Disease and Medication Knowledge Improvement: A Swiss Single-center Randomized Controlled Trial With Heart Failure Inpatients

Study type:	Other clinical trial according to ClinO, Chapter 4
Risk categorization:	risk category A
Study registration:	Intended for submission to the federal clinical trials database (SNCTP) and the international database, clinicaltrial.gov
Sponsor:	None
Principal Investigator	Mégane Jermini Rue Gabrielle Perret Gentil 4 CH-1205 Geneva Mégane.Jermini@hcuge.ch
Intervention studied:	Educational pharmaceutical intervention for hospitalized heart failure patients
Protocol identification	2022-00731
Version and Date:	Version 2 (dated 7/22/2022)

PRIVACY STATEMENT

PROTOCOL SIGNATURE FORM*

Title of the study	Disease and Medication Knowledge Improvement: A Swiss Single-center Randomized Controlled Trial With Heart Failure Inpatients
Protocol identification	2022-00731

The Sponsor-Investigator has approved this version of the protocol and hereby confirms that the study will be conducted in accordance with the protocol, the current version of the World Medical Association Declaration of Helsinki, the ICH-GCP guidelines or ISO 14155 and applicable local legal requirements.

Investigator:

Name: Ms. Mégane Jermini

Date: _____ Signature:

Department Head (Sponsor):

Pharmacy of the HUG: Pr. Pascal Bonnabry

Date: _____ Signature:

Associate Physician Assistants:

Department of Internal and General Medicine: Dr. Jérôme Stirnemann

Date: _____ Signature:

Cardiology Department: Dr. Philippe Meyer

Date: _____ Signature:

*The original signed form sets at the end of this document.

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GLOSSARY AND ABBREVIATION S

AE	Adverse Event
BASEC	Business Administration System for Ethical Committees
BMQ	Beliefs about Medicines Questionnaire
CDMS	ClinicalTrial Data Management System
OClinO	Clinical Trials Ordinance
CRA	Clinical Research Associate
CRCC	Clinical Research Centre
CRF	Case Report Form
CRTs	Cardiac Resynchronization Devices
DAI	Dimplantable automatic defibrillator
DPA	Data Protection Act
eCRF	Electronic Case Report Form
Educ-IC	Therapeutic education in heart failure patients
eGFR	Testimated glomerular filtration rate
FOPH	Federal Office of Public Health
GCP	Good Clinical Practice
GPD	Gilet portable defibrillator
HF	heart failure
HFrEF	Heart failure with reduced ejection fraction
HFmrEF	Heart failure with mildly reduced ejection fraction
HUG	University Hospitals of Geneva
ICH	International Conference on Harmonisation
LLAI	lower limb arterial insufficiency
LRHL	Law on Research on Human Beings
LVAD	Left ventricular assist device
LVEF	Left ventricular ejection fraction
MEMS	Medication Event Monitoring System
NYHA	New York Heart Association
PDC	Proportion of days covered
PROM	Patient Related Outcome Measure
RR	Relative risk
SAE	Serious Adverse Event
SARS-Cov-2	Severe acute respiratory syndrome coronavirus 2
SNCTP	Swiss National Clinical Trials Portal
STEMI	IST-segment elevation myocardial infarction
TPE	Therapeutic patient education
TIA	Transient ischemic attack
UNIGE	University of Geneva

1 SYNOPSIS OF THE STUDY

Sponsor-Investigator	Megane Jermini University Hospitals of Geneva Rue Gabrielle Perret Gentil 4 CH-1205 Geneva Mégane.Jermini@hcuge.ch
Study Title	Disease and Medication Knowledge Improvement: A Swiss Single-center Randomized Controlled Trial With Heart Failure Inpatients
Short title / Study ID	Educ-IC 2022-00731
Protocol version and date	Version 2.0 (22.07.2022)
Study Registration	Intended for submission to the federal clinical trials database, Swiss National Clinical Trials Portal (SNCTP) and the international database, clinicaltrial.gov
Study category and Rationale	Clinical trials with interventions that are neither a therapeutic product nor a transplant, category A Other clinical trial according to ClinO, chapter 4
Background and Rationale	People with heart failure are at risk of frequent hospitalization for cardiac decompensation. The stability of heart failure with reduced left ventricular ejection fraction (LVEF) is dependent on adequate and regular use of many medications. One reason for cardiac decompensation is poor medication adherence. To improve adherence, we would like to increase the knowledge of heart failure patients about their disease and their medication by conducting a therapeutic patient education (TPE) intervention. This research project consists in setting up a pharmaceutical intervention with an educational aim for the patient during his hospitalization. The intervention consists of a therapeutic education interview conducted by a clinical pharmacist using playful tools adapted to the needs of heart failure patients. This intervention will take place at the hospitalized patient's bed. It will be associated with a preparation interview for the hospital discharge and a follow-up of the continuity of care during the week of the return home.
Risk/benefit assessment	The educational intervention of the pharmacist does not present any risk for the patient because it will not impact his medical management. It will be given in addition to the standard basic advice provided to patients and will provide them with quality medical information on heart failure (definition, symptoms, follow-up) and its treatments (indications, benefits, risks). It will allow the patient to be autonomous in monitoring the evolution of his disease and in the attitudes to adopt in case of aggravation of his disease.
Objective(s)	The primary objective is to evaluate the change in heart failure patients' knowledge about their disease and medications using standardized inpatient teaching, accompanied by telephone follow-up on return home. The secondary objective is to evaluate whether this change alters patients' beliefs about their heart failure

	medications as well as improving their adherence to the treatments they receive. In the short term, this educational intervention could have an effect on the risk of readmission for acute heart failure at 1 month after hospital discharge or on mortality and thus have an impact on healthcare system costs.
Endpoint(s)	Primary Endpoint: Patients' level of knowledge about their disease and heart failure medications before the educational pharmaceutical intervention and after the intervention, as well as at 1 month after hospital discharge. It will be measured by means of a 17-question questionnaire specifically developed for this project. This level is valued by a minimum score of 0 points and a maximum of 17 points. This criterion will also be assessed for both groups during hospitalization and at 1 month after discharge. Secondary endpoints : Beliefs about medication will be measured via the specific Beliefs about Medicine Questionnaire (BMQs) score before the intervention and at 1 month after hospital discharge. Adherence will be assessed with the Three Item Self Report Scale before the procedure and at 1 month after discharge. These two criteria will also be assessed in both groups, during hospitalization and at 1 month after discharge. Patient satisfaction will be assessed directly after the teaching intervention and at 1 month after hospitalization. The consumption of unplanned care such as re-hospitalizations, emergency medical visits will be evaluated at 1 month of hospitalization as well as the death rate at 1 month of hospitalization. A follow-up questionnaire on the return home will allow us to identify the patient's feelings and experiences on their return from the hospital The usability of a smartphone application, CardioMeds® , developed for heart failure patients by the University Hospitals of Geneva (HUG) will be explored at 1 month after the return home of patients who have agreed to install it on their smartphone and to use it. Their self-care skills following the use of this mobile (smartphone) application will also be measured using a validated questionnaire.
Study Design	Single-center randomized controlled trial
Statistical considerations	The final analysis will use an intention-to-treat analysis, including all patients who were randomized into the study. Continuous variables will be expressed as means ± standard deviations, median and interquartile range. The categorical variables will be described by their numbers and the proportion as a percentage.

	Some continuous data such as age, income, left ventricular ejection fraction (LVEF), laboratory data, length of hospital stay, number of pre- and post-hospitalization medications, and number of hospitalizations will be reclassified into categories. Differences in outcomes between the intervention and control groups will be analyzed using the t-test for continuous variables and a Chi-square test for categorical variables. The main analysis assessing knowledge status will compare the knowledge score (dependent variable) between the two randomization groups (main independent variable) after adjusting for prior knowledge status using a linear regression or ANCOVA model. For continuous secondary outcomes (medication beliefs and adherence), a Student's t-test will be used to compare the mean values between the two groups. For binary outcomes (rehospitalization or new emergency department visit within 1 month), a Chi-2 or Fisher exact test (if smallest expected number<5) will be used to compare proportions between the two randomization groups. For the satisfaction outcome, which is an ordinal qualitative variable, a Chi-2 or Fisher exact test (if the smallest expected number of participants<5) will be used.
Inclusion/exclusion criteria	Inclusion criteria: -Hospitalization in the Department of General Internal Medicine or Cardiology for decompensated heart failure with lowered LVEF (≤40%) from any cause or mildly lowered LVEF (41-49%) with the presence of heart failure-specific drug therapy -Stability of the patient's clinical condition - ≥ 2 heart failure medications - ≥18 years -Full capacity of discernment -Absence of cognitive impairment -Ability to speak, understand and read in French -Get a personal telephone (mobile or landline) -Consent form signed by the participant Exclusion Criteria: -Inability to follow study procedures -Institutionalized persons -Asylum seekers, homeless people, prisoners -Incapacity of judgment and discernment
Number of participants with rationale	The mean knowledge score found in heart failure patients hospitalized at the HUG and naïve to any educational program was 7.95 points out of 17 points, with a standard deviation of 2.67. A 30% difference in score improvement was chosen as the smallest

