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

Statistical Analysis Plan

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Glossary of abbreviations and acronyms

ABDA ABDA-Bundesvereinigung Deutscher Apothekerverbände e.V. (Federal Union of German Associations of Pharmacists)
ACEi Angiotensin-Enzyme Converting Inhibitor
ADR Adverse Drug Reaction
AN(C)OVA Analysis Of (Co)Variance
ANCOVA Analysis Of Covariance
ARB Angiotensin Receptor Blockers
ATC Anatomical Therapeutical Classification

BB Beta Blockers
BMI Body Mass Index
BNP B-Type Natriuretic Peptide

CEC Clinical Event Commitee
CHF Chronic Heart Failure
CONSORT Consolidated Standards of Reporting Trials
COPD Chronic Obstructive Pulmonary Disease
CV Cardiovascular

DDD Defined Daily Dose
DMP Disease Management Program
DRP Drug-Related Problems
DSM-IV Diagnostic and Statistical Manual of Mental Disorders

eCRF Electronic Case Report Form
EF Ejection Fraction

GFR Glomerular Filtration Rate
GKV Gesetzliche Krankenversicherung (Statutory health Insurance)
GP General Practitioner

HbA1c Hemoglobin A1c
HDL High Densitiy Lipoproteins
HFmrEF Heart Failure with Mid-range Ejection Fraction
HFpEF Heart Failure with Preserved Ejection Fraction
HFrEF Heart Failure with Reduced Ejection Fraction

ITT Itention To Treat
IZKS Interdisziplinäres Zentrum Klinische Studien (Clinical Research For Medical Advance)

KHK Koronare Herzkrankheit (Coronary Heart Disease)
KV Kassenärztliche Vereinigungen (Associations of Statutory Health Insurance Physicians)

LDL Low Density Lipoproteins
LVEF Left Ventricular Ejection Fraction

MLHFQ Minnesota Living with Heart Failure Questionnaire
MRA Mineralocorticoid Receptor Antagonist

NT-pro-BNP N-Terminal Pro-B-Type Natriuretic Peptide
NYHA New York Heart Association

PDC Proportion of Days Covered
PGA Patient Global Assessment
PHARM-CHF Pharmacy-based Interdisciplinary Program for Patients with Chronic Heart Failure
PHQ Patient Health Questionnaire
PKV Private Krankenversicherung (Private Health Insurance)
PP Per Protocol
PRIME-MD Primary Care Evaluation Of Mental Health Disorders
PRN pro re nata

QoL Quality of Life

SAS Statistical Analysis Software
SHI Statutory Health Insurance
SQL Structured Query Language

TIA Transient Ischemic Attack

V Visit

WHO World Health Organization

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1 Background

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

1.1 Objectives

The aim of PHARM-CHF 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 CHF.

The primary efficacy variable is medication adherence to cardiovascular medication, pre-specified as a significant difference of the proportion of days covered (PDC) between the intervention and control group within 365 days following randomization measured by pharmacy claims data.

The primary safety variable is days lost due to blindly adjudicated unplanned cardiovascular hospitalizations or death of any cause.

1.2 Sample size considerations

Assuming a baseline PDC for cardiovascular medication of 0.7 and a standard deviation of the PDC of 0.22 a sample size of N=176 (88/group) patients is needed to detect a 10% difference 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 planning is based on a two-sided t-test and performed by means of SAS Version 9.4.

1.3 Study design

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

The following inclusion criteria are defined:

- Age: 60 years and older
- Diagnosis of chronic heart failure (CHF)
- Stable* CHF medication including a diuretic (thiazide, loop diuretic and/or MRA). *Stable CHF medication is defined as no relevant change of HF medication in terms of drug therapy started/terminated or dose change, especially of (loop-)diuretics within past 4 weeks.
- Hospitalization for decompensated heart failure within past 12 months or a value of B-type natriuretic peptide (BNP) ≥350 pg/mL or N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) ≥1400 pg/mL
- Written informed consent

The following exclusion criteria are defined:

- Regular/assisted 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.

In the following table, the visit schedule is shown. Visit 2 and visit 4 will be performed as telephone visits; the other visits will be performed at the medical practices.

Table 1 Visit schedule and data collection

	Screening / V1 (month 0)	V2 (after 6 months)	V3 (after 12 months)	V4 (after 18 months)	V5 (after 24 months)	V6 (end of study)
In- and exclusion criteria	X					
Heart failure (leading cause, duration)	X					
CV-risk factors	X		X		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 list	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	

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

Events (hospitalizations and death of any cause) are recorded continuously in the medical practices.

1.4 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.

2 Analysis populations

2.1 Total population

The total set consists of all patients recruited including subjects withdrawn from the study.

2.2 Intention-to-treat population

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 – that is, 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.

The following violations of entry criteria are defined as major and will lead to exclusion from the ITT population:

- Violation of inclusion criteria
  - Hospitalization more than 12 months ago
  - No diuretic (thiazide, loop diuretic and/or MRA) at baseline
- Patient did not undertake the medication review at the pharmacy
- Meeting any exclusion criteria
- Post baseline data not available

Those violations will be displayed by absolute frequencies.

In the following table, patients with violation of major entry criteria and the intention-to-treat population are shown.

Table 2 Violation of major entry criteria and intention-to-treat population

Population	Intervention group	Control group	Total
Randomized (total population)	130	128	258
- patients excluded: no medication review at the pharmacy/consolidated medication plan not available	17	0	17
- patients excluded: violation of major entry criteria	3	1	4
No diuretic	2	1	3
No hospitalization for decompensated heart failure within past 12 months or no BNP/NT-proBNP level above cutoff	1	0	1
ITT	110	127	237

2.3 *Per-protocol population*

The per-protocol (PP) population consists of all subjects of the ITT population who completed the study without major protocol violations – that are violation of inclusion criteria, meeting any exclusion criteria, post-baseline data not available, consolidated medication plan not available (intervention group patients only) and terminated the study prematurely (except death).

