUDY	The mean follow-up is expected to 24 months with a minimum of 12 months.
NUMBER OF SUBJECTS	N = 248 - Estimated effect of intervention: 10% (SD 22%) - α = 0.05, power: 85% - Calculated sample size: 176 + 30% drop out
STUDY SITES	Approximately 40 medical practices Approximately 80 pharmacies
STUDY VISITS	Intervention and control group: - Visits in the medical practice at baseline (V1), after 12 months (V3), and at the end of the study (V6), and, if applicable, after 24 months (V5) - Telephone visits by the medical practice after 6 months (V2) and, if applicable, after 18 months (V4)
INTERVENTION	Regular, pharmacy based intervention conducted in cooperation with the treating physician: - Medication review (Type 2a) at baseline: Recording of all medicines currently taken (prescribed medication and self-medication), check for drug-related problems, consolidation of a medication plan considering medication list of treating physician - Regularly (weekly or bi-weekly): Dose-dispensing of the medication (weekly dosing aid), discussion and counselling regarding medication, adherence, potential side effects, and signs and symptoms of cardiac decompensation, blood pressure and pulse measurement, updating medication plan if necessary - If required: Contact with patients' physician
FOCUS OF INTERVENTION	- Improving medication adherence - Early detection of signs and symptoms of cardiac decompensation - Detection, solution, and prevention of drug-related problems

4 Scientific Background

Heart failure is one of the most prevalent diseases. In Germany, approximately 2.8 million patients suffer from heart failure [1]. The prevalence increases with age and amounts to 10% in elderly people aged 80 and older [2]. Heart failure is the most frequent cause for hospital admission in Germany and the third most frequent cause of death [3]. In 2008, the costs for treatment of patients with heart failure were estimated to 3.2 billion Euro [4]. The continuous intake of several medicines is an essential part of the therapy [5]. Several large clinical studies have reported that pharmacotherapy taken according to the guidelines, can increase quality of life, improve morbidity, and decrease mortality [5]. However, in daily practice this effect can often not be achieved. Reasons include non-adherence and other drug-related problems.

Non-adherence with pharmacotherapy affects 20-50% of all patients with chronic diseases [6–8]. Reasons for non-adherence include forgetfulness, high complexity of the drug regimen, wrong expectations, and experienced side effects [8–10]. Prospective studies and register studies showed that adherence with pharmacotherapy correlates with the morbidity and mortality in patients with chronic diseases [6, 11] such as chronic heart failure (CHF) [12]. For example, a subgroup analysis of the large heart failure study CHARM showed that the hazard ratio for mortality was 35% lower for patients with an adherence > 80% compared to patients with an adherence < 80% [13]. So far, only comprehensive interventions, which combined several different elements, were shown to improve adherence [14]. Effective interventions included elements such as education and counselling, motivation, intensive interaction between patient and health care professionals, reminder, and the dispensing of medicines in dosing aids. A pharmacist care program combining education and counselling with the preparation of medicines in a weekly dosing aid led to an increased adherence (61% to 97%). This improvement was associated with improved blood pressure and lipid values. Clinical endpoints, such as hospitalizations or mortality, have not been assessed [15]. The current literature shows that poor adherence cannot be “cured” and decreases after interventions to improve adherence end. Therefore, there is a need for a continuous strategy.

Patients diagnosed with CHF in Germany received an average of 43.1 prescriptions per patient in 2008 [1]. Older patients receiving several medicines are at a high risk to experience drug-related problems (DRP), e.g. problems with the application of the drug, double medication, interactions, adverse drug reactions. Gastelurrutia et al. found risks for drug-related negative outcomes in 78% of the patients with heart failure; 94% of those were considered preventable and 86% could have been resolved by an intervention of a pharmacist. Non-adherence was one of the most frequent drug-related problems detected [16].

Rapid weight gain as well as deterioration of symptoms are early indicators of a cardiac decompensation in CHF. Adherence with weight monitoring was found to be associated with a lower mortality [17]. Guidelines recommend that patients with chronic heart failure should weigh themselves daily and record weight in a protocol [5]. Patients should contact a health care provider in case of a rapid weight gain or worsening of symptoms, such as dyspnoea. However, studies reported delays in contacting health care providers. CHF patients frequently either do not monitor weight and symptoms or do not recognize the signs [18,19]. Interventions, which have been found to improve medication adherence, might also be effective to improve adherence with symptom monitoring.

A meta-analysis of pharmacist-led or pharmacy-based studies in patients with CHF found a significant reduction of hospitalizations and a non-significant reduction of mortality [20]. Patients with CHF who received a medication review (including clinical data) had a 37% lower risk of hospitalizations compared to patients receiving usual care [21]. Studies were most successful, when the pharmacist acted as part of a multidisciplinary team. The interventions consisted of education and counselling about pharmacotherapy, control of weight changes, recommendations for visiting physicians, and adherence

assessment. However, reported data cannot directly be applied to the German setting, as studies have been conducted in different health care systems. In addition, the methodology of the included studies varied widely, e.g. some studies were not sufficiently powered. Furthermore, all interventions consisted of few intensive patient contacts. Based on literature [11], we hypothesize that regular and long term patient contacts will lead to an improved medication adherence and an early detection of signs of cardiac decompensation and drug-related problems, which may result in a decreased mortality and reduced hospitalizations eventually.