	difference to be detected with clinical significance (i.e., a score difference of 2.39) to be detected. Assuming a study power of 80% and an alpha error of 5% (two-sided), it would be necessary to recruit a total of 80 patients (40 per group) to be able to detect such a difference between the two groups. We anticipate 10% loss to follow-up, which leads to a sample size of 90 subjects in total, or 45 per group. This sample size was calculated with STATA 17 (STATA Corporation, College Station, Texas). We expect to include approximately 124 patients during the 12-month inclusion period. Indeed, 200-300 patients are hospitalized annually at the HUG in the Department of General Internal Medicine or Cardiology for heart failure with reduced LVEF, i.e., about 16-25 patients per month. Taking into account refusals to participate and patients we will not have time to include, we think we can reach 62 patients per group.
Study Intervention	The intervention by a clinical pharmacist includes - Targeted education on patient needs related to heart failure, heart failure medications and self-care; - a pre-discharge interview to consolidate key teaching messages and prepare the patient for their discharge treatment plan; - a telephone call the week of discharge to ensure pharmaceutical follow-up between hospital care and return home (continuity of care).
Control Intervention	Hospitalized heart failure patients with reduced or mildly reduced LVEF who do not benefit from the pharmacist's educational intervention but do benefit from the usual standard of care.
Study procedures	Each working day, the investigator will identify all patients with heart failure with a lowered left ventricular ejection fraction (LVEF) and hospitalized for cardiac decompensation at the HUG. He will assess whether they meet the eligibility criteria for this study. The investigator or a trained clinical research associate (CRA) will come and present the study to the eligible patients by giving them the information sheet and the consent form to sign if they agree to participate. They will be given at least 24 hours to think about whether they want to participate. Once the patients are included (eligibility criteria validated and consent signed), they will be randomly assigned to the intervention or control group according to the randomization list. For patients in the intervention group, the therapeutic education intervention will be scheduled on the same day or the next day. The pre-test questionnaires (knowledge, beliefs, and adherence) will be given to them before the educational intervention. The post-test questionnaires and satisfaction survey will be given to the participants directly after the intervention. A second discharge interview will be organized shortly before final discharge from the general internal medicine or cardiology department. A call within 7

	days of discharge will be made and an assessment at 1 month of hospitalization of the primary (knowledge) and secondary (beliefs, adherence, satisfaction, consumption of unplanned care) endpoints will be made either by e-mail, postal mail, or telephone call by the CRA only. For patients in the control group, the pre-test questionnaires on knowledge, beliefs and adherence will be given to them on the same day or the day after inclusion. A post-test evaluation of knowledge, beliefs, adherence and rate of consumption of unplanned care will be performed at 1 month after hospitalization.
Study duration and Schedule	12 months Planned from 09/2022 for inclusion of first participant Planned to 09/2023 for inclusion of last participant
Investigator(s)	Mégane Jermini, PhD candidate, HUG Pharmacy
Study Center	University Hospitals of Geneva Rue Gabrielle Perret Gentil 4 CH-1205 Geneva
Data privacy	All data collected during the study will be coded to maintain confidentiality of all participants. The coding key will be accessible only by the study investigator and recorded in a protected Excel document stored on a secure server at the HUG. Data will be stored during the study using an electronic clinical data management system validated by the HUG Clinical Research Center for data management, mySQL ver.7.x for REDCap™ to which only the investigator and a trained CRA will have access. Once the study is completed, all data collected will be archived in a secure registry of the University of Geneva recognized by the CRC of the HUG.
Ethical consideration	This study will show whether a therapeutic teaching intervention with heart failure patients carried out by a pharmacist can improve patients' knowledge and thus optimize their beliefs about medication, improve their adherence to taking them and reduce their risk of cardiac decompensation. This disease particularly affects an elderly population that is at risk of suffering from polymedication and cognitive disorders. Only patients without cognitive disorders will be included to avoid biasing the evaluation. This project does not present any risk for the patient because it does not impact the therapeutic management by the medical and nursing staff.
GCP Statement	This study will be conducted in accordance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP, the HRA, and other relevant local legal and regulatory requirements.

2 BACKGROUND AND RATIONALE

Heart failure is a chronic progressive disease that affects 2-4% of the Swiss population, i.e. approximately 150,000-200,000 people. (1,2) The mortality at 4-5 years is estimated at 50%. (3–5). Patients hospitalized for acute heart failure, also called cardiac decompensation, have an increased risk of mortality (6,7). A rehospitalization rate is estimated at 25% at 30 days (8–10) and 50% at 1 year (11–13).

This disease is the leading cause of hospitalization in the elderly (2,5). According to the internal statistics of the Department of General Internal Medicine of the University Hospitals of Geneva (HUG), it was the first cause of hospitalization in 2019 and the 6ème cause in 2021 in a context where the majority of patients managed in medicine suffered from COVID 19 and its complications. According to internal hospital data obtained in 2019 with SQLape®, 7% of patients hospitalized for cardiac decompensation were rehospitalized within 30 days of discharge.
The main causes of rehospitalization in the heart failure patient can be multiple. They include worsening of baseline disease, poor adherence to prescribed therapies, or lack of medication adjustment (14–16).

These rehospitalizations have a negative impact on patients' quality of life and their use of care (17,18). They are also costly for the institution and for society. Indeed, it is estimated that 1-2% of healthcare expenditures are caused by patients with heart failure in both North America and Europe, and that 2/3 of these costs are for their hospital management (19–22). According to the hospital's cost accounting data in 2017, a hospitalization at the HUG for cardiac decompensation was equivalent to an average cost of 21,615 CHF and 18,606 CHF in the case of a readmission within 18 days (n =1548 patients hospitalized with cardiac decompensation), i.e., a high cost for the institution and the healthcare system.

Patients with heart failure must adapt their lifestyle in view of their physical abilities, which have been severely impaired by the disease. It is therefore recommended that they follow a restrictive therapeutic regime involving an adaptation of their lifestyle, the introduction of numerous medications, and even the integration of medical devices (pacemaker, CRT, ICD, LVAD, PDA) into their daily lives in order to improve their symptoms and reduce their morbidity and mortality (23–25).

Several studies and American and European medical societies have noted the importance of integrating heart failure patients into multidisciplinary care and rehabilitation programs to improve their quality of life and decrease their rate of rehospitalization (11,26,27). In Geneva, there is a specific cardiac rehabilitation program for heart failure patients that allows them to be informed, trained and equipped to build an environment adapted to their needs and to ensure good adherence to their therapy. The number of patients with heart failure who benefit from this therapeutic follow-up program is still low in Geneva today, around 30 to 40 patients per year. A reinforcement of the offer of such programs, the implementation of a targeted therapeutic accompaniment by means of follow-up consultations for heart failure patients or the creation of therapeutic education programs (ETP) would be an asset for many patients. In Switzerland, the Valais Hospital recently implemented a therapeutic education project for patients with heart failure, including reinforced inpatient follow-up within 30 days of discharge from hospital for cardiac decompensation (2).

Several research teams have been able to show the positive effect of educational and/or continuity of care support from a health care professional (5,11,28–32). Among this rich literature, two meta-analyses are worth mentioning: *Van Spall et* al (5) and *Son et* al (33). They showed that home nursing follow-up associated with a continuity of care or TPE intervention on medication, self-care and self-monitoring significantly reduced readmissions of patients with heart failure with a relative risk (RR) of 0.78 (CI 0.62-0.98) and an RR of 0.75 (CI 0.66-0.85)

respectively. These data corroborate other results from randomized controlled trials demonstrating the strong impact of face-to-face educational interventions delivered by caregivers or pharmacists on cardiac event rates, improved medication adherence, quality of life, and risk of all-cause rehospitalization. (31,32,34,35)

The clinical pharmacist makes a significant contribution to the education of hospitalized heart failure patients by providing continuity of care activities to support them until a few days after hospitalization (28,29,36–38). Meta-analyses by *McKay et al* (28)*Viswanathan ((*36) *et al, Mekonnen et* al (37) or *Ruppar et* al (29) demonstrate this. Indeed, pharmacists' interventions at discharge from hospital, including PTE, medication reconciliation or any other service aimed at improving therapeutic adherence;

- increase the likelihood of reducing the 30-day all-cause hospital readmission rate by 54%. (28)
- reduced the risk of hospitalization of patients with heart failure from any cause (HR = 0.55% CI 0.39-0.77 (36), RR =0.81 (CI 0.81-0.97) (including readmissions for adverse drug events (RR = 0.33 CI =0.20-0.53) (36,37)
- Reduces the risk of mortality in heart failure patients (RR = 0.89 (0.81-0.99))(29)

These positive data also include other test results that are less positive.
This is a major challenge for researchers to demonstrate the real impact of continuity of care interventions on clinical endpoints such as rehospitalization within 30 days, emergency room visits, and even mortality in heart failure patients. Consider two examples:

- the study by *Garnier et* al (30) study, which did not demonstrate an effect of its enhanced continuity of care and PTE intervention on decreasing the readmission rate or length of stay associated with readmission within 30 days of hospital discharge for cardiac decompensation.

- The randomized controlled trial by *Bell et* al (39) which did not find that clinical pharmacist intervention could decrease the readmission rate by 30% in hospitalized heart failure patients despite a large sample size (n = 862).

One of the major challenges is the need to consider ever-larger sample sizes in an attempt to demonstrate an effect on lowering these endpoints, particularly the 30-day hospital readmission rate. Some studies have calculated large sample sizes such as more than 600 patients to reduce the 30-day readmission rate by 8% (α = 0.05, 1-β = 80%) ((40), more than 1400 patients to detect a relative risk of 28% (α = 0.05, 1-β = 80%) (41)

The other problem is the wide variety of evaluated continuity of care or TCE services considered in these papers. There are no guidelines to follow as to what PTE and continuity of care benefits should be applied or studied to demonstrate a positive effect of these types of pharmacy activities. *Bethishou et* al (42) in their review concluded that no single pharmaceutical intervention appears to be more effective than another in reducing the rate of patient re-hospitalization.

In this project we do not wish to consider setting up a trial to demonstrate the impact of this new pharmacist service on a clinical judgment criterion such as the 30-day or 6-month readmission rate because, although these seem to be the indicators of choice for evaluating the effect of the changes on the disease, some re-hospitalizations are unavoidable due to the presence of other factors such as co-morbidities, socio-economic factors and age, for example. Moreover, the choice of a clinical endpoint would require the inclusion of a very large number of patients to demonstrate their reduction, which does not seem feasible in the context of this research project, which is part of a doctoral thesis.
Based on recently published data and wishing to be maximalist, the 30-day rehospitalization rate in the standard population is estimated to be 15%, for an absolute difference of 3.75%

between the two groups to be detectable one would have to include approximately 2544 patients (α = 0.05, 1-β = 80%). This seems hardly feasible.