The following protocol violations are defined as major and will lead to exclusion from the PP population:

- Terminated the study prematurely (except death) within the first twelve months

This will result in the following sizes of the analysis populations:

Table 3 Major protocol violation and per-protocol population

Population	Intervention group	Control group	Total
Randomized	130	128	258
ITT	110	127	237
- patients excluded: termination within the first twelve months	8	2	10
withdrawal of informed consent	6	1	7
discontinued	2	1	3
PP	102	125	227

2.4 CONSORT flow diagram

The CONSORT flow diagram displays the number of randomized patients, patients included in the ITT population and PP population. This will be displayed overall and for each group (IG/CG) separately. For each group the reason and number of patients affected for exclusion from the ITT population and PP population will be presented.

3 Scope

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 (GKV/PKV) and data from health insurance funds about hospitalizations. The main analysis will be performed by the IZKS Mainz. The PDC will be determined by the pmv research group (University Cologne) and will be submitted to the IZKS Mainz for further analyses. 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.

4 Study centers and study regions

In total, 258 patients have been recruited. 130 patients were randomized into the intervention and 128 in the control group. 110 patients from the intervention group and 127 patients from the control group could be included in the ITT population.
In total, 31 study centres (family physicians/GPs, internal medicine specialists, and both office- and hospital-based cardiologists) and 69 community pharmacies are taking part.
Pharmacies and physicians from nine different Federal States of Germany are taking part – that is, Baden-Württemberg, Bayern, Rheinland-Pfalz, Niedersachsen, Nordrhein-Westfalen, Saarland, Sachsen, Sachsen-Anhalt und Thüringen.

5 Variables

5.1 *Timing of the data completion*

Estimated data completion date: June 2018

5.2 *Participating physicians and pharmacies*

Minimization is used to ensure balance of study regions. Therefore, the study region will be automatically documented at screening. The participating physicians will be assigned to their specialist's group.

5.3 *Demographics and patient characteristics*

The following demographic variables will be documented at screening / visit 1:

- Sex (male / female)
- Date of birth
- *Derived: Age [years] = Date of screening – date of birth*
- *Derived: Age will also be categorized as ≤ 75 years and > 75 years*
- Height (cm)
- *Derived: BMI = weight [kg] / (height [cm] / 100)2*
- *Derived: The BMI will also be categorized as underweight (< 18.5 kg/m2) / normal (between 18.5 kg/m2 and 25 kg/m2) / overweight (≥25 kg/m2)*

The following baseline characteristics will be documented at screening / visit 1:

- Informed consent available (yes/no)
- In- and exclusion criteria
- Randomization result
- Main reason for chronic heart failure (ischaemic, non-ischaemic, other)
- Date of first diagnosis of chronic heart failure (month/year)
- *Derived: Time since first diagnosis [years] = date of screening - date of first diagnosis of chronic heart failure (month/year)*
- Date of last hospitalization due to acute cardiac decompensation
- *Derived: Time since last hospitalization [years] = date of screening - date of last hospitalization due to acute cardiac decompensation*
- *Derived: The time since the index hospitalization will be classified as < 3 months and ≥ 3 months*
- Left ventricular ejection fraction (LVEF, %) at baseline, if available. The LVEF will also be categorized as <40% indicating HFrEF, 40%-49% indicating HFmrEF, ≥50% indicating HFpEF

The following characteristics will be documented at visits 1, 3, and 5:

- Weight (kg)
- Blood pressure (systolic blood pressure, diastolic blood pressure [mmHg]
- Pulse at rest [/min]
- Care level (Pflegestufe; none/1/2/3/missing/unknown)
- Attendance at Disease Management Program (DMP) KHK (yes/no)
- Attendance at DMP KHK – module heart failure (yes/no)
- Heart pacemaker incl. ICD/CRT (yes/no/unknown) (if yes, with or without a defibrillator)
- New York Heart Association Functional Classification (NYHA class I, II, III or IV)
- *Derived: The NYHA class will also be categorized as I/II and III/IV.*
- Smoking status (smoker, non-smoker, former smoker)
- Minnesota Living with Heart Failure Questionnaire (MLHFQ)) (total score) *Derived:* physical and emotional sub-scores, *total score at baseline will be categorized as* < 24, between 24 and 45, > 45)
- Patient Health Questionnaire PHQ-9 (total score)
- *Derived: The PHQ-9 total score at baseline will be categorized as < 10 and ≥ 10*
- Medication adherence (self-reported) (0%-100% in 5% steps)
- PDC
    - PDC at Baseline (183 days)
    - PDC ACEI/ARB at Baseline (183 days)
    - PDC BB at Baseline (183 days)
    - PDC MRA at Baseline (183 days)
    - PDC statins at Baseline (183 days)
    - *Derived: all PDC-values will be categorized as:* < 80% and ≥ 80% and < 88% and ≥ 88%
- Current diagnoses including CV risk-factors (diabetes mellitus, hypertension, hyperlipidemia, family anamnesis of coronary heart disease, coronary heart disease, condition after myocardial infarction, cardiomyopathy, valvular disease, atrial fibrillation, chronic renal disease, COPD, stroke/TIA, depression, malignant tumor, peripheral arterial occlusive disease, sleep apnea, asthma, and further diagnoses)
- Laboratory parameters (HbA1c [%], potassium [mmol/l], creatinine [mg/dl], total cholesterol [mmol/l and mg/dl], HDL-cholesterol [mmol/l] and mg/dl], LDL-cholesterol [mmol/l and mg/dl], triglycerides [mg/dl], BNP, if available [pg/ml], NT-proBNP, if available [pg/ml], urea [mg/dl])
- *Derived: The GFR will be calculated using the Cockcroft and Gault formula*
- Medication plan (eCRF - physician)
    - *Derived: number of drug classes, number of drug packages, number of drug substances, number of single doses per day, number of drug intakes per day*
- First consolidated medication plan (intervention group – pharmacists, visit 1)

- *Derived: number of drug classes, number of drug packages, number of drug substances, number of single doses per day, number of drug intakes per day*

5.4 Hospitalization during study participation and mortality

5.4.1 Documentation

Events (hospitalizations and death of any cause) are recorded continuously in the medical practices. Additionally, health insurance funds will be asked to provide data about hospitalizations. For patients with withdrawal of informed consent no data will be provided by health insurance funds. The different sources and the result of the blinded adjudication by the CEC will be documented.
Apart from hospitalizations and death no further adverse events are collected.