To the best of our knowledge, PHARM-CHF is worldwide the first prospective randomized study to investigate the effects of a continuous interdisciplinary intervention using regular contacts with the local pharmacy and weekly dosing aids in patients with CHF. PHARM-CHF is the first prospective randomized study in patients with CHF with clinical endpoints performed in cooperation of physicians and pharmacists in Germany. Pharmacists and physicians will cooperate to improve adherence, prevent and solve drug-related problems and improve the monitoring of symptoms.

5 Aim of the Study

The aim of the study is to investigate, whether a continuous interdisciplinary intervention improves medication adherence, and leads to a reduction of hospitalizations and mortality in elderly patients with chronic heart failure (CHF). The intervention, consisting of regular contacts with the local pharmacy and weekly dosing aids, aims to improve medication management.

6 Study Objectives

6.1 Primary Variables

Primary efficacy variable: Medication adherence to cardiovascular medication, pre-specified as a significant difference between the intervention and control group using pharmacy claims data for three CHF medications (angiotensin-converting enzyme inhibitors or angiotensin receptor blockers [ACEi/ARB], ß-blockers [BB], and mineralocorticoid receptor antagonists [MRA]) prescribed at baseline. Medication adherence will be calculated based on the proportion of days covered (PDC) during the 365-days following randomization, adjusted for inpatient days, medication switches, medication fills prior to randomization, and death.

Primary safety variable: All-cause mortality or unplanned cardiovascular hospitalizations as days lost due to unplanned cardiovascular hospitalizations or death of any cause.

6.2 Secondary Variables

Secondary efficacy variables

- PDC for each drug class (ACEi/ARB, BB, MRA), percentage of patients with a mean PDC ≥80% (=adherent), and percentage of patients with a PDC ≥80% for each drug class (sensitivity analyses for a cutpoint ≥88%).
- Quality of life (Minnesota Living with Heart Failure Questionnaire) after one year and after two years
- Self-reported patient global assessment (PGA) after one year and after two years (scale)
- Patient Health Questionnaire (PHQ-9) after one year and after two years
- Self-estimated medication adherence (Scale 0-100%) after 1 year

Secondary safety variables

- All-cause mortality or unplanned cardiovascular hospitalizations as recurrent event (number)
- Unplanned cardiovascular hospitalizations (recurrent event, number)
- Unplanned hospitalizations for heart failure (recurrent event, number)
- Days lost due to hospitalizations of any cause or death
- Unplanned all-cause hospitalizations
- All-cause mortality

7 Study Design

PHARM-CHF is a prospective multicentre, randomized controlled study.

7.1 Enrolment

7.1.1 Medical Practices and Pharmacies

Approximately 40 medical practices and 80 pharmacies from different regions in Germany will be enrolled.

7.1.2 Patients

Recruitment of patients takes place in participating medical practices. At least, 248 patients shall be recruited and randomized in the control and the intervention group.

7.2 Inclusion and Exclusion Criteria

7.2.1 Inclusion Criteria

- Age: 60 years and older
- Diagnosis of chronic heart failure (CHF)
- Stable CHF medication including a diuretic
- Hospitalization for decompensated heart failure within past 12 months OR a value of ≥ 350 pg/mL for BNP or ≥ 1400 pg/mL for NT-proBNP [22,23]
- Written informed consent

7.2.2 Exclusion Criteria

- Use of a weekly dosing aid
- Unwillingness or inability to visit the participating pharmacy once a week
- Planned cardiac surgery
- Life-expectancy < 6 months
- Unwillingness or inability to comply with the study protocol (including drug abuse or alcohol dependency)
- Participation in other studies (currently or in the last 4 weeks)

No subject will be allowed to be enrolled in this study more than once.