Finally, the quality of evidence for the effect of heart failure disease management programs on clinical end points is described as low to moderate according to a recent Cochrane review (43) which seems discouraging to researchers.

It seems important to be able to measure the effect of transition of care interventions in heart failure patients on other indicators of success such as Patient Related Outcome Measure (PROM), adverse event rate, satisfaction, quality of life or medication adherence rate, for example.

A more recent review (44) points out the interest and even the need to answer this question because the studies measuring it are still few.
It also highlights the importance of deploying TVE services that integrate the dimension of continuity of care from the time of the patient's admission and not only at the time of discharge from the hospital. The assessment of knowledge of heart failure is one of the elements to be considered before the discharge of these patients from hospital in order to better target their needs in terms of skills to be acquired to ensure self-care and self-monitoring to be applied at home, and monitoring on return home.

All these elements lead us to be particularly interested in these questions and these lines of research.

In the research group of hospital pharmacy of the University of Geneva of Pr Pascal Bonnabry, we have been interested for some years in the deployment of innovative teaching methods in the field of medication for both health professionals and patients. The creation of a reinforced standardized therapeutic education on medication for the hospitalized patient with heart failure and the evaluation of its impact by means of PROM seems to be a new research avenue in the field of pharmaceutical sciences.

In this project, it may be astute to assess a PROM such as IC patients' level of knowledge about their disease and especially about the medications that treat it. In a second step, measuring their beliefs associated with the medication, their adherence to the medication and their satisfaction are other patient-related criteria that will be considered.

Indeed, increasing patients' knowledge about their heart disease and its management would be a key first step to improving their adherence to therapy. This would promote better treatment effectiveness, reduce unplanned health care consumption and thus health care costs. This is the hypothesis we are raising and to which we wish to respond through a research project.

Currently, patients with heart failure hospitalized at the HUG do not benefit from standardized therapeutic education on heart failure and its treatments by a health professional. The aim of our study is to set up and evaluate this type of activity.

The research project consists in developing a pharmaceutical service led by a clinical pharmacist which consists of:

- A therapeutic education interview adapted to the patient's needs on the disease of heart failure, the medications to treat it and self-care practices at home;
- a pre-discharge interview to reinforce the key notions acquired during the teaching and to prepare the patient for the management of his treatments at home (new medication plan, changes). A mobile application for smartphones (CardioMeds®) developed at the HUG and containing medical information on heart failure as well as assistance in managing medication and monitoring self-care parameters will be offered to participants.

- a telephone follow-up in the days following the return home to ensure continuity of care.

It is desirable to measure, through a clinical study, the impact of this type of care delivery to see if it is useful and beneficial to patients. This impact will be assessed by measuring the progression of patients' knowledge about heart failure disease and medications. A secondary analysis will measure the impact on beliefs associated with heart failure medications and adherence to them, and finally clinical outcomes such as readmission rates, 30-day emergency room visits, and mortality will not be overlooked.

The research question this project seeks to answer is: Does a targeted educational pharmaceutical intervention for the hospitalized heart failure patient improve their knowledge of their heart failure disease and medications?

3 STUDY OBJECTIVES AND DESIGN

3.1 Research hypothesis and first objective

We hypothesize that the therapeutic education intervention performed by a clinical pharmacist will improve the knowledge of patients hospitalized for heart failure decompensation with reduced (<40%) or slightly reduced (41-49%) left ventricular ejection fraction (LVEF) in the presence of drug therapy for heart failure. This intervention should also modify the beliefs that some patients may have about the disease and its treatment, improve medication adherence, and thus decrease unplanned care consumption (e.g., rehospitalizations or emergency room visits).

The primary objective is to evaluate the impact of a structured educational pharmaceutical interview during hospitalization on the knowledge of the heart failure patient by conducting a randomized controlled trial in general internal medicine and cardiology departments of a university hospital. It will be evaluated whether there is a change in the level of knowledge between the patients benefiting from the pharmacist's intervention and the control group that does not benefit from it. It will also be evaluated if there is a progression in the patients' level of knowledge after the pharmaceutical interview and if this level is maintained after 30 days of hospital discharge (D30 post discharge).

As a secondary objective, we will evaluate whether this educational program will influence patients' beliefs about their medication, improve therapeutic adherence to heart failure medication, and reduce the risk of unplanned care consumption (rehospitalization, for example) in better educated patients. The death rate at 1 month after hospitalization will also be evaluated.

A final secondary objective is to propose a mobile application specific to heart failure patients called CardioMeds® and to measure its use, its usefulness and its impact on a measure of self-care skills on a small sample of participants.

3.2 Primary and secondary endpoints

The primary endpoint was the level of patient knowledge by setting an improvement of at least 30% (relative gain) as the smallest gain to be detected at 1 month of hospitalization in the intervention group compared with the control group.

This value was chosen arbitrarily based on what has been found in other published research (45–56) and also based on the experience gained from other research projects conducted at the pharmacy in the field of education.

The level of knowledge of the patients will be measured using a knowledge score that is in the form of a knowledge assessment questionnaire created specifically for this project (Appendix 1).

It assesses patients' knowledge on two topics: heart failure disease and heart failure medications. It is composed of 17 questions, 8 of which are multiple-choice questions of category K' (several correct answers), 6 of type A (only one correct answer) and 3 open-ended questions (free text evaluated by keyword).
Six questions are related to the theme of heart failure disease and assess different elements of knowledge such as the definition of the disease, the notion of chronicity and progression, the symptomatology of decompensated disease, the precipitating factors of decompensation and the correct actions to adopt in case of decompensation of the disease. The remaining 11 questions assess patients' knowledge of their heart failure medications, including the identification of heart failure medications among all treatments, the usefulness of these medications, the duration of treatment, the continuous adjustment of doses, the risks of non-optimal therapeutic adherence, the adverse effects of the main classes, and the correct actions to take in the event of the occurrence of adverse effects of these medications and of forgetting to take them. Each correct answer is worth 1 point. The scoring or quotation of the answers will be done in the following way:

Simple choice question with a dichotomous notation: Right answer 1 point and wrong answer 0 point

Multiple choice question with partial credit scoring 50 (PS50): score with partial reward where: 1 if all propositions correct; 0.5 if more than 50% of propositions correct; 0 points otherwise.

Open-ended question with partial scoring based on subjective keyword evaluation.
For example for question n° 2: 1 point if predefined keyword present; 0,5pt if partial keyword but general concept correct; 0 pt otherwise.

The final score can vary from 0 (no knowledge) to 17 points (excellent knowledge).
The questionnaire has never been used in an experimental context or for psychometric analysis. There is no threshold to say that a patient has good knowledge or not.
It was developed by an internal pharmacist and an assistant pharmacist trained in TVE. It is based on educational objectives derived from educational sessions with patients and meetings with two patient partners from the HUG (Appendix 2). It was previously evaluated with them and on three occasions with a group of hospitalized heart failure patients (10 patients per version of the questionnaire).

To determine a first basic level of knowledge of the heart failure patients hospitalized at the HUG, the final version of the questionnaire was tested with 10 patients who had not received any educational intervention. This analysis shows that:

- The average baseline score is 7.95 pts out of 17.00pts (with a standard deviation of 2.67) or 46.76% of correct answers;
- The median score of 8.25pts out of 17.00 pts (min. 4; max. 13) or 48.53% of correct answers.

In this clinical study, we wish to assess the level of knowledge of the intervention group before the teaching interview, directly after the teaching interview, and at 1 month after the participant's discharge from the hospital.
This study includes a control group in order to evaluate the real effect of the therapeutic teaching intervention. The level of knowledge of the control group will be evaluated at inclusion for the pre-test and at 1 month after hospitalization for the post-test.

Secondary endpoints included differences in medication belief and adherence scores and the difference in the rate of unplanned care use between the two groups at 1 month post-hospitalization.

They also focused, for the intervention group, on the difference in belief and therapeutic adherence scores between the period before the educational intervention during hospitalization and the period following this intervention, i.e., one month after hospital discharge.
Four additional endpoints will be assessed after the pharmaceutical intervention with the study population in the intervention group.

- Satisfaction with the pharmacist's teaching and services
- The patient's experience and feelings upon returning home
- The rate of re-hospitalization and emergency department visits within 30 days of discharge.
  Death rate at 1 month after hospitalization

Two parameters will be measured, from a pilot project point of view, only with the participants of the intervention group who agreed to install and use the CardioMeds® mobile application after hospitalization.

- The use and usability of a specific mobile smartphone application for heart failure patients (CardioMeds®).
- Self-care skills learned through information delivered on the mobile app.

Beliefs about medicines will be assessed using the Beliefs about Medicines Questionnaire (BMQ) developed by Horn et al. (57). This questionnaire has been validated in many chronic diseases, including cardiac pathologies (58–61). It is composed of 18 questions that are evaluated according to a 5-point Likert scale ranging from 1 "strongly agree" to 5 "strongly disagree". The questionnaire is separated into 2 parts. A specific BMQ part with 10 items measuring specific beliefs about the prescribed treatment, in terms of its necessity and worries or concerns, and a general BMQ part with 8 other items measuring general beliefs about medicine, including the perception of harm and overuse. This second part will not be evaluated in this project.
The specific BMQ is composed of two 5-question subscales. It is presented in Appendix 3. Five items assess patients' representations of their medical prescription, or more precisely, their beliefs about the need to adhere to the prescribed drug treatment (= specific need) and 5 items measure beliefs about the risk of dependence and side effects caused by the treatments (= specific concerns).
Scores range from 5 to 25 points for both subscales. The higher the score for specific necessity, the more it means that the patient has a strong perception that he or she needs the medication to be healthy and live. For specific concern, the higher the score, the more concerned the patient is about a potential negative effect from taking the medication. A third score can be calculated by subtracting the specific concerns from the specific needs. This gives a score of -20 to +20. A positive value means that the need for the treatment exceeds the concerns about taking it. This questionnaire has adequate internal consistency in a cardiac population (Cronbach alpha = 0.76) and correlates well with other measures of beliefs (57). The validated French version is used in this project. (62).