5.4.2 Event classification (according to CEC Charta Version 3.0)

A blinded Clinical Event Committee (CEC) will adjudicate all hospitalizations occurring after randomization according to pre-specified criteria in the CEC Charta:

Hospitalization

For this study, 'hospitalization' is defined as a hospital admission (elective or emergency as documented in the electronic case report form (eCRF) resulting in an overnight stay with date change even if total duration is less than 24 hours. It also includes emergency room visits with date change.

Planned hospitalization

Hospitalizations for diagnostic procedures, elective interventions (such as change of a device battery), or rehabilitative measures are considered to be 'planned hospitalizations' and will not be counted as a hospitalization event with regards to the primary or secondary variables of this study.
For the avoidance of doubt, for a hospitalization that is considered a 'planned hospitalization', the patient must not have had signs or symptoms of worsening cardiovascular diseases.
If in doubt and if data is available, a 'planned hospitalization' can be characterized due to a time-gap between indication and admission.
If the health insurance company has to give a confirmation to cover the costs of the planned hospitalization prior admission to the hospital, this information can be cross-checked.

Cardiovascular hospitalization

Cardiovascular hospitalization will be defined as a hospitalization due to cardiovascular disease or development of a cardiovascular condition during a hospitalization that is

considered to have caused a prolonged hospital stay. Cardiovascular diseases include heart failure, angina, myocardial infarction, syncope, arrhythmia (including atrial fibrillation), stroke, transient ischemic attack, acute peripheral vascular emergencies, pulmonary embolism or other cardiovascular conditions.

Hospitalization with worsening heart failure

A cardiovascular hospitalization will be classified as 'with worsening heart failure' if the reason for admission is worsening heart failure or worsening heart failure is one of the major components of the admission. Hospitalization with worsening heart failure includes signs and symptoms of heart failure induced by supraventricular or ventricular arrhythmias, acute coronary syndromes or renal dysfunction due to worsening of cardiac function (cardio-renal syndrome). If arrhythmias are associated with signs or symptoms of heart failure, the hospitalization will be adjudicated as 'hospitalization with worsening heart failure'. The CEC diagnosis will be made using the criteria described below, irrespective of the investigator and/or discharge diagnosis.
The following two criteria must apply to adjudicate 'hospitalization with worsening heart failure:
(1) Presence of two typical heart failure signs or symptoms (including shortness of breath, dyspnoea on exertion, paroxysmal nocturnal dyspnoea, orthopnoea, fatigue, reduced exercise tolerance, pulmonary oedema, jugular vein distensions, pulmonary rales, S3 on cardiac auscultation, hepatojugular reflux, altered hemodynamics, peripheral oedema, and cardiomegaly)
OR:
Objective evidence for worsening heart failure (as revealed by echocardiography, chest radiography, or measurement of a natriuretic peptide)
AND:
(2) Intensification of heart failure therapy (e.g. changes/introduction of intravenous medication (i.e. a vasodilator or an inotropic agent, or a diuretic) or an increase in oral diuretic therapy for heart failure (e.g. an increase of furosemide ≥40 mg or equivalent or the addition of a loop diuretic to a thiazide diuretic)).
For the avoidance of doubt, if the patient developed worsening of heart failure during a hospitalization (but heart failure was not the reason or a major component of the respective hospital admission), this will not be judged a 'hospitalization with worsening heart failure' but will be deemed a '(planned) cardiovascular hospitalization', if the respective criteria are fulfilled.

Other hospitalizations

Hospital admissions not related to cardiovascular diseases will be classified as 'other hospitalization' (i.e. non-cardiovascular hospitalization).

5.5 *Pharmacy claims data from data processing centres and health insurance funds*

All known German data processing centres (Apothekenrechenzentren) will be asked to send pharmacy claims data of prescribed medicinal products dispensed at community pharmacies for PHARM-CHF patients to the cost of any statutory health insurance (SHI) funds for the whole study duration and additionally for the measurement of baseline adherence for the 183 days before randomization. In addition, health insurance funds (SHI and private) will be asked to provide data about reimbursed medicinal products dispensed at community pharmacies for the same period. The prescribed medicinal product together with dispensing date and the source of information will be documented.

For patients with withdrawal of informed consent no pharmacy claims data will be available. Therefore, the PDC for these patients cannot be calculated.

5.6 *Primary efficacy variable*

The primary efficacy variable is medication adherence, 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.
Medication adherence will be calculated based on the PDC during the 365-days following randomization. The dose information documented at screening / visit 1 or in case of switches at visit 3 will be used. Medication switches, stockpiling, inpatient days (hospital stays), medication fills prior to randomisation, and death will be considered.
To measure baseline adherence, the PDC for the period 183-days before randomization to randomization for each drug class (ACEi/ARB, BB, MRA) will be analysed.
In case of inpatient days, the proportion will be adjusted by excluding days from both the numerator and denominator assuming that patients did not deplete their medication on their medication supply on those excluded days. If a patient switches medications within a class (including ACEi/ARB), the patient's medication supply will be replaced with the new medication supply. If a patient dies, all days following the death will be censored.
Existing medication at randomization (=day 1) and medication dispensed during 14 days after randomization (=day 1) will be considered if at least one additional dispensing occurred during the 365-days follow-up. Existing medication at randomization will be captured, but only the days during the 365-days follow-up will contribute to the final proportion.
Adherence for all three CHF medication classes, if prescribed, will be calculated and can range from 0 to 1.0 (perfect adherence) and will then averaged across all non-missing classes of medications to derive the summary PDC.