8 Study Procedures

8.1 Time Schedule Medical Practices

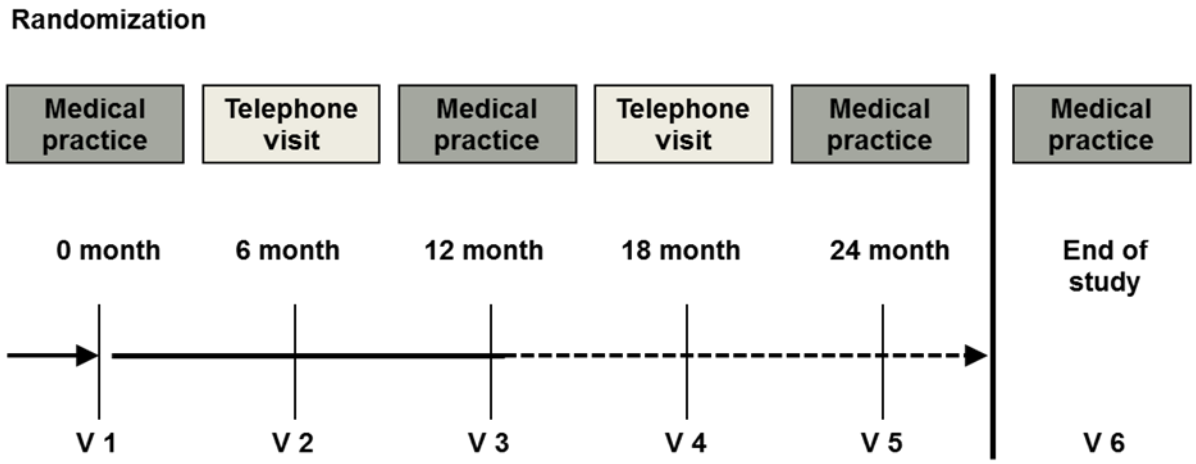

Figure 1 Time Schedule Medical Practices

8.2 Visits / Data Collection in Medical Practices

8.2.1 Screening / Visit 1 (V1)

Eligible patients are informed about the study and participating pharmacies in the medical practice. The patient receives the patient's information and signs and dates the informed consent after his approval. The physician signs and dates the informed consent and archives it. The patient receives an original of the informed consent. The physician documents the contact data of the patient and e.g. family members or other caregivers, who could be contacted.

The patient is allocated into the intervention or control group by the medical practice using the Online Randomization tool "RandomiXer" (see 11.4.6).

Furthermore, the physician records patient characteristics (e.g. vital signs, medical history, medication) and patients are asked to fill in questionnaires (e.g. PHQ-9, MLHFQ) (table 1).

Screening visit, randomization and visit 1 can be conducted in one single visit.

8.2.2 Medical Practice Visits 3 and 5 (V3, V5)

The medical practice records patient characteristics (e.g. vital signs, medical history, and medication) after 12 months (V3) and, if applicable, after 24 months (V5). Furthermore, the patients are asked to fill in questionnaires (table 1).

8.2.3 Medical Practice Visit 6 (V6)

The IZKS Mainz informs the medical practice and the pharmacy about the end of the study, the medical practice performs visit 6 (table 1).

8.2.4 Telephone Visits (V2, V4)

The medical practice calls the patient after 6 months (V2) and, if applicable, after 18 months (V4) to inquire about hospitalizations. If a consultation takes place at this time, the medical practice can ask the patient face-to-face (table 1).

8.2.5 Continuous Data Collection of Events

Additionally to the visits, events are recorded continuously in the medical practices. When death or an unplanned hospitalization occurs, the date and, in case of an unplanned hospitalization, the referral letter and the duration of the event are sent to IZKS Mainz as soon as possible.

	Screening / V1 (month 0)	V2 (after 6 months	V3 (after 12 months)	V4 (after 18 months)	V5 (after 24 months)	V6 (end of the study)
In- and exclusion criteria	**X**					
Heart failure (leading cause, duration)	**X**					
CV-risk factors	**X**					
Sociodemographic data	**X**					
Height	**X**					
LVEF (if available)	**X**					
DMP participation	**X**		**X**		**X**	
Medical history	**X**		**X**		**X**	
Device treatment	**X**		**X**		**X**	
Medication plan	**X**		**X**		**X**	
NYHA class	**X**		**X**		**X**	
Care level (*Pflegestufe*)	**X**		**X**		**X**	
Blood pressure	**X**		**X**		**X**	
Pulse	**X**		**X**		**X**	
Weight	**X**		**X**		**X**	
Documentation of laboratory values	**X**		**X**		**X**	
Hospitalization		**X**	**X**	**X**	**X**	**X**
Quality of life questionnaire (MLHFQ)	**X**		**X**		**X**	
Patient health questionnaire (depression module, PHQ-9)	**X**		**X**		**X**	
Self-estimated medication adherence (Scale 0-100%)	**X**		**X**		**X**	
Self-reported patient global assessment (PGA)			**X**		**X**	

Table 1. Data collection at visits V1, V2, V3, V4, V5, and V6

Abbreviations: BNP/NT-proBNP, (N-terminal fragment) brain natriuretic peptide; CV, cardiovascular; EF, ejection fraction; DMP, disease management program; NYHA, New York Heart Association; MLHFQ, Minnesota Living with Heart Failure Questionnaire; PHQ, patient health questionnaire; PGA, patient global assessment

8.3 Data Collection at the end of the study

Health insurance funds as well as data processing centres are asked for information on prescribed medicinal products dispensed at community pharmacies, and health insurance funds about hospitalizations at the end of the study.

8.4 Control and Intervention Group

8.4.1 Control Group

8.4.1.1 Medical Practice

Patients receive usual medical care. Usual medical care is defined as the treatment of chronic heart failure at the discretion of the treating physician.

8.4.1.2 Pharmacy

Patients visit their usual pharmacy/pharmacies to receive their medication and usual care. Participating pharmacies are not informed about the enrolment of patients in the control group.

8.4.2 Intervention Group

8.4.2.1 Medical Practice

Patients receive the usual medical care. Additionally, the medical practice interacts closely with the pharmacy, e.g. for consolidation of the medication plan or discussion of DRP.

Patients in the intervention group can choose one of the participating pharmacies. They are advised in the medical practice to contact the selected pharmacy within 7 days after inclusion. The medical practice informs the pharmacy about the inclusion of the patient and provides the patient's medication plan.