Medication adherence will be assessed by means of a self-report questionnaire entitled "Three-item self-report scale (63). This questionnaire consists of 3 questions: one that evaluates the number of days that medication was forgotten in the last month, one that evaluates the frequency of taking medication as prescribed by the doctor, and the third that measures the patient's level of competence in taking medication correctly. Responses are

converted to a scale of 0 to 100 (0 being the lowest adherence and 100 the highest). An average of the three responses is used to assign the adherence score. This questionnaire has a high internal consistency (Cronbach alpha = 0.87) and correlates well with other measures of adherence (POC and MEMS). (63–65). We translated this questionnaire into French (Appendix 4) according to the methodology proposed by de Sousa et al. (66).

Study participants' **satisfaction** will be assessed using a 13-question questionnaire (Appendix 5) after the teaching interview to evaluate the usefulness and quality of the teaching service. A second satisfaction questionnaire consisting of 5 questions will be sent at 1 month after hospital discharge to assess the patient's overall satisfaction with the pharmacist's care (Appendix 6). These results will allow us to determine whether this new service should be continued and to identify its strengths and weaknesses.

The patient's **experience and feelings** upon returning home will be assessed during a telephone call between D3 and D7 after the patient's discharge from the hospital. The objective will be to identify the patient's needs, their feelings about going home, what they liked, what they missed. It will also be assessed if the patient has obtained a treatment card, has organized to go and get his medication and has organized to integrate it into his daily life. A list of medications will be collected from the patient. The questions asked are presented in Appendix 7.

The **rate of rehospitalization or emergency room visits** will be evaluated during the telephone call made by a research assistant at D30 post hospital discharge. The cause of hospitalization will be determined by means of the computerized hospital patient file if he is rehospitalized at the HUG or say^{cte} to the patient (or his attending physician depending on the patient's cognitive functions) if he is hospitalized in another hospital. It is interesting to assess whether the patient consumed unplanned care and whether it was related to instability of his heart failure. This outcome was not chosen as a primary indicator because of the need to include very large cohorts (>1000 participants) to demonstrate a statistically significant impact as shown in the scientific literature in this area to date (5,11,30,39,67,68).

The **rate of death at 1 month after hospitalization** will be assessed in both groups. This information can be collected from the participants' computerized patient records if mentioned or from the participants' relatives or attending physician.

The **use and usability** of **the mobile** smartphone **application** (CardioMeds®) will be explored by the research assistant during the telephone call at D30 post hospital discharge using a validated standardized questionnaire (69) (Appendix 9). This tool to help with medication administration was developed specifically for patients with heart failure and jointly by the Cardiology Department, the Information Systems Department and the Pharmacy Department of the HUG. It includes some of the information provided during the teaching and offers the participant the possibility to create and use his electronic medication plan and to follow some parameters of self-administered care such as weight and symptoms monitoring. It will be offered to study participants by the pharmacist investigator during the pre-discharge interview. If the patient wishes to use it for their return home, the investigating pharmacist will install the application on the participant's smartphone/tablet and explain how to use it.

The **self-care skills** of patients using CardioMeds® will be explored using a validated questionnaire composed of 22 questions (70) (Appendix 10) to measure the effect of this application on patients' level of empowerment in their care.

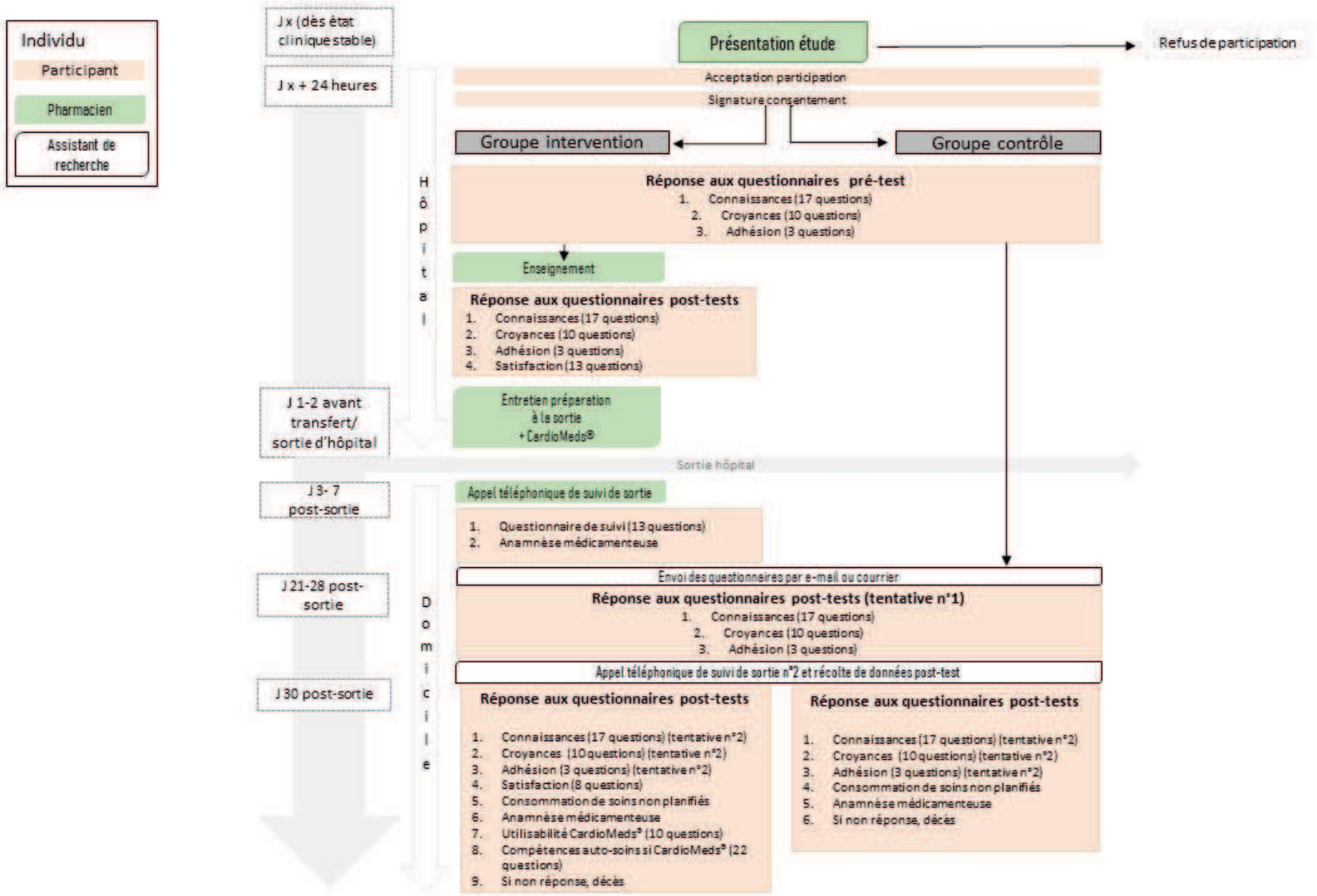
During hospitalization, the four questionnaires (knowledge, beliefs, therapeutic adherence, and satisfaction) will be sent to the participants in paper or electronic format (on a tablet) according to the patient's wishes by the pharmacist investigator or the research assistant. These questionnaires will be sent again to the participants at 1 month after discharge from hospital, as well as the two questionnaires for the participants using CardioMeds®. They will be sent either by e-mail or by post to be completed by the patient and returned to the investigator. In the event that these questionnaires are not returned, they will be addressed orally during a telephone interview by a research assistant.

3.3 Study design

The design of the clinical study chosen is a parallel randomized controlled trial. This design will allow us to evaluate the effect of our intervention without the confounding effects and selection biases inherent in observational studies, which strengthens the internal validity of the project.

The design of the study is schematized and detailed in French only in Figure 1 below.

Figure 1 : Design of the clinical study



3.4 Study intervention

The control group will receive the usual care offered by the internal medicine service without the therapeutic education intervention of the pharmacist during their hospitalization.

The intervention will be conducted by the pharmacist investigator with patients in the intervention group. These are heart failure patients with reduced LVEF, polymedicated, hospitalized for cardiac decompensation in the 10 general internal medicine units of the HUG. They will benefit from the usual medical care. The intervention will consist of an educational pharmaceutical interview associated with a second interview to prepare for hospital discharge (pre-discharge interview), followed by a telephone call a few days after hospital discharge.

The therapeutic education intervention that the patient will receive will be structured in three parts:

1. The first part consists of a 60-90 minute interactive edutainment session that will take place in the patient's bed. It will be carried out from the 3rd day of admission for a cardiac decompensation. The teaching is structured in two subparts, which will allow it to be carried out in one or two sessions if necessary to reduce its duration and preserve the patients' level of concentration. One or two appointments will be scheduled with the patient to ensure that they are available throughout the interview.
   The teaching will address 3 themes related to the disease of heart failure: the pathology, the drugs to treat it and the self-care and self-monitoring actions to adopt. A pedagogical scenario has been designed to serve as a detailed description of the teaching and as a teaching guide for the pharmacist trainer. It is presented in the appendix (Appendix 11).
   The teaching is standardized and can be used for all patients, regardless of their level of knowledge. Indeed, the elements and the games used are flexible according to the skills of the participants. The trainer will be able to vary his level of investment according to their needs, their wishes and their skills.
   Below is a brief description of the elements used in this interview:

   - The pathology will be approached by means of an existing video developed by the Cardiology Service of the HUG explaining the definition, the mechanism of the disease, its effects, its complications and the causes. This video will be viewed by the patient after having answered the pre-test questionnaires. After viewing the video, a discussion with the patient, using active communication techniques (open questions, rephrasing,) and tools such as photolanguage, picture cards, and card games, will allow the patient to contextualize his or her disease, and to discuss the notions of chronicity of the disease, cardiac decompensation, and associated symptoms.