PDC:

- PDC at Baseline (183 days), 365 days, 730 days and Individual Follow-up time
- PDC ACEI/ARB at Baseline (183 days), 365 days, 730 days and Individual Follow-up time
- PDC BB at Baseline (183 days), 365 days, 730 days and Individual Follow-up time
- PDC MRA at Baseline (183 days), 365 days, 730 days and Individual Follow-up time
- PDC statins at Baseline (183 days), 365 days, 730 days and Individual Follow-up time
- *Derived: all PDC-values will be categorized as:* < 80% and ≥ 80% and < 88% and ≥ 88%

Table 4 PDC analyses - definition for 365 days' follow-up

	Intervention group (IG) and control group (CG)
ITT	Version 1) From randomization until 365 days following the randomization If a patient dies: the sum of days between randomization and date of death Version 2) If a patient discontinues within 365 days: the sum of days between randomization and discontinuation

5.7 *Primary safety variable*

The primary safety variable is all-cause mortality or unplanned cardiovascular hospitalizations as days lost due to unplanned cardiovascular hospitalizations or death of any cause between baseline (day of randomization) and 365 days. For death, the remaining days to 365 days will be counted. The days spent in hospital will be added to the days after death until 365 days.

The percentage of days lost due to hospitalisation and death will be calculated as the ratio of the sum of the number of days lost due to death and spent in hospital during the 365-days follow-up and the respective patient follow-up time, expressed in percent.

If a patient terminated the study within 365 days, the days lost between the day of randomization and the day of discontinuation will be analysed accordingly.
For days lost due to unplanned cardiovascular hospitalizations, the admission und discharge day will be counted as one day. Calculations will be done in days.

5.8 Secondary efficacy variables

5.8.1 Adherence to medication

We will analyse the PDC during the 365-days follow-up 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%). In addition, we will perform the different types of calculating the PDC between baseline and 730 days.

If a patient discontinues within 730 days, the days between randomization and the day of discontinuation will be analysed. Days after death will be censored.

We will analyse the PDC for lipid modifying agents accordingly (at baseline, during 365-days follow-up, during 730-days follow-up, percentage of patients with a mean PDC ≥80% (=adherent; sensitivity analyses for a cutpoint ≥88%).

The different calculations of the PDC will be performed by the pmv research group.

It will be checked, if the PDC data are suited for a non-parametric approach by checking the histogram for the distribution of the PDC data. If the PDC are not suited for a parametric / non-parametric analysis approach, categorization of the data will be considered.

5.8.2 Quality of Life (QoL)

Change in MLHFQ -questionnaire overall score between baseline and 365 days (main secondary outcome) and between baseline and 730 days (other secondary outcome). The Minnesota Living with Heart Failure (MLHF) questionnaire will be filled out at screening, visit 3 (after 12 months), and visit 5 (after 24 months). The MLHF is specific for chronic heart failure and consists out of 21 items which are scored on a 6 point Likert-scale (0=”not at all” to 5=”very much”). Each question is about how much a special facet prevented the patient from living as desired. The total score is calculated as the sum over all non-missing items and ranges from 0 to 105: higher scores indicate worse QoL. A score of < 24 signifies a good, a score between 24 and 45 signifies a moderate, and a score > 45 signifies a poor QoL.

5.8.3 Patient Global Assessment (PGA)

The PGA scale consists of a simple judgement indicating improvement, no change, or worsening since the start of the study and is documented after 12 months (visit 3) and at visit 5 (24 months) on a 7 point Likert scale (1=”very much improved” to 4=”unchanged” to 7=”very much worsened”).
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.

5.8.4 Patient Health Questionnaire (PHQ-9)

Change in depression measure by the Patient Health Questionnaire (PHQ-9D = validated German version of the PHQ-9) between baseline and 365 days (main secondary outcome) and between baseline and 730 days (other secondary outcome). The PHQ-9D will be filled out at screening, visit 3 (after 12 months) and visit 5 (after 24 months). The PHQ-9D is a self-administered version of the PRIME-MD diagnostic instrument common mental disorders. The PHQ-9 is the depression module, which scores each of the 9 DSM-IV criteria. It has been validated for use in primary care. The PHQ-9D questionnaire will be analysed by assigning 0 point for the category “never”, 1 point for the category “at some days”, 2 points for the category “at more than 50% of the days” and 3 points for the category “nearly every day”. The total score will be calculated building the sum of all items and therefore ranges between 0 and 27. The cut-off for signs of depression was set at a PHQ-9 score of ≥10.

5.8.5 Self-estimated adherence

The self-estimated adherence is documented at visit 1, 3, and 5 on a scale from 0 to 100 percent in 5 % steps and absolute values by visit and changes will be analysed between baseline and visit 3, and visit 5, respectively.

5.9 Secondary safety variables

The following secondary safety outcomes will be evaluated during 365-days follow-up according to the primary safety variables:

- Percentage of days lost due to unplanned cardiovascular (CV) hospitalizations or all-cause death
- 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
- Percentage of days lost due to hospitalizations of any cause or death of any cause
- Unplanned all-cause hospitalizations
- All-cause mortality

The following secondary safety outcomes will be evaluated during the patient’s individual time within study (=individual follow-up time):

- 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)
- Percentage of days lost due to unplanned cardiovascular hospitalizations
- Percentage of days lost due to hospitalizations of any cause
- Unplanned all-cause hospitalizations

- All-cause mortality

Table 5 Secondary safety variables - Definition of patients' individual follow-up time

	Intervention group (IG) and control group (CG)
ITT	From randomization until end of study. End of study: - 31.12.2016 - If date of visit 6 or last visit in 2017: 31.12.2016 - If date of final study visit before 30.06.2016: Date of visit 6 - Death: date of death - Withdrawal of informed consent: date of withdrawal - Premature termination of study: date of premature termination

The percentage of days lost due to hospitalisation will be calculated as the ratio of the sum of the number of days lost due to stays in hospital during the respective patient follow-up time and the respective patient follow-up time, expressed in percent.