8.4.2.2 Pharmacy

Patients receive the following interventions: At baseline, the pharmacist performs a medication review (Type 2a according to the Pharmaceutical Care Network Europe (PCNE) classification) in the community pharmacy with the aim of generating a medication plan, consolidated between the patient, his physician(s) and the pharmacist. Thereafter, the patient visits the pharmacy regularly to collect his medication in weekly dosing aids prepared in the pharmacy. Consultation between the pharmacist and the physician takes place in case of the necessity to update the medication plan, when new DRP appear or signs/symptoms of cardiac decompensation are reported by the patient to the pharmacist.

The committee action plan drug safety (AMTS) of the Federal Ministry of Health (BMG) has developed a template for a medication plan [24]. This template will be used in this study.

8.4.2.2.1 Medication Review

Patient interview
Patients in the intervention group are advised by the physician to visit or to arrange an appointment at the selected pharmacy within the next week. This appointment should take place within two weeks after randomization. The pharmacist asks the patients to bring their entire medication currently taken, including non-prescription (OTC) drugs, to this appointment. Patients, who do not contact the pharmacy within 7 days after inclusion, will be contacted by the pharmacy.
To prepare the interview, the pharmacist performs a preliminary risk check based on the medication plan provided by the medical practice and the medication history recorded in the pharmacy (if available).

The patient brings all medicines currently taken including non-prescription (OTC) drugs to the appointment. The pharmacist documents all medicines currently taken by the patient, the dosage and the application time according to the information given by the patient. In addition, potential side effects and (potential) problems administering the medication are documented.

Medication plan
After the interview, the pharmacist checks for drug-related problems (DRP) based on the patient interview, the medication dispensing history available in the pharmacy, and the medication plan

provided by the medical practice and pays special attention to potential discrepancies. To ensure a standardized approach, the pharmacists uses a checklist summarizing DRP such as double medication or drug-drug-interactions. If necessary, the pharmacist contacts the physician to discuss detected (potential) DRP. The physician decides about medical interventions. The pharmacist documents (potential) DRP discussed with the physician as well as DRP, which are resolved directly by the pharmacist.

Based on the consolidated medication plan the patient receives his first weekly dosing aid together with a printout of the medication plan, at the latest two weeks after the appointment.

8.4.2.2.2 Weekly Pharmacy Visit

Preparing the weekly dosing aids
The pharmacy chooses the type of weekly dosing aid together with the patient. The dosing aid contains all medications in a day- and time-specific manner for one week and is clearly labelled with information regarding the patient, contents and contact information of the pharmacy. The pharmacy prepares the weekly dosing aid of the patient based on an up-to-date medication plan. The preparation follows the recommendations of the Federal Chamber of Pharmacists (BAK).

Newly prescribed medication that is indicated for immediate treatment (e.g. antibiotics) is taken by the patient in addition to the dosing aid. In general, changes in the medication are included in the weekly dosing aid whenever the next aid is due. Therefore, it is important that the physician's office or the patient inform the pharmacy about a change in medication. Furthermore, the pharmacist asks at every visit about potential changes. With every change, the pharmacist checks for DRPs, contacts the physician if necessary and updates the medication plan. The physician decides about medical interventions. The pharmacist documents (potential) DRP discussed with the physician as well as DRP, which are solved directly by the pharmacist.

Pharmacy visit
The patient visits the pharmacy once a week to collect the medication in a weekly dosing aid. The pharmacist provides the patient with information about the medication (especially at the beginning of the intervention and if a new medication is prescribed) and motivates the patient to take the medication, to self-manage symptoms and weight changes (e.g. daily weighing, weight diary).

During these weekly visits, the pharmacist inquires after potential side effects, medication adherence, as well as signs and symptoms of a potential cardiac decompensation (e.g. shortness of breath). The pharmacist measures blood pressure and pulse (SOP BAK, see 9.1). If significant changes in vital signs are detected or if the patient reports relevant symptoms or signs (e.g. a significant weight increase), the pharmacist contacts the physician or recommends the patient to contact his physician.
If the patient does not collect his medication, the pharmacy contacts first the patient or his caregiver(s). Additionally, in case of difficulties, the pharmacy contacts the medical practice.

Adoption of the intervention
a) Once the patient has attended the weekly visits in the pharmacy for a minimum of four continuous weeks and if needed, the patient and his pharmacist can agree on bi-weekly visits to the pharmacy.

b) When a patient cannot visit the pharmacy, e.g. the patient is ill/home-bound, the pharmacy can either deliver the weekly dosing aid to the patient's home or it can be dispensed to a caregiver. If the patient is absent for longer than a week, e.g. on holiday, the pharmacy can supply the patient with more than one weekly dosing aid. As the pharmacy visit is an essential part of the intervention, it is important, that the patient attends the interview at the pharmacy regularly. Hence, the supply of weekly dosing aids for more than two weeks should be strictly limited to these exceptions.