   - Each of the patient's medications prescribed for heart failure during hospitalization will be visualized and explained (role, mechanism of action) as well as their benefits. A game board will be used as a teaching aid. It will allow the patient to associate images of his medication boxes in the different therapeutic classes. Real-life scenarios will be used to address the risks involved in forgetting to take medication. A discussion on the notion of chronicity of medication intake and the continuous adjustment of medication doses will be initiated. Finally, the main adverse effects of some therapeutic classes will be reviewed by means of a quiz and a discussion on the information given on the package inserts of medications.
   - The proper daily actions that a heart failure patient should follow to assess the progress of his or her disease and know when to seek medical attention will be reviewed in subpart 1. Behaviors in case of medication-related side effects and forgetting to take medication will also be discussed in sub-section 2.

2. The **second part of the intervention is** characterized by a discharge interview between the pharmacist and the patient. It will be conducted between 1-2 days prior to discharge from the General Internal Medicine Service, whether the patient is going home or being transferred for a rehabilitation care stay. Its purpose is to prepare the patient for discharge from the hospital, his or her future treatment plan and self-care practices. It differs from the discharge interview conducted by the physician who is in charge of handing out the official discharge documents (discharge notice with the next medical appointments planned or to be organized, a prescription for medication and a treatment plan)

   The pharmacist will ensure that the following elements of continuity of care are established:
   - the patient has a community pharmacy where he/she can collect his/her medication and which can follow him/her;
   - the organization of the medication at home is adapted to the needs and lifestyle of the patient;
   - Resource persons are identified when needed.

   He will give the patient a document in the form of a "memory card" that will highlight the important key points of the heart failure medication education. It is the patient himself, during this interview, who will take care to complete this document to visualize his current list of heart failure medications and the adverse effects to be followed. A flyer entitled "control of heart failure" developed by the Cardiology Service of the HUG will be given to them so that they have a reference scale to rely on to evaluate their symptomatology and the need to consult or not and to remember the good self-care gestures to adopt at home. At this stage, the patient will also be asked if he/she would like to have a treatment card in paper format (made by the internal physician) or in digital format available on a smartphone (CardioMeds®).
   In case the patient wishes to benefit from this digital tool, the CardioMeds application® will be presented and installed by the pharmacist.

3. The **third step of the intervention** consists of a telephone call to the patient between D3 and D7 after discharge from hospital by the pharmacist (including patients who have stayed in a rehabilitation unit). This call will allow the pharmacist to ensure that the patient has picked up their medications and is clear on their treatment plan. It will also serve to ensure that the patient is not showing signs of decompensation of their heart failure. He or she will be available for any questions the patient may have regarding his or her health and will refer the patient to the appropriate resource people if necessary.

The tools used to create the teaching interview and the pedagogical scenario were developed by a clinical pharmacist in general internal medicine, inspired by existing tools for heart failure patients and helped by the information needs of heart failure patients at the HUG, the opinion of two patient partners, and the opinion of health professionals at the HUG (clinical pharmacists, cardiologist, nurse).
The scenario was validated by a group of experts composed of a clinical pharmacist specialized in TPE, a cardiology nurse specialized in the follow-up of heart failure patients, a cardiology assistant physician in charge of the heart failure and rehabilitation unit, as well as heart failure patients and two patient partners. The teaching was tested with three pharmacy students and two partner patients, one of whom had heart failure.

The research project was validated by two assistant physicians: the assistant physician of the Department of General Internal Medicine and the cardiologist in charge of the heart failure unit of the HUG.

4 STUDY POPULATION AND STUDY PROCEDURES

4.1 Inclusion and exclusion criteria, rationale for study population

Patients hospitalized with acute heart failure with reduced LVEF, poly-mediated from the Departments of General Internal Medicine and Cardiology of a Swiss university hospital in Geneva, will be included.
This is a very frequently hospitalized patient population on these services. Heart failure was the leading cause of hospitalization in general internal medicine in 2019 and is currently in the top 10 reasons for hospitalization despite the appearance of SARS-Cov-2 infection and its respiratory complications. There are other reasons why we chose this population to evaluate the impact of hospital-based education:

- There is currently no therapeutic education offer for hospitalized heart failure patients at the HUG compared to other populations such as diabetic patients, patients suffering from chronic obstructive pulmonary disease or patients who have had a STEMI with the ELIPS program.

- Not all patients with this pathology can be followed in the hospital by the interdisciplinary heart failure team of the HUG.

- The evidence-based medicine guidelines written by the European Society of Cardiology have been updated in 2021. They will impact the drug management of heart failure patients. They encourage the introduction of medication in patients with reduced heart failure (LVEF < 40%) and also in patients with slightly reduced function (41-49%). In addition, the introduction of recent first-line drug therapies such as Entresto® and renal SGLT-2 co-transporter inhibitors (Forxiga® or Jardiance®) will result in changes in prescribing and the need for closer monitoring of adverse events. The reinforcement of a multi and interdisciplinary management is also strongly encouraged in these latest recommendations. Our project is in line with these recommendations.

- This population is at risk for multiple cardiac decompensations and potentially avoidable healthcare consumption (rehospitalization, unplanned physician visits, or emergency room visits).

- Clinical practice shows that many hospitalized patients with heart failure do not know what their disease is and how it is treated. A small field survey on the information needs of these patients was conducted with about ten patients in the General Internal Medicine Department of the HUG in 2021 and showed that patients were not able to define their heart failure disease, nor to explain the role of their medication and that they were eager to obtain more targeted information on their disease and their medication.

All hospitalized patients with left heart failure with a decreased LVEF ≤40% (HFrEF) as well as those with LVEF between 41 and 49% (HFmrEF) only if treated with heart failure specific drug therapy will be approached to introduce them to the study provided they meet the inclusion criteria.

The vast majority of the heart failure population is elderly and at risk for cognitive impairment. This may negatively influence the results of this score and bias the real impact of the educational intervention. To address this issue, only patients without cognitive impairment will be included. To identify the cognitive status of each patient, the following items will be analyzed in order of priority.

- Judgment of the internal physician in charge of the patient.

- If the physician is in doubt about the patient's cognitive status, a Mini Mental Status (MMS) and a clock test (only if the MMS is greater than 24) will be performed by the investigator or a geriatric liaison nurse attached to the General Internal Medicine Service. Cognitive impairment is possible if MMS score ≤ 24 and if MMS ≥ 24 and clock test score ≤ 7.

Patients hospitalized at the University Hospital of Geneva meeting the following inclusion criteria are eligible for the study:

- Hospitalized in the Department of General Internal Medicine or Cardiology for decompensated heart failure (also called cardiac decompensation, acute heart failure)
    - with lowered left ventricular ejection fraction (LVEF) (≤40%) of any origin;
    - with slightly reduced left ventricular ejection fraction (LVEF) (41-49%) only if treated with the specific drug therapy for heart failure

  Or

- Hospitalized in the Department of General Internal Medicine or Cardiology and presenting during hospitalization with decompensated heart failure (also called cardiac decompensation, acute heart failure)
    - With lowered left ventricular ejection fraction (LVEF) (≤40%);
    - with slightly reduced left ventricular ejection fraction (LVEF) (41-49%) only if treated with the specific drug therapy for heart failure

- Stability of clinical condition as judged by the internal physician in charge of the patient including:
    - hospitalization in acute unit only
    - absence of oxygen dependence or oxygen dependence outside of heart failure
    - weight loss initiated if diuretic is present
- ≥ 2 medications to treat heart failure
- ≥ 18 years
- Full capacity of discernment
- Absence of cognitive impairment (notion of cognitive impairment in the patient record or judgment of the internal physician in charge of the participant or MMS ≤ 24 / MMS ≥ 24 and clock test score ≤ 7)
- Ability to speak, understand and read in French
- Has a personal telephone (mobile or landline)
- Signed the consent form (Appendix 8)

The presence of any of the following criteria will result in the exclusion of the participant:

- Inability to follow study procedures, e.g., due to a somatic medical condition such as confusion, language problem, psychological disorder, cognitive impairment)
- Institutionalized persons (e.g., nursing home, home for the aged)
- Asylum seekers, homeless people, prisoners
- Person under guardianship
- Short life expectancy (patient at end of life or comfort care)

4.2 Recruitment, screening and informed consent process

The investigating pharmacist will identify each working day (Monday to Friday) the patients hospitalized for cardiac decompensation in the Internal Medicine and Cardiology Departments of the University Hospitals of Geneva by means of the computerized patient records.

A computerized rule has been designed by the HUG Pharmacy to highlight the patients of the Services of General Internal Medicine and Cardiology presenting in their medical problems a cardiac decompensation.
The pharmacist will analyze the most recent echocardiography report for each of these patients to determine the LVEF value of the heart. This identification step can be completed by the weekly lists sent by e-mail to the hospital cardiologists and to the investigating pharmacist, of the patients who have received a cardiac echocardiography (transthoracic and/or transoesophageal) by the Cardiology Department.

The eligibility of patients with heart failure with diminished LVEF will be assessed by analysis of the computerized patient records, applying the inclusion and exclusion criteria, and by discussion with the internal physician in charge of the patient, particularly with regard to the capacity for discernment. If there is no notion of cognitive disorders in the patient's file, this will be discussed with the internal physician in charge of the patient to find out whether or not the patient has cognitive disorders. If the physician suspects it, an MMS test and possibly a clock test will be performed by the investigating pharmacist or by a nurse from the geriatric liaison team. If a patient has an MMS score of less than 24 or an MMS score of more than 24 with a clock test score of less than or equal to 7, he or she may have cognitive impairment and cannot be included.