For days lost due to unplanned cardiovascular hospitalizations, the admission und discharge day will be counted as one day. Calculations will be done in days.

5.10 Other variables

5.10.1 Adverse events

Apart from hospitalizations and deaths no further adverse events are specifically collected within this study.

5.10.2 Laboratory parameters

The following laboratory parameters will be documented at visit 1, 3, and 5:

- HbA1c [%]
- Potassium [mmol/l]
- Creatinine [mg/dl]
- Total cholesterol [mg/dl] and [mmol/l]
- HDL-cholesterol [mg/dl] and [mmol/l]
- LDL-cholesterol [mg/dl] and [mmol/l]
- Triglycerides [mg/dl] and [mmol/l]
- BNP [pg/ml], if available
- NT-proBNP [pg/ml], if available
- Urea [mg/dl]

5.10.3 Vital signs

The following vital signs will be documented at visit 1, 3, and 5:

- Systolic blood pressure [mmHg]
- Diastolic blood pressure [mmHg]
- Pulse [/min]

5.10.4 Documentation of intervention

5.10.4.1 Medication review

DRP (drug-related problems)

Pharmacists detected possible DRP in the medication review at the first patient interview after inclusion (intervention group only). They used a brown bag review and existing pharmacy patient records for information on current medication. They compared these sources with the medication plan provided by the recruiting physician (eCRF). For a standardized procedure, pharmacists used a checklist to identify and document possible DRP. Omission and commission of drugs, other deviations in dosing regimen, duplications, interactions, contraindications, adverse drug reactions (ADR), non-adherence, problems in drug handling, splitting of tablets that must not be split, and “others” were defined as DRP in this study. The pharmacists aimed to solve the DRP and document the result of the intervention. Throughout the study, pharmacists documented DRP continuously. The documented DRP will be classified by the Department of Medicine, ABDA.

Discrepancies

Deviations between physician’s medication plan (eCRF), pharmacist’s brown bag interview (paper based) and first consolidated medication plan (eCRF) were defined as discrepancies. Those include in particular omissions and commissions of drugs, mixing up intended long-term and as needed (PRN) use as well as non-exclusive deviations in frequency, number of units, timing of administration and drug strength. Discrepancies will be identified and classified by the Department of Medicine, ABDA.

5.10.4.2 Weekly pharmacy visits

In the intervention group, the patient visits weekly or biweekly the pharmacy to collect their prepared medication. In case a collection by the patient or a relative was not possible, pharmacists documented the reason and delivered the medications to the patient’s home, if appropriate. Pharmacists were required to ask the patient several health-related questions to record possible changes and to identify a need for an (immediate) doctor’s visit. Content was the health status, newly developed symptoms, decrease in performance, adherence to medication regimen, changes in weight or blood pressure and pulse.

The following parameters will be assessed:

- The choice of weekly or biweekly visits
- Number and percentage of weeks where medication was dispensed
- The way patient got medication (at the pharmacy, delivered at home, got medication in advance, not dispensed due to hospitalization, not dispensed due to stay at nursing home, not dispensed due to other reasons, patient died)
- Consultation of physician is recommended (yes, no, could not be assessed)

- Direct consultation of the physician performed (yes, no, could not be assessed)
- Reason for consultation (chest pain, dyspnoea, oedema, change of performance, dizziness/faint, extra systole, pulse, blood pressure, non-adherence, drug related problems (DRP), other).
- Changes of the medication plan

5.10.4.3 Survey on satisfaction of participating physicians and pharmacists

Participating physicians and pharmacists completed a survey on different aspects of PHARM-CHF after the study. They were asked to evaluate the study and the cooperation between physician and pharmacist within the study.

6 Missing values and outliers

6.1 Missing values

No substitution of missing values will be done.

6.2 Outliers

No methods for detection of outliers will be employed.

7 Statistical analyses

Categorical variables will be presented by numbers and percentages. If not otherwise stated, the missing values will be shown as an additional missing category and the percentages will be calculated based on all non-missing values.

Continuous variables will be summarised by the descriptive statistics n, mean, standard deviation, minimum, 25%-quartile, median, 75%-quartile and maximum.

All variables will be shown for each treatment group and in total.

All variables documented in the eCRF will be provided by patient in Excel datasheets.

7.1 Timing of final analysis

When all data from the eCRF, the data processing centres and the health insurance funds will be collected, study data will be prepared for determination of the PDC. Afterwards the final analyses will be performed.

Estimated timing of final analysis: February 2019

All outcomes will be analysed collectively.

7.2 *Patient disposition*

The following patient disposition variables will be presented by numbers and percentages for the total, ITT and the PP population:

- Randomized
- Major protocol violations (with details listed)
- Deaths
- Discontinued except death (with reasons listed)
- Time within the study (≥12 months) of the patients who died
- Time within the study (≥12 months) of the patients who discontinued except death
- Time within the study of all patients

365 days follow-up
- Terminated prematurely
  - Withdrawal of informed consent
  - Discontinuation
- Death
- Completed first 365 days of study

Follow-up between 365 and 730 days:
- Terminated prematurely
  - Withdrawal of informed consent
  - Discontinuation
- Death
- Study duration <730days
- Completed 730 days of study

The following patient disposition variables will be presented by sample characteristics for the total, ITT and the PP population:

- Number of events
- Number of unplanned cardiovascular hospitalizations
- Number of unplanned cardiovascular hospitalizations (365 days)
- Number of events per patient
- Time within the study of the patients who died
- Time within the study who discontinued except death
- Time within study overall
- Time within study of patients who terminated the study regularly

The participation on visit 1, visit 3, and visit 5 as well as the possible reason for drop out will be will be tabulated for the ITT.
The individual duration of study will be calculated for each patient by duration = (date of end of study – date of randomization) + 1 and will be analysed descriptively.