9 Training and Monitoring

9.1 Training and Information Material

Training will be performed by ABDA, UdS and IZKS Mainz. Participating pharmacists and physicians are trained either by telephone, on site or during a workshop about study-specific aspects and will receive information material. They receive standardized material including study guidelines, checklists and forms, the study protocol, study material, information about the electronic case report form (eCRF), and a contact list.
A telephone hotline to UdS as well as a website (www.pharm-chf.de) is available as information source and for requests of participating pharmacists and physicians. When necessary, questions will be forwarded to ABDA or IZKS Mainz.
Medication is dose-dispensed based on the recommendations of the BAK, i.e. by dual control. A SOP of the BAK for the measurement of blood pressure and pulse is available in the intervention pharmacies.

9.2 Monitoring

Monitoring visits are conducted by the IZKS in the medical practices. As described in the study specific monitoring manual, monitoring will be done either by personal visits of a clinical monitor or by telephone contacts according to SOP of the IZKS Mainz (if applicable). The monitor checks the informed consent forms and reviews the entries into the eCRF based on source documents. The physician allows the monitor access to all essential documents and provides support to the monitor.
The IZKS Mainz assists the physician to conduct the study according to the protocol as well as regulatory and ethical requirements.

Moreover, pharmacists are assisted to conduct the study according to the protocol by employees (research associates) of ABDA.

10 Data Management

10.1 Responsibilities

On behalf of the sponsor, IZKS Mainz conducts the data management of the PHARM-CHF study. A detailed methodology for the data management in this study will be documented in a data management plan. The document may modify the procedures outlined in this protocol. However, any major modifications of the data handling will also lead to a protocol amendment.

10.2 Data Collection

Obtained data is documented in an electronic case report form (eCRF), with an exception of the patient questionnaires. Patients answer questionnaires using a paper form. All protocol-required information collected during the study is entered by the investigator, or a designated representative in the eCRF. The paper-based data is entered by the IZKS Mainz into the study database. The investigator and the study site staff will receive system documentation, training and support for the use of the eCRF. In case of new study site staff, the training can be performed by personnel at the study site. IZKS Mainz can be contacted to support the data entry.

All data changes (entry, modification and deletion) are recorded automatically in an electronic audit trail by storing the individual subject, the original value, the new value and time and date of the change. Previous data can be viewed or restored by the audit trail. All electronic data is entered by the site in compliance with applicable record retention regulations.

The system is secured to prevent unauthorized access to the data or the system. Only people provided with a user ID and a password are able to enter or change data. The investigator maintains a list of individuals who are authorized to enter data.

Computer hardware and software (for accessing the eCRF data) will be maintained at the site. The remote data entry (RDE) system is capable to make exact copies of data in legible paper form for audits. The architecture of the computer system of the IZKS Mainz will be described in the data management plan.

10.2.1 Additional Sources for Data Collection

To complete the data obtained from pharmacies and medical practices, there are also other sources to obtain information e.g., about events. Health insurance funds (Statutory Health insurance (SHI) and private) are asked for information, as well as German data processing centres (*Apothekenrechenzentren*) and comparable resources, e.g. registration offices (*Einwohnermeldeämter)* or health offices. All data will be kept in safe and confidential custody at IZKS Mainz.

10.2.2 Assessment of Safety

In case of hospitalizations, the blinded documents are sent to the clinical event committee (CEC) for adjudication according to pre-specified criteria in the CEC charter. Adjudicated events will be categorized by their cause and assigned into cardiovascular and non-cardiovascular events.

10.3 Data Handling

During data entry, integrity checks help to minimize entry failures. These data entry checks are defined in the data validation plan. The data entry system allows the study monitors to control the entry process with the help of the system-own review functions. Comments and requests can be processed by the study site just in time.

During the study, data is exported into the statistical analysis system (SAS) and checked additionally for plausibility, consistency and completeness. Based on these checks, queries are produced. Any missing data or inconsistencies are reported back to the respective site and clarified by the responsible investigator. If all corrections are done, the database is closed and used for statistical analyses.

All collected data will be processed according to the German Data Protection Law and handled in strictest confidence. To cover all relevant aspects of data protection a data protection commissioner is involved. A Data-Safety concept will be implemented and specified in a separate document. The latter will be prepared in cooperation with and handed in for approval to the data protection commissioner. Personal data will be strictly separated from the study database.

10.4 Storage and Archiving of Data

The investigator archives all study data (e.g. subject identification list, informed consent) and relevant correspondence in a standardized project folder. This folder, all source data and all documents are archived after finalization of the study according to the legal regulations.

IZKS Mainz assures storage and archiving of the electronic data during the study. After completion of the study all electronic data is handed over to the sponsor.