For all eligible patients, the investigating pharmacist will introduce them to the study on the second day of hospitalization. He will explain the nature of the study, its objectives, the procedures involved, the expected duration and the potential risks and benefits of participating. He will explain that the study is composed of two arms and that it is randomly determined in which group each participant is assigned.
Each participant will be informed that participation is voluntary and that he/she may withdraw from the study at any time. Participation in or withdrawal from the study will not affect his or her therapeutic management. They will also be informed that their medical records will be consulted by the investigating pharmacist.
All participants will receive a study information sheet and a consent form to sign in order to make an informed decision about whether or not to participate in the study (Appendix 8). The patient will be given 24 hours to decide whether or not to participate in the study. Formal consent will be obtained by collecting the consent form signed by the participant. It will be countersigned by the investigator or his representative. The consent form will be kept in the study file and a copy given to the participant. As soon as the patient's informed consent to participate is obtained, an appointment will be scheduled with the patient for the first stage of the intervention.
Each eligible participant included in the study will be assigned an authentication number in order to anonymize their data and an electronic case report form (eCRF) or observation sheet will be created.

A randomization list by random size block will be established beforehand by the HUG methodological support unit. This list will be held by the pharmacist in charge of the clinical trials, Mrs Fabiana Tirone, within the HUG pharmacy (person external to the project). Randomization will be automated in the Clinical Trial Data Management System CDMS RedCAP™ and activated for each new participant who will require the creation of a new eCRF. In case of malfunction of this software, Mrs. Tirone will be notified by the system and will be able to assign each participant to the arm according to the predefined list.
The investigator will identify the assigned arm for each participant after collecting the patient consent form. The investigator will schedule the therapeutic education intervention on the same day for the participants in the intervention arm and collect the pre-test data from the participants.

Follow-up up to 1 month post-discharge involves a potential risk of loss of participants. Some may withdraw from the study. These cases will be reported as, "withdrawal of informed consent" or "loss to follow-up". Data from patients who die during the study will be considered for final data analysis.

Participants will not be compensated for their involvement in the study. They will have the right to request the final results of this study.

4.3 Study procedures

Duration of inclusion: 52 weeks (June 01, 2022 to May 31, 2023)
End of follow-up: 1-2 months (end in 08/2023)

Table 1: Study Schedule

Recruiting														
	Evaluation at 1 month post-hospitalization													
													Analysis of the results	
Sept.22	Oct.22	Nov.22	Dec. 22	Jan. 23	Feb. 23	Tue 23	Apr. 23	May.23	Jul. 23	Jul . 23	Aug.23	Sept.23	Oct. 23	Nov .23	Dec.23

Conduct of the study

Patient eligibility and inclusion

Inclusion criteria:

- Hospitalized in the Department of General Internal Medicine or Cardiology for decompensated heart failure (also known as cardiac decompensation, acute heart failure) with lowered LVEF (≤40%) from any cause or slightly lowered LVEF (41-49%) with heart failure-specific drug therapy
- Stable clinical condition as judged by the internal physician in charge of the patient
- ≥ 2 heart failure medications
- ≥18 years
- Full capacity of discernment
- Absence of cognitive impairment
- Ability to speak, understand and read in French
- Has a personal telephone (mobile or landline)
- Consent form signed by the participant

Exclusion Criteria:

- Inability to follow study procedures
- Institutionalized persons
- Asylum seekers, homeless people, prisoners
- Incapacity of judgment and discernment

Inclusion process (~124 patients)

- Collection of basic data
- Evaluation of the participant's knowledge by means of a questionnaire (pre-test)
- Belief- and concern-based adherence assessment (specific BMQ)
- Evaluation of the participant's therapeutic adherence (3-items self report)

Usual care (~62 patients)

- No evaluation

Teaching (~62 patients)

- Primary Ocoma: Assessment of knowledge (post-test)
- Evaluation of patient satisfaction with the teaching interview (questionnaire)

Pre-discharge interview

- No evaluation
- Proposal and installation of CardioMeds®

Post-discharge telephone call (between D3 and D7)

- Qualitative evaluation of the patient's feelings and experiences (questionnaire)
- Collection of the patient's medication list

Follow-up at 1 month post hospitalization

- Primary Outcome: Assessment of patient knowledge (post-test)
- Secondary outcomes: Assessment of beliefs and therapeutic adherence (specific BMQ and 3-items self report), rate of rehospitalization or emergency room visits, patient satisfaction with the pharmacist intervention, exploration of the usability of CardioMeds® and its impact on self-care skills, rate of death at 1 month after hospitalization
- Collection of the patient's medication list

Data collected

Baseline patient information, medical data, heart failure data, laboratory data, vital parameter data, medication data will be collected for each patient included in the study once the consent form is completed. Other study data will be collected for pre-testing after randomization.
The data collected for the intervention group will be collected after the teaching interview, during the telephone call upon discharge and for the post-test at 1 month after discharge. Data for the control group will be collected for the post-test at 1 month after discharge.

All these data are presented in Table 2.

Table 2: Patient characteristics collected

	Data	Origin	Details
Patient information			
A *	Name	Medical record	Name
B*	Date of birth* (if applicable)	Medical record	Date of birth: ...../...../.....
C*	Mailing Address* (if applicable)	Medical record	Address:
D*	Phone number* (if applicable)	Medical record and patient interview	Phone number : Cell phone number :
E**	E-mail address	Medical record and patient interview	Address:
1	Participant number		
2	Age	Medical record	Age:
3	Type	Medical record	❑ Male ❑ Woman
4	Civil status	Medical record	❑ Single ❑ Married ❑ Divorced ❑ Widow(er)
5	Origin	Medical record	❑ Switzerland ❑ Central Europe ❑ Southern Europe ❑ Southeast Europe ❑ Northern Europe ❑ Western Europe ❑ Eastern Europe ❑ Africa ❑ Asia ❑ Other
6	Ethnicity	Patient interview	❑ Caucasian ❑ African ❑ Asian ❑ African American

			❑ Other
7	Level of education	Patient interview	❑ Primary level (compulsory school) ❑ Vocational secondary level (CFC, ECG) ❑ Secondary II general level (Federal Maturité) ❑ Higher vocational training I (Federal diploma, ES) ❑ Higher Vocational Education II (Federal Master's Degree) ❑ Universities I (Bachelor) (UNI/HES/EPF) ❑ Universities II (Master) (UNI/HES/EPF) ❑ Universities III (PhD) (UNI/HES/EPF) ❑ Other
8	Employment	Patient interview	❑ Full-time professional activity ❑ Part-time professional activity ❑ Unemployed ❑ Retired ❑ Unemployed (house parent) ❑ Unemployed (DI, social assistance) ❑ Other
9	Annual income	Patient interview	❑ < 20'000 CHF ❑ 20'000-50'000 CHF ❑ 50'000-100'0000 CHF ❑ 100'000-200'000 CHF ❑ > 200'000 CHF ❑ I do not wish to answer
10	Mother tongue	Medical record and patient interview	❑ French ❑ Swiss-German ❑ Italian ❑ Romanche ❑ German ❑ English ❑ Spanish ❑ Portuguese ❑ Other
11	Level of understanding of the French language	Patient interview	❑ Native ❑ Excellent ❑ Good ❑ Average ❑ Low
12	Level of expression in French language	Patient interview	❑ Native ❑ Excellent ❑ Good ❑ Average ❑ Low
13	Assay-Curological Profile	Medical record and patient interview	❑ Basic insurance ❑ Supplementary insurance ❑ Private Insurance
14	Life context	Medical record and patient interview	❑ Lives alone ❑ Lives with partner ❑ Lives with children ❑ Other
15	Owner of a smartphone or a tablet	Patient interview	❑ Yes ❑ No
16	Computer owner	Patient interview	❑ Yes

			❑ No
17	Internet connection at home	Patient interview	❑ Yes ❑ No
18	Ability to use a smartphone, tablet, computer	Patient interview	❑ Basic (phone, SMS) ❑ Means (e-mail, internet search Some basic applications) ❑ Advanced (daily use, application installation)
19	Preference of the means of communication for contact at home	Patient interview	❑ Phone ❑ E-mail ❑ Mail ❑ Video-conference
20	Frequency of e-mail use	Patient interview	❑ Every day ❑ Several times a week ❑ 1 time per week ❑ A few times a month ❑ A few times a year ❑ Never, because I don't have an e-mail address
Medical data			
21	Active co-morbidities	Medical record	Names to be specified:
22	Cardiovascular history	Medical record	❑ Acute coronary syndrome ❑ Angina ❑ Atrial fibrillation ❑ Rhythm disorders ❑ Valvulopathy ❑ Cardiac decompensation ❑ Pericarditis ❑ Myocarditis ❑ Endocarditis ❑ Dilated/hypertrophic/restrictive cardiomyopathy ❑ Sarcoidosis ❑ Congenital heart disease ❑ Cardiogenic shock ❑ Cardiorespiratory arrest ❑ Cardio-renal syndrome ❑ Coronary artery disease ❑ Arterial insufficiency of the lower limbs ❑ Thrombo-embolic disease ❑ Cerebrovascular accident ❑ Pulmonary embolism ❑ Other
23	Cardiovascular risk factors	Medical record	❑ Hypertension ❑ Diabetes ❑ Dyslipidemia ❑ Obesity ❑ Tobacco ❑ Alcohol ❑ Drug ❑ Family history IM

24	Psychic disorders	Medical record/patient interview/investigating physician	❑ Absent ❑ Present Type if present : ❑ Depression ❑ Anxiety ❑ Bipolar Disorders ❑ Other
25	Cognitive disorders	Medical Record/Patient Testing	❑ Absent ❑ Present
26	MMS Score	Medical Record/Patient Testing	Number and date: ..... (...../...../.....)
27	Score Clock Test	Medical Record/Patient Testing	Number and date: ..... (...../...../.....)
Heart Failure Data			
28	NYHA classification of IC (at admission)	Medical record	❑ Class I ❑ Class II ❑ Class III ❑ Class IV
29	FEVG (before admission if known)	Medical record	Number (%) and date: .....% (...../...../.....) Category: ❑ HFrEF <40%. ❑ HFmrEF 41-49
30	LVEF (on admission to hospital)	Medical record	Number (%) and date: .....% (...../...../.....) Category: ❑ HFrEF <40%. ❑ HFmrEF 41-49
31	Cause of acute heart failure	Medical records/Patient's physicians	❑ High blood pressure ❑ Ischemic heart disease ❑ Rhythmic heart disease ❑ Valvular heart disease ❑ Cardiomyopathy (hypertrophic, dilatative, restrictive, myocarditis etc.) ❑ Infiltrative heart disease (sarcoidosis, amyloidosis, connectivitis, hemochromatosis)