7.3 Adherence to intervention

The exposure will only be assessed for the intervention group by counting the weekly visits at the pharmacies if patient got medication. Hospital stays and the choice of weekly and biweekly visits will be considered. The number of visits at the pharmacy and the number of visits at the pharmacy per duration of study in weeks will be tabulated for the intervention group.

7.4 Participating physicians and pharmacies

The number of pharmacies, physicians and patients per study region, the number of patients per pharmacy and physician and the number of physicians per specialist's group will be tabulated.

7.5 Demographics and patient characteristics

The following variables will be presented for ITT and the PP population.

7.5.1 Demographics

All variables mentioned in chapter 5.3 will be tabulated.

Exploratory p-values of the Chi-Square test on differences between the treatment groups will be shown for categorical variables. They will be interpreted on a significance level of 5%.

Exploratory p-values of the t-test on differences between treatment groups assuming unequal variances will be shown for continuous variables. They will be interpreted on a significance level of 5%.

7.5.2 Patient characteristics

All variables mentioned in chapter 5.3 will be tabulated for the baseline visit. If variables will also be collected at subsequent visits, the variables will also be displayed by visit (e.g. laboratory parameters and vital signs).

Exploratory p-values of the Chi-Square test on differences between the treatment groups will be shown for categorical variables. They will be interpreted on a significance level of 5%.

Exploratory p-values of the t-test on differences between treatment groups assuming unequal variances will be shown for continuous variables. They will be interpreted on a significance level of 5%.

7.6 Medication therapy

The following variables will be presented for ITT and the PP population.

7.6.1 Medication therapy documented by physicians and pharmacists

Medication therapy will be presented by numbers and percentages. Drug substances will be coded in the most current version according to WHO ATC.

Medication therapy will be provided by ATC 2 and 4 levels for the medication plan provided by the recruiting physician (eCRF, at baseline, after 12 months, and after 24 months), the first consolidated medication plan (intervention group) and the medication plan documented by the pharmacy over time (intervention group).

Medication therapy will be provided by ATC level 5 for medicines belonging to the ATC code 1st level C ('cardiovascular system') provided by the recruiting physician (eCRF at Baseline, after 12 months, and after 24 months) and the first consolidated medication plan (intervention group).

The number of brand products (drug packages like Aspirin® or RAMIPRIL comp-CT® 5 mg/25 mg), the number of drug classes (level 4, distinct ATC-codes), the number of drug substances (counting each drug substance of fixed combinations: e.g., RAMIPRIL comp-CT® 5 mg/25 mg = 2 drug substances i.e. ramipril and hydrochlothiazide), the number of single doses per day and the number of drug intakes per day (e.g. morning, noon, evening, at night) will be presented for data provided by the physician (eCRF at baseline, after 12 months, and after 24 months) and first consolidated medication plan (intervention group).

Number of single doses per day counts every intake of a brand product per day per patient. Number of intakes per day counts, how often the patient takes medicine per day.

For the ATC code 1st level C (cardiovascular system) the number of brand products (drug packages like Aspirin® or RAMIPRIL comp-CT® 5 mg/25 mg), the number of drug classes (level 4, distinct ATC-codes), the number of drug substances (counting each drug substance of fixed combinations: e.g., RAMIPRIL comp-CT® 5 mg/25 mg = 2 drug substances), the number of single doses per day and the number of drug intakes per day (e.g. morning, noon evening, at night) will be presented for data provided by the physician (eCRF at baseline, after 12 months and after 24 months) and first consolidated medication plan (intervention group).

For heart failure medication (ACEi/ARB, BB, MRA and their combinations) and lipid modifying agents (statins, others) the dosage per day (baseline, visit 3, and visit 5) in DDD and the changes between visit 1, 3, and 5 (new medications, stopped medications, changes regarding strength and dosage, number of single doses) and one versus half a tablet (splitting) will be presented.

7.6.2 Pharmacy claims data

The number of patients with data from data processing centres (Apothekenrechenzentren) and data from statutory health insurance (SHI) funds will be analysed.

7.7 Hospitalization during study participation

Events regarding hospitalization are recorded in the medical practices (eCRF) and will be provided by health insurance funds. The number of events provided by medical practices and provided by health insurance funds will be tabulated. The number of events adjudicated as unplanned hospitalization by the CEC will be compared between the two sources. For patients with both data sources, the amount of underreporting will be calculated.

7.8 Primary efficacy analysis

The primary efficacy analysis is the analysis of the PDC between baseline (day of randomization) and 365 days. The pharmacy claims data will be provided by data processing centres and health insurance funds. However, health insurance data were not available for all patients included in the study. Differences between patients with data from data processing centres and data from health insurance funds cannot be excluded. Therefore, an analysis will be performed comparing the data from health insurance funds and data processing centres. The analysis will be conducted twice. On the one hand, the analysis will be adjusted for data from health insurance funds (yes/no). And on the other hand, the analysis will be adjusted for data from health insurance funds (yes/no) and for baseline adherence (yes/no).

Analysis adjusted for data from health insurance funds only
The PDC (adjusted for data from health insurance funds only) 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 level of significance will not be divided among further hypotheses.

The following hypothesis will be tested:
H0: mi=mc vs. H1: mi≠mc,

Where mi denotes the median value of the intervention group and mc denotes the median value of the control group.

The following SAS code can be used:

```
proc freq data=xxx;
    table updated*treatment group*PDC / cmh scores=modridit noprint;
    run;
```

Analysis adjusted for data from health insurance funds and baseline adherence
The PDC (adjusted for data from health insurance funds and baseline adherence) will be analysed by an analysis of covariance (ANCOVA). Treatment group will serve as a fixed effect and baseline adherence will serve as a random effect. Treatment groups will be compared on a two-sided level of significance of 5%. The level of significance will not be divided among further hypotheses.