11 Biometrics

11.1 Sample Size

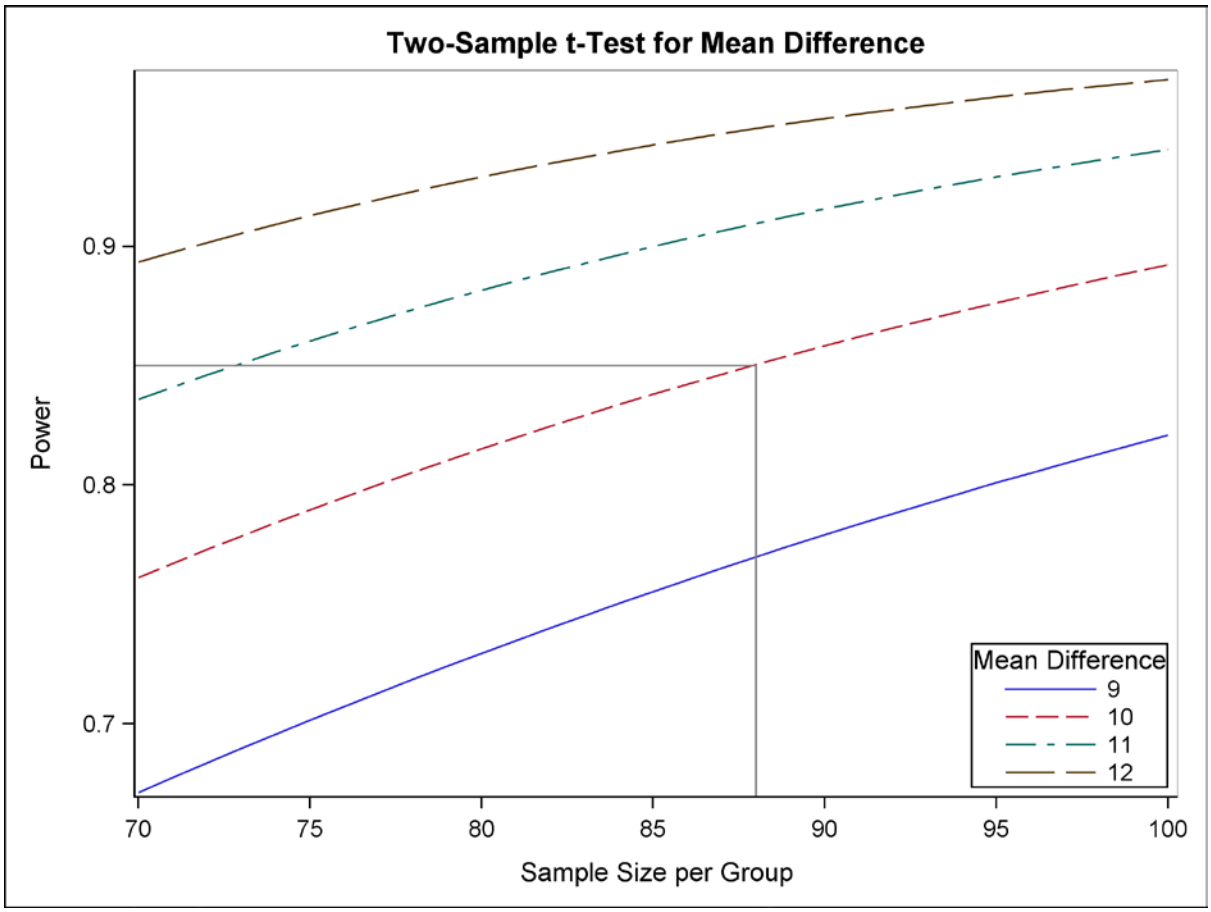

Figure 2: Sample Size Calculation

The primary efficacy variable is adherence to CHF medication. We conservatively assume an improvement of the summary PDC ≥10% in the intervention group compared to usual care as clinically relevant.

Assuming a mean PDC in the year before randomization of approximately 0.7 a sample size of N=176 patients (88/group) is needed to detect a 10% (SD 22%) improvement between the intervention group and the usual care group with a power of 85% and an alpha of 5%. Assuming a dropout and lost to follow up of 30% N=248 patients have to be enrolled in the study.
The study is powered for the primary efficacy variable only.

11.2 Interim Analysis

No interim analysis will be performed.

11.3 Analysis Populations

Intention to treat
The intention to treat (ITT) population consists of all patients who have post-baseline data available and who did not fail to satisfy major entry criteria. Patients in the intervention arm (with or without withdrawal of consent), for whom no consolidated medication plan is available i.e., subjects failed to comply with

the study protocol at entry (i.e. did not undertake the medication review at the pharmacy - which is comparable of not taken any trial medication), have no post-baseline data available.

Per Protocol
The per protocol (PP) population consists of all subjects of the ITT population who completed the study without major protocol violations. These are violation of inclusion criteria, meeting exclusion criteria, post-baseline data not available, consolidated medication plan not available (intervention group patients only) and premature termination (except death). As data for patients withdrawn (with withdrawal of consent) from the study will be anonymized immediately, pseudonymized data acquisition from other sources e.g., health insurance funds is impossible.

11.4 Statistical Methods

The main analysis comprises the eCRF data and pharmacy claims data of prescribed medicinal products dispensed at community pharmacies from data processing centres (*Apothekenrechenzentren*) and health insurance funds (statutory and private) and hospitalization data from health insurance funds. On behalf of the sponsor, IZKS Mainz conducts the main analysis of the PHARM-CHF study. The PDC will be determined at the PMV (Universitiy Cologne) and will be submitted to the IZKS Mainz for further analysis. Analyses regarding the intervention in participating pharmacies like analyses of drug-related problems (DRPs) and medication discrepancies are based on the eCRF and data documented during the intervention from pharmacists. These analyses will be performed by the Department of Medicine, ABDA, Berlin. The detailed methodology for the statistical analysis of this study will be documented in a statistical analysis plan (SAP). The SAP has to be signed by the scientific heads of the study, the statistician at IZKS and the study coordinator at ABDA.