			❑ Structural heart disease ❑ Medicated/Toxic ❑ Endocrinopathy ❑ Systemic infection ❑ State of shock ❑ Poor adherence to therapy ❑ Hypervolemia ❑ Renal insufficiency ❑ Other
32	New diagnosis of heart failure	Medical records/Patient's physicians	❑ Yes ❑ No
33	History of hospitalization for heart failure	Medical records/Patient's physicians	❑ Yes ❑ No
34	Hospitalization for cardiac decompensation in the last 12 months	Medical record and patient interview	❑ Yes ❑ No
35	Cardiovascular medical device	Medical record	❑ Pacemakers ❑ Cardiac Resynchronization Therapy (CRT) ❑ Automatic Implantable Defibrillators (AIDs)/ ❑ Left ventricular assist (LVA)
Laboratory data			
36	NT-proBNP (admission)	Medical record	Number (ng/L) and date: ..... ng/L (...../...../.....)
37	Creatinemia (admission)	Medical record	Number (µmol/L) and date: ..... µmol/L (...../...../.....)
38	eGFR (admission)	Medical record	Number (mL/min/1.73 m^2) and date: ..... mL/min/1.73 m^2 (...../...../.....)
Vital parameters data			
39	Heart rate (admission)	Medical record	Number (bpm) and date: .....bpm (...../...../.....)
40	Systolic blood pressure (admission)	Medical record	Number (mmHg) and date: .....mmHg (...../...../.....)

41	Diastolic blood pressure (admission)	Medical record	Number (mmHg) and date: .....mmHg (...../...../.....)
42	Weight (admitted)	Medical record	Number (kg) and date : .....kg (...../...../.....)
43	Weight (exit)	Medical record	Number (kg) and date : .....kg (...../...../.....)
44	Body mass index (Kg/m^2)	Medical record	❑ <18 ❑ 18-24.9 ❑ 25-29.9 ❑ 30-34.9 ❑ 35-39.9 ❑ ≥40 ❑
		Drug Data	
45	Medication at home before admission	Medical record	Date: (...../...../.....) Specialty / INN / Dosage / Dosage *e.g. Forxiga, dapagliflozin, 10mg, i.d*
46	Number of medications before hospitalization	Medical record/patient interview/	❑ 0 ❑ 1-2 ❑ 3-4 ❑ >4
47	Number of heart failure medications prior to hospitalization	Medical record/patient interview/	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ >5

48	Heart failure medication list (home)	Medical record	❑ Diuretic ❑ Beta-blocker ❑ IECA/ARA ❑ ARNI ❑ Aldosterone antagonist (ARM) ❑ SGLT2 inhibitor ❑ Ivabradine ❑ Digoxin ❑ Vericiguat
49	Heart failure medication list (hospitalization)	Medical record	❑ Diuretic ❑ Beta-blocker ❑ IECA/ARA ❑ ARNI ❑ Aldosterone antagonist (ARM) ❑ SGLT2 inhibitor ❑ Ivabradine ❑ Digoxin ❑ Vericiguat
50	Heart failure medication list (hospital discharge)	Medical record	❑ Diuretic ❑ Beta-blocker ❑ IECA/ARA ❑ ARNI ❑ Aldosterone antagonist (ARM) ❑ SGLT2 inhibitor ❑ Ivabradine ❑ Digoxin ❑ Vericiguat
51	Medication management in the home	Patient interview	❑ Autonomous ❑ Nursing care ❑ Pharmacy ❑ Caregivers
52	Medication management tool	Patient interview	❑ Paper Medication Plan ❑ Electronic Medication Plan ❑ Weekly/Plus ❑ Daily unit dose sachet ❑ Unit discount by the pharmacy ❑ Other
53	Frequency of visits to your regular pharmacy	Patient interview	❑ Several times a week ❑ 1 time per week ❑ 2-3 times a month ❑ 1 time per month ❑ 1 time every 2-3 months ❑ 2 times a year ❑ 1 time per year ❑ Never
54	Quality of the relationship with your city pharmacist	Patient interview	❑ No particular relationship ❑ Wrong ❑ Neither good nor bad ❑ Good ❑ Very good
Pre-test data			
55	Knowledge Questionnaire	Patient interview	*Answer for each question (detailed in the documents specific to the questionnaires)*
56	Score	Calculation	Value:
57	Belief questionnaires	Patient interview	*Answer for each question (detailed in the documents specific to the questionnaires)*

58	Need score	Calculation	Value:
59	Concern score	Calculation	Value:
60	Differential score	Calculation	Value:
61	Membership questionnaire	Patient interview	*Answer for each question (detailed in the documents specific to the questionnaires)*
62	Membership score	Calculation	Value:
Post-interview FTE data (for intervention group only)			
63	Knowledge Questionnaire	Patient interview	*Answer for each question (detailed in the documents specific to the questionnaires)*
64	Score	Calculation	Value:
65	Satisfaction questionnaire	Patient interview	*Answer for each question (detailed in the documents specific to the questionnaires)*
Output data (3-7 days) (for intervention group only)			
66	Length of stay in acute care hospitals	Medical record	Number of days : Category: ❑ 0-3 days, ❑ 3-7 days ❑ 7-10 days ❑ 10-14 days ❑ 14 -30 days ❑ > 30 days
67	Place of transfer at the end of the hospitalization	Medical record	❑ Home ❑ Rehabilitation Service ❑ Other acute care unit ❑ Other acute care service ❑ Other hospital
68	Follow-up by a cardiologist	Patient interview	❑ Yes ❑ No
69	Date of cardiologist's visit	Patient interview	date: (...../...../.....)
70	Weight at home	Patient interview	Number (kg) and date : .....kg (...../...../.....)
71	Increase in weight	Patient interview	❑ Yes ❑ No If yes, number of kilograms :
72	Symptoms of heart failure	Patient interview	❑ Water accumulation in the ankles, legs, abdomen or lungs ❑ Shortness of breath when making an effort ❑ Difficulty breathing, sometimes with a dry cough

			❑ The sensation of suffocation in the supine position ❑ Rapid weight gain (>2kg in 3 days) ❑ Fatigue ❑ Dizziness ❑ Palpitations ❑ Chest pain
73	Pharmacy visited	Patient interview	Name: Date: ...../...../..... Number of days after hospitalization: .....
74	Obtaining medication	Patient interview	❑ Yes ❑ No If so, what type? ❑ Delayed delivery time of 1-2 days because your pharmacy had to order certain medications. ❑ Delayed delivery time of more than 1 week because your pharmacy had to order certain medications. ❑ Delayed time to obtain and date of obtaining still undetermined ❑ Inability to get to the pharmacy on your own ❑ You forgot to pick them up ❑ Other (please specify): ....
75	Heart failure medication list	Patient interview	Date: (...../...../.....) Specialty / INN / Dosage / Dosage *e.g. Forxiga, dapagliflozin, 10mg, i.d*
76	Adverse drug reactions	Patient interview	❑ Extreme fatigue ❑ Dizziness when you stand up ❑ Vision problems ❑ Headaches ❑ A frequent need to urinate ❑ Low blood pressure (<110mmHg) ❑ A low heart rate (<60 bpm) ❑ Rapid weight gain (>2kg in 3 days)

			❑ Worsening of shortness of breath or edema ❑ Dry cough ❑ Dry mouth and intense thirst ❑ Dry skin
77	Physical and moral feelings of the patient on returning home	Patient interview	Free response
78	Experience and feeling of going home	Patient interview	Free response
Post-test data at 1 month			
79	Knowledge Questionnaire	Patient interview	*Answer for each question (detailed in the documents specific to the questionnaires)*
80	Score	Calculation	Value:
81	Belief questionnaires	Patient interview	*Answer for each question (detailed in the documents specific to the questionnaires)*
82	Score need	Calculation	Value:
83	Concern score	Calculation	Value:
84	Differential score	Calculation	Value:
85	Membership questionnaire	Patient interview	*Answer for each question (detailed in the documents specific to the questionnaires)*
86	Score	Calculation	Value:
87	Satisfaction questionnaire	Patient interview	*Answer for each question (detailed in the documents specific to the questionnaires)*
88	CardioMeds Usability Questionnaire	Patient interview	*Answer for each question (detailed in the documents specific to the questionnaires)*
89	CardioMeds Self-Care Questionnaire	Patient interview	*Answer for each question (detailed in the documents specific to the questionnaires)*
90	Heart failure medication list	Patient interview	Date: (...../...../.....) Specialty / INN / Dosage / Dosage *e.g. Forxiga, dapagliflozin, 10mg, i.d*
91	Re-hospitalization 1 month after hospitalization	Patient interview	❑ Yes ❑ No
92	Emergency visits (Hospital/Ambulatory) 1 month after hospitalization	Patient interview	❑ Yes ❑ No
93	Deaths 1 month after hospitalization	Medical records, relatives, attending physician	❑ Yes ❑ No

*This participant identification data will not appear in the participant's Case Report Form (CRF). It will be collected by the investigator and stored separately from the CRF in a secure electronic file accessible only by the investigator and the CRA.
** The e-mail address will be visible in the eCRF but only consultable by the investigator and the clinical research associate. It must appear in the CDMS (RedCap™) to allow the setting of the sending of the questionnaires at 1 month for the participants having wished to receive them by e-mail. As soon as all the participant's data have been collected and the study is closed, the e-mail addresses will be deleted from the CDMS.

For any data that is not complete during hospitalization, it will be obtained by phone call upon the participant's return home.

Assessment of the level of knowledge (primary outcome):

The level of knowledge of the patients will be assessed in the intervention group by a questionnaire (Appendix 1) on three occasions: at time 0 before any intervention as a pre-test, after the teaching interview as post-test n°1 and finally at 1 month post-discharge as post-test n°2.