The following hypothesis will be tested:

H0: $\mu i = \mu c$ vs. H1: $\mu i \neq \mu c$,

Where μi denotes the mean value of the intervention group and μc denotes the mean value of the control group.

The primary analysis population for both adjustment types is the ITT population. However, the primary analysis (both adjustments) will be repeated for the PP population for sensitivity. As a further sensitivity analysis an analysis of (co)variance (AN(C)OVA) for the PDC will be done with PDC as dependent variable, and the further fixed effects treatment (intervention vs. control), data from health insurance funds (yes/no), sex (male vs. female), age (≤75 vs. >75 years), NYHA functional class (I and II vs. III and IV), PHQ-9 score (score <10 vs. ≥10) and diabetes mellitus (yes vs. no). The study region will be omitted since this may lead to an over determination of the analysis model.

7.9 Primary safety analysis

The primary safety variable is all-cause mortality or unplanned cardiovascular hospitalizations as number of days lost due to unplanned cardiovascular hospitalizations or death between baseline (day of randomization) and 365 days.
The percentage of days lost due to death of any cause or unplanned cardiovascular hospitalizations as the fraction of maximum possible days alive and out of hospital 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.

7.10 Secondary analyses

All parameters will be tested for the ITT population on a two-sided level of significance 5%. All p-values will be interpreted in an exploratory way.
All secondary variables will also be analysed for the PP population. These analyses will be considered as exploratory only.

7.10.1 Secondary efficacy analyses

7.10.1.1 Adherence to medication

The primary efficacy analyses will also be repeated 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%).

We will also perform the different types of calculating the PDC for lipid modifying agents.

We will additionally perform the different types of calculating the PDC between baseline (day of randomization) and 730 days and baseline and individual follow-up time.

7.10.1.2 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 (LSMEAN 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.

7.10.1.3 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.

7.10.1.4 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), treatment group and in total. T-tests for comparing treatment groups will be performed.

7.10.1.5 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.

7.10.2 Secondary safety analyses

All-cause mortality or unplanned cardiovascular hospitalizations as recurrent event

All-cause mortality or unplanned cardiovascular hospitalizations will be analysed by Negative Binomial Regression with treatment as factor and data from health insurance funds (yes/no) and time within study as offset variable. The logarithm will be used as link function.

Events regarding hospitalization are recorded in the medical practices (eCRF) and will be provided by health insurance funds. However, health insurance data were not available for all patients included in the study. Differences between patients with and without data from health insurance funds cannot be excluded. Therefore, the analysis will be adjusted for data from health insurance funds (yes/no).

The following SAS code can be used:

```
PROC GENMOD DATA=indata;
        CLASS treatment;
        MODEL primsafetyendpoint = treatment … / LINK=log DIST=negbin
OFFSET=log_time
        LSMEANS treatment / DIFF CL;
RUN;
```

The results are provided showing parameter estimates, LSMEANs and LSMEAN-differences together with their corresponding p-values and 95% confidence intervals as well as the negative binomial dispersion parameter.
Additionally, the number of deaths and unplanned cardiovascular hospitalizations will be analysed descriptively.
Although statistical guidelines (“Points to consider on adjustment for baseline covariates”) suggest adjusting the primary 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.
Several analyses for sensitivity are performed.
1. The analysis is repeated for the PP population
2. The analysis is repeated, but the characteristics from the randomization process are also included in the analysis model (sex (male vs. female), age (<75 vs. ≥75 years), NYHA functional class (I and II vs. III and IV), PHQ-9 score (score <10 vs. ≥10), diabetes mellitus (yes vs. no). All characteristics are included in the model as covariates at the same time without any interaction terms.
3. There is a Kaplan-Meier analysis for the time to first event (death or unplanned cardiovascular hospitalization, whatever occurs first). If no event is reported, time will be censored at the time of last contact. The median time to event will be displayed together with the 25% and the 75% quartile.

Unplanned cardiovascular hospitalizations (recurrent event, number)

The number of unplanned cardiovascular hospitalizations will be analysed by Negative Binomial Regression with treatment and data from health insurance funds (yes/no) as factor and time within study as offset variable. The logarithm as link function will be used.
Additionally, the number of unplanned hospitalizations and the cumulative number of unplanned cardiovascular hospitalizations per visit will be analysed descriptively by treatment group and in total. Explorative p-values for the difference between treatment groups will be shown. There will be a Kaplan-Meier analysis for the time to first unplanned cardiovascular hospitalization. If no unplanned cardiovascular hospitalization is reported, time will be censored at the time of last contact or death. The median time to unplanned cardiovascular hospitalization will be displayed together with the 25% and the 75% quartile.

Unplanned hospitalizations for heart failure (recurrent event, number)

The number of unplanned hospitalizations for heart failure will be analysed by Negative Binomial Regression with treatment and data from health insurance funds (yes/no) as factor and time within study as offset variable. The logarithm as link function will be used.
Additionally, the number of unplanned hospitalizations for heart failure and the cumulative number of unplanned hospitalizations per visit will be analysed descriptively by treatment group and in total.
The analysis will be adjusted for data from health insurance funds (yes/no).
There will be a Kaplan-Meier analysis for the time to first unplanned hospitalization for heart failure. If no unplanned hospitalization for heart failure is reported, time will be censored at the time of last contact or death. The median time to unplanned hospitalization for heart failure will be displayed together with the 25% and the 75% quartile.