11.4.1 Primary Efficacy Analysis

The primary efficacy analysis is the analysis of the PDC for three CHF medications (ACEi/ARB, BB and MRA). The pharmacy claims data are provided by data processing centres and health insurance funds. If health insurance data are not available for all patients, an analysis will be performed comparing the data from health insurance funds and data processing centres. The analysis will be adjusted for data from health insurance funds (yes/no).

The PDC will be analysed by a two-sided stratified Wilcoxon signed-rank test (van Elteren test) on a two-sided level of significance of 5%.

The following hypothesis will be tested:

H_0: $m_i = m_c$ vs. H_1: $m_i \neq m_c$,

Where m_i denotes the median value of the intervention group and m_c denotes the median value of the control group.

Although statistical guidelines (“Points to consider on adjustment for baseline covariates”) suggest adjusting the analysis for all stratification variables of the randomization process, this is omitted. It is desired to get a robust result, if one treatment regimen is favourable to the other across all stratification factors. Nevertheless, supportive analyses adjusting for the stratification factors will be conducted as sensitivity analyses.

11.4.2 Primary Safety Analysis

The primary safety variable is all-cause mortality or unplanned cardiovascular hospitalizations as days lost due to unplanned cardiovascular hospitalizations or death.

The number of days lost due to death of any cause or unplanned cardiovascular hospitalizations will be analysed by a Wilcoxon signed-rank test comparing both treatment groups. Additionally, the number of days lost due to death of any cause or unplanned cardiovascular hospitalizations will be analysed descriptively by treatment group and in total.

11.4.3 Secondary Efficacy Analyses

11.4.3.1 Adherence to medication

The primary efficacy analyses will also be repeated for each drug class (ACEi/ARB, BB, MRA). The percentage of patients with a mean PDC ≥80% (=adherent), and percentage of patients with a PDC ≥80% for each drug class (sensitivity analyses for a cutpoint ≥88%) will be calculated.

11.4.3.2 Quality of life (Minnesota Living with Heart Failure Questionnaire, total score)

The changes to baseline of the total score of the Minnesota Living with Heart Failure Questionnaire after 1 year and, if sufficient data are available, after 2 years will be analysed by an ANCOVA, including treatment as fixed effect and total score at baseline as covariate. Parameter estimates and adjusted mean differences will be shown together with their corresponding p-values and 95% confidence intervals.

Additionally, the total score as well as the corresponding change to baseline will be analysed descriptively by visit, treatment group and in total.

11.4.3.3 Patient global assessment (PGA)

The self-reported patient global assessment (PGA) will be displayed by numbers and percentages by visit (after 1 year and, if sufficient data are available, after 2 years), treatment group and in total. A Chi-Square test for treatment comparison will be used.

11.4.3.4 PHQ-9

The PHQ-9 total score and the changes to baseline will be analysed descriptively by visit (after 1 year and, if sufficient data are available, after 2 years) for each treatment group and in total. t-tests for comparing treatment groups will be performed.

11.4.3.5 Self estimated adherence

Self-estimated adherence will be analysed descriptively by visit (after 1 year and, if sufficient data are available, after 2 years), for each treatment group and in total. T-tests for comparing treatment groups will be performed.

11.4.4 Secondary Safety Analyses

The following secondary safety variables will be analysed by descriptive methods and exploratory p-values:

- All-cause mortality or unplanned cardiovascular hospitalizations as recurrent event (number)
- Unplanned cardiovascular hospitalizations (recurrent event, number)
- Unplanned hospitalizations for heart failure (recurrent event, number)
- Days lost due to hospitalizations of any cause or death
- Unplanned all-cause hospitalizations
- All-cause mortality

All primary and secondary variables are also analysed for the PP Population. These analyses are only considered as exploratory.

11.4.5 Subgroup Analyses

Several pre-specified subgroups will be explored.
The following subgroups are planned:

- Minimization-criteria:
  - Sex (male/female)
  - Age (<75, ≥75 years)
  - NYHA functional class (I and II, III and IV)
  - PHQ-9 (depression score <10, ≥10)
  - Diabetes mellitus (yes/no)
  - The study region will be omitted since this may lead to an over determination of the analysis model.
- Time between last heart failure hospitalization and randomization (≤ 3 months vs. > 3 months before study)
- Number of different drug substances (median at randomization), as an indicator of the level of illness burden
- Number of different co-morbidities (median at randomization), as a further indicator of the level of illness burden
- Heart failure medication at baseline (BB versus BB plus ACEi/ARB, BB plus ACEi/ARB versus BB plus ACEi/ARB/MRA) (subpopulations)
- Heart rate at baseline (≤ 75 vs. > 75 min-1)
- QoL score (MLHFQ Median)
- HFrEF vs. HFmrEF/HFpEF (LVEF <40% vs. ≥ 40%)

Each subgroup and the corresponding interaction with treatment group will be included into the analysis model (the PDC of each drug class will be analysed by an ANOVA, for the mean PDC ≥80% a logistic regression model will be used).