This questionnaire will be proposed in the control group at time 0 (pre-test) and at 1 month after hospitalization (post-test).

During hospitalization, the questionnaire will be sent to the patient by the investigating pharmacist and will be completed by the patient himself with the help of the pharmacist if necessary.
At 1 month after discharge, the questionnaire will be sent to the patient by email or post. If no return is obtained, the research assistant will address the questionnaires to them during a phone call.

Assessment of beliefs about medications (secondary outcome)

Beliefs about medicines will be assessed indirectly using the Beliefs about Medicines Questionnaire (Appendix 3) at time 0 (pre-test) after obtaining the consent form and at 1 month after hospitalization (post-test) in both groups.
During hospitalization, the questionnaire will be sent to the patient by the investigating pharmacist and it will be filled in by the patient himself with the help of the pharmacist if necessary. One month after discharge, the questionnaire will be sent to the patient by email or post. If no return is obtained, the research assistant will send them the questionnaires during a telephone call.

Assessment of therapeutic adherence (secondary outcome)

Adherence to therapy will be assessed for all participants with the 3-item self-report questionnaire (Appendix 4) on two occasions. It will be presented to the participant by the investigator at time 0 after obtaining the consent form (pre-test), as well as at 1 month post-hospitalization. During hospitalization, the questionnaire will be sent to the patient by the investigating pharmacist and completed by the patient himself with the help of the pharmacist if necessary.
At 1 month after discharge, the questionnaire will be sent to the patient by email or post. If no return is obtained, the research assistant will address the questionnaires to them during a phone call.

Rate of rehospitalization and emergency room visits (secondary outcome)

All study participants will be asked during the 1-month postdischarge telephone call whether they have been readmitted to the hospital since discharge and for what reason, whether they have been seen in the hospital or by their physician for signs of cardiac decompensation.

Death rate (secondary outcome)

In case of non-response of participants to the post-test questionnaires, it will be investigated by means of the computerized patient record of the hospital or with the relatives or the attending physicians in charge of the participants if the participants died within one month of the hospital discharge.

Assessment of satisfaction (secondary outcome)

Satisfaction with the teaching interview will be assessed by means of a questionnaire that the patient will complete directly after the teaching interview (Appendix 5).
Overall satisfaction with the pharmacist's care will be assessed at 1 month post discharge. They will be evaluated only in the intervention group
The questionnaire will be sent to the patient by email or regular mail. If no return is obtained, the research assistant will address the questionnaires to them during a telephone call (Appendix 6).

Evaluation of the patient's experience and feelings upon return home (secondary outcome)

The patient's experience and feelings on returning home will be evaluated for the intervention group during a telephone call between D3 and D7 of the hospital discharge by the investigating pharmacist using a questionnaire sent by the investigating pharmacist (Appendix 7)

Use of the electronic treatment plan (secondary outcome)

Patients who were presented with and installed the CardioMeds mobile application® during hospitalization will be asked if they used it and if they were satisfied with it. It will be the research assistant who will collect these elements during the telephone call at 1 month post hospital discharge using a validated standardized questionnaire (Appendix 9). In addition, as the mobile application is specifically designed to empower the patient in his care, a validated standardized self-care questionnaire will also be filled out on this occasion (Appendix 10).

Other item evaluated

The participant will be asked during the 1-month telephone call if he/she has entered a specific cardiac rehabilitation program for heart failure. He/she will also be asked to provide his/her last medication list to analyze if there have been any changes in the treatment of heart failure since discharge.

4.4 Withdrawal and interruption

A participant may withdraw from the study at any time if he or she no longer wishes to participate. A participant will be withdrawn from the study if he/she dies, if his/her health condition deteriorates to the point where he/she can no longer meet the inclusion criteria or be physically able to follow the pharmacist's intervention, if he/she loses his/her capacity of discernment, if he/she cannot be reached by telephone after discharge from the hospital.

A study with temporal follow-up is associated with a significant risk of break in follow-up or

withdrawal of informed consent. Therefore, we choose to implement an intention-to-treat analysis. The data collected will be retained until the loss of a participant. The number of lost to follow-up will be specified in the results in the form of a flowchart. All data used in the analysis will be anonymized afterwards.

5 STATISTICS AND METHODOLOGY

This chapter of the protocol describes the research hypotheses, statistical analysis plan, sample size, and treatment of missing data.
It was submitted to Pr Gayet-Agéron, head of the methodological support unit of the HUG clinical research center, who assisted us in the construction of these elements and their validation.

The final analysis will be based on the intention-to-treat principle, i.e. including all patients who were randomized in the study.

For the basic data, continuous variables will be described as means and standard deviation, median and inter-quartile range.

The discrete or categorical variables will be described by their numbers and relative proportion, or even the mean and standard deviation, depending on the variables

Some continuous data such as age, left ventricular ejection fraction (LVEF), laboratory data, length of hospital stay, number of pre- and post-hospitalization medications will be reclassified into categories and presented as numbers and relative proportion of each category. Differences in outcomes between the intervention and control groups will be analyzed using the t-test for continuous variables and a Chi-Square test for categorical variables.

The main analysis assessing knowledge status will compare the knowledge score (dependent variable) between the two randomization groups (main independent variable) after adjusting for knowledge status at baseline using a linear regression model or ANCOVA.

For continuous secondary outcomes (medication beliefs and medication adherence), a Student's t test will also be used to compare mean values between the two groups. For binary outcomes (re-hospitalization or new emergency department visit within 1 month), a chi-2 test (or Fisher exact test if the smallest expected number of patients is <5) will be used.
For the satisfaction outcome, which is an ordinal qualitative variable, a Chi-2 test (or Fisher's exact test if the smallest expected number of participants is <5) will be used.

5.1 Statistical analysis plan and sample size calculation

Research Hypotheses

The hypothesis of this project is that patients with heart failure who have received an educational interview combined with follow-up by the hospital pharmacist show an increase in their knowledge score after the intervention compared with the control group at 1 month after hospital discharge.

The null hypothesis is that there is no improvement in the knowledge score at 1 month after hospital discharge.

This hypothesis leads us to evaluate the primary endpoint: the improvement of knowledge about heart failure and its medications at 1 month after hospital discharge of patients hospitalized for

cardiac decompensation.

Sample size

To test our hypothesis, we need to define an adequate sample size.

To do this, we initially consulted the literature. Several studies have demonstrated an improvement in patient knowledge after pharmacist intervention with approximately 100-200 patients (45–56).

The questionnaire used to measure patient knowledge has never been studied to date. We tested it in 10 hospitalized heart failure patients who were naïve to any teaching intervention.

This analysis shows that:

- The average baseline score is 7.95 pts out of 17.00pts (with a standard deviation of 2.67), i.e. 46.7% of correct answers;
- The median score of 8.25pts out of 17.00 pts (min. 4; max. 13) is 48.5% correct answers.

By setting a relative gain of 30% as the smallest difference to be detected, this would be equivalent to showing an improvement in the mean score of at least 2.39 points (±7.01) (i.e., a mean score increase from 7.95 to 10.34pts).

Assuming a two-sided alpha of 5% and a power of 80%, 40 subjects per group should be included, for a total of 80 subjects. Considering a loss to follow-up in about 10% of the study subjects, the required sample size would be at least 90 subjects (45 subjects per group). This sample size was calculated with STATA 17 (STATA Corporation, College Station, Texas).

We also need to consider the average number of patients hospitalized at the HUG for left heart decompensation with decreased LVEF to define the inclusion time and feasibility of this project. Note that according to internal hospital statistics, the number of patients hospitalized in general internal medicine for left heart decompensation (all severities and LVEFs combined) in 2019 was 641 and 434 between January and November 2021. It is considered that 50% of these patients have a reduced LVEF, equivalent to 200-330 patients per year who could benefit from our intervention or approximately 16-25 patients per month. A certain number of these patients will not meet the inclusion criteria and a small number, approximately 30%, will agree to participate, as shown by certain studies in heart failure patients (71–74). In addition, some patients will be missed by the investigator who will only work part-time on this project.

Based on all these elements, we expect to include approximately 124 patients (62 per group) over 12 months, to show a progression of knowledge which is a sufficient number to guarantee the statistical power of the study.

Planned analyses

Primary analysis

To answer the main research question, a linear regression (or ANCOVA) will be performed to compare the estimated mean scores at 1 month between the two randomization groups after adjustment for the baseline knowledge score. For subjects for whom the knowledge score could not be obtained at post-test, we will use the baseline value as post-test value in order to avoid missing data. The threshold of statistical significance under the null hypothesis is set with a type I error, $\alpha < 0.05$

The primary analysis will be carried out by a statistician from the Methodological Support Unit of the HUG Clinical Research Centre, who will be commissioned by the investigator once the data of the last patient included have been collected.

Secondary analyses

Comparisons of continuous secondary outcomes between the two randomization groups will be made by Student's t tests; comparisons of categorical or ordinal qualitative secondary outcomes will be made using a Chi-2 test or Fisher's exact test (in case of smaller expected number <5). The analyses will be carried out by a statistician from the methodological support unit of the HUG clinical research center on a specific and recognized computer software.

Deviation(s) from the original statistical plan

Any deviation from the original statistical plan will be noted and explained in the final report.

5.2 Handling missing data and dropouts

The status of a longitudinal study is related to a high degree of loss to follow-up. In subjects for whom the knowledge score could not be obtained at post-test, we will use the baseline value as the post-test value in order to avoid missing data.

6 REGULATORY AND SAFETY ASPECTS

6.1 Local regulations / Helsinki declaration

This study is conducted in accordance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP. If the clinical trial is not conducted in accordance with the ICH-GCP, the above paragraph must be adapted accordingly (ClinO Art. 5, Abs 2), to the HRA as well as to other locally relevant legal and regulatory requirements.

6.2 Adverse events (serious)

An adverse event (AE) is any untoward medical occurrence in a patient or clinical study subject that is not necessarily causally related to the trial procedure. Thus, it can be any adverse or unintended