Percentage of days lost due to unplanned cardiovascular hospitalization of any cause or death of any cause

The SECONDARY safety variable is all-cause mortality or unplanned cardiovascular hospitalizations as percentage of days lost due to unplanned cardiovascular hospitalizations or death between baseline (day of randomization) and individual follow up date.
The number of days lost due to death of any cause or unplanned cardiovascular hospitalizations as the fraction of maximum possible days alive and out of hospital 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

Percentage of days lost due to hospitalization of any cause or death of any cause

The number of days lost due to hospitalization of any cause or death of any cause as the fraction of actual days alive and out of hospital will be analysed by a two-sided stratified Wilcoxon signed-rank test (van Elteren test) comparing both treatment groups. Additionally, the number of days lost due to hospitalization or death of any cause will be analysed descriptively by treatment group and in total.

The analysis will be adjusted for data from health insurance funds (yes/no).

Unplanned all-cause hospitalizations

The number of unplanned all-cause hospitalizations will be analysed by Negative Binomial Regression with treatment and data from health insurance funds (yes/no) as factor and time within study as offset variable. The logarithm as link function will be used.
Additionally, the number of unplanned all-cause hospitalizations and the cumulative number of unplanned all-cause hospitalizations per visit will be analysed descriptively by treatment group and in total.
There will be a Kaplan-Meier analysis for the time to first unplanned all-cause hospitalization. If no unplanned all-cause hospitalization is reported, time will be censored at the time of last contact or death. The median time to unplanned all-cause hospitalization will be displayed together with the 25% and the 75% quartile.

All-cause mortality

All-cause-mortality (time to death from any cause) will be analysed using the logrank test. The time to death from any cause will be displayed by a Kaplan-Meier curve. The median time to death from any cause will be displayed together with the 95% confidence interval. If no death is reported, time will be censored at the time of last contact. Additionally, the time to death will be analysed descriptively by treatment group and in total.

7.11 Subgroup analyses

Exploratory subgroup analyses will be performed for the primary efficacy and primary safety variables. Additionally, subgroup analyses for the PDC of each drug class, the mean PDC ≥80%, all-cause mortality or unplanned cardiovascular hospitalizations as recurrent event, unplanned cardiovascular hospitalizations as recurrent event, and all-cause mortality will be performed.

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). 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),
- Time between last heart failure hospitalization and randomization (< 3 months vs. ≥3 months)Number of different drug substances (median at randomisation), as an indicator of the level of illness burden
- Number of different co-morbidities (median at randomisation), 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%)

The subgroup analyses will be displayed by the interaction term as well as descriptive statistics by subgroup.

7.12 Other parameters

7.12.1 Adverse events

Hospitalizations and mortality will be documented and analysed in safety analyses. No further adverse events will be documented.

7.12.2 Laboratory parameters

Laboratory parameters and their changes to baseline will be analysed descriptively by visit. Lipids (total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides) will be displayed in [mmol/L] and [mg/dL]. Lipids will also be presented for the subgroup of patients using lipid-modifying agents.

7.12.3 Vital signs

Blood pressure, pulse and weight will be analysed descriptively by visit, treatment group and in total. In addition, the change from baseline will be tabulated for pulse and weight. Blood pressure will also be presented for the subgroup of patients suffering from hypertension.

7.13 Analyses of intervention

7.13.1 DRP

The following analyses will be performed by ABDA: Analysis of DRP detected by pharmacist in the study will be performed descriptively. Therefore, we present the total number of DRP, the number of DRP per drug, the number of DRP per patient and the number of DRP in the defined categories throughout the study. We also present the number of solved DRP. Data will be presented in totals, median and inter quartile (1st and 3rd quartile) ranges, mean and standard deviation or percentages.

7.13.2 Discrepancies

Analysis of discrepancies detected in post-hoc examinations by the Department of Medicine, ABDA, will be performed descriptively. We present the total number of drugs with at least one discrepancy and the total number of patients with at least one discrepancy in their medication. Medications will be analysed considering the distribution of discrepancies per drug and the types of discrepancies (exclusive: omission, commission, mix up; non-exclusive: deviations in frequency, number of units, timing of administration and drug strength. In addition, the distribution of drugs with omission or commission will be analysed considering the type of recruiting physician. Data will be presented in totals, median and inter quartile (1st and 3rd quartile) ranges, mean and standard deviation or percentages.

7.13.3 Weekly pharmacy visits

Analysis of weekly pharmacy visits will be conducted descriptively. We describe the regular cycle of visits per patient and the results of the documentation of the medication supply. In addition, we describe the documentation on pharmacist's recommendation to the patient regarding a doctor's visit to clarify identified problems such as DRP. We will quantify the identified problems and give examples of uncategorized problems ("Other"). Data will be presented in totals, median and inter quartile (1st and 3rd quartile) ranges, mean and standard deviation or percentages.
The parameters:

- The way patient got medication (at the pharmacy, delivered at home, got medication in advance, not dispensed due to hospitalization, not dispensed due to stay at nursing home, not dispensed due to other reasons, patient died)
- Consultation is recommended (yes, no, could not be assessed)
- Direct consultation of the physician performed (yes, no, could not be assessed)
- Reason for consultation (e.g. chest pain, dyspnoea, oedema, change of performance, dizziness/faint, pulse, blood pressure, non-adherence, drug related problems (DRP), other)
- Changes of the medication plan

will be displayed by descriptive statistics.

7.13.4 Survey on satisfaction of participating physicians and pharmacists with patients of the intervention group

The survey contains multiple-choice questions and open text questions. The multiple-choice questions will be analysed descriptively. The answers of the open text questions will be checked for signal statements, which will be extracted for the evaluation.

7.14 Interim analyses

No interim analyses will be performed.

8 Software

All analyses by IZKS will be performed using the Statistical Analysis Software (SAS), Version 9.4.
Analyses by ABDA will be performed using Microsoft Office Excel 2016.
Analyses by PMV will be performed using Microsoft SQL 2016.

9 References

Recommendations for a minimum set of items that should be addressed and included in SAPs for clinical trials were considered where appropriate[1].

1. Gamble C, Krishan A, Stocken D et al. Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. JAMA 2017; 318: 2337–43.

10 Appendices

The Planned tables and figures will be displayed in an additional document.