11.4.6 Randomization

Eligible patients are assigned in a 1:1 ratio to the intervention or control group. Minimization with 20% residual randomness is used to ensure balance of the following characteristics: Gender (male/female), age (<75, ≥75), NYHA functional class (I and II, III and IV), PHQ-9 (score <10, ≥10), diabetes mellitus (yes/no), study region (according to regional Associations of Statutory Health Insurance Physicians (KV-Region)).
A web-based randomization tool developed by IZKS Mainz is used within this study allowing investigators to randomize patients via a secure web interface.
Subjects withdrawn from the study retain their identification codes (i.e. patient number). New subjects must always be allotted a new identification code.

11.4.7 Blinding

PHARM-CHF is a prospective multicentre, randomized controlled study. Patients are randomized by the recruiting physician on an individual level. Pharmacists are unaware of the control patients. All other investigators, committees, and staff remain fully blinded throughout the study to the randomization status of the patients.

11.5 Methods to Avoid Bias

11.5.1 Selection Bias

See randomization.

11.5.2 Performance Bias

Potential bias:

Physicians (unblinded) treat patients of the intervention group differently than patients of the control group to reach the aim of the study.
→ Difficult to avoid, the design of the study seems necessary for a realistic study setting. However, the interdisciplinary approach to improve medication adherence is part of the study design. In addition, the CHF medication in both groups will be analysed at V1 and V5.

Contamination at medical practices: physicians intensively engage with the topic (i.e. heart failure, medication adherence and drug-related problems) and apply this additional knowledge to the control patients.
→ Difficult to avoid, the design seems necessary for a realistic study setting. Pharmacists are unaware of the control patients.

Higher detection rate of potential events: Patients in the intervention group receive a more intensive care and have a more intensive contact with health care professionals. The intensified contact could lead to a higher detection rate of events. There is a risk that the recording rate of events differs between control and intervention group.
→ Involvement of e.g. health insurance companies to collect events recorded in the health insurance files.

11.5.3 Exclusion Bias

Potential bias:

Patients of the intervention group may stop following the study protocol because they do not want to visit the pharmacy as frequent as required or because they do not like the weekly dosing aids.
→ Intention-to-treat-analysis

12 Adverse Events

Due to the fact that no investigational medical drug or device is tested, the standard of care is not altered during the study and hard endpoints for this study are chosen (mortality or unplanned hospitalization). Therefore, only hospitalizations and mortality will be documented.

13 Ethical and Legal Aspects

The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that all persons involved in the study abide by Good Clinical Practice (GCP) so far applicable and the ethical principles described in the current revision of the Declaration of Helsinki. The study is carried out according to the legal and ethical requirements (e.g. data protections laws). Written informed consent is obtained from all patients.

13.1 Responsibilities of Scientific Heads

The scientific heads ensure that all persons assisting with the study are adequately informed about the protocol, any amendments to the protocol, the study procedures, and their study-related duties and functions. They maintain a list of all qualified persons to whom they have delegated significant study-related duties.

13.2 Approval of Study Protocol and Amendments

Before the start of the study, the study protocol, informed consent document, and any other appropriate document are submitted to the independent Ethics Committees (EC). Before the first subject is enrolled in the study, all ethical and legal requirements must be met.

13.3 Ongoing Information for Independent Ethics Committee

The EC will be informed of all subsequent protocol amendments, which might require formally approval.

14 Committees

Three different committees are involved in this study:
A Steering Committee (Executive Board) is in charge of strategic advice. Furthermore, a blinded clinical event committee (CEC) for adjudication of hospitalizations and a Committee for Data Protection (DPC) have been implemented. These committees follow a specified charter, which describes the working procedures.

15 Agreements

15.1 Financing of the Study

The study is financed by ABDA, and the pharmacists' state chambers or foundations of Bavaria (Lesmueller-Foundation), North Rhine, and Westphalia-Lippe as well as the Foundation Pharmaceutical Care (FI).

15.2 Reports

ABDA prepares reports in collaboration with Leipzig University, PMV and IZKS Mainz.

15.3 Publication

All information concerning the study is confidential before publication. However, the study protocol will be accessible on the homepage developed for the study (www.pharm-chf.de) for authorized users. The study has been appropriately registered with Clinical Trials.gov Identifier: NCT01692119, before the first patient has been enrolled.

16 Signatures

The present study protocol (Version 3.0) was subject to critical review and has been approved in the present version by the persons undersigned. The information contained is consistent with

- the current risk-benefit assessment of the study treatment(s) and
- the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and the principles of GCP so far applicable.

Date: _____	Signature:	_____
	Name (block letters):	Prof. Dr. Ulrich Laufs
	Function:	Scientific Head of Study
Date: _____	Signature:	_____
	Name (block letters):	Prof. Dr. Martin Schulz
	Function:	Scientific Head of Study
Date: _____	Signature:	_____
	Name (block letters):	Dipl.Math. Christian Ruckes
	Function:	Biometrician IZKS Mainz
Date: _____	Signature:	_____
	Name (block letters):	Dr. Nina Griese-Mammen
	Function:	Study Coordinator at ABDA
Date: _____	Signature:	_____
	Name (block letters):	Dr. Lukas Schollenberger
	Function:	Study Coordinator at IZKS Mainz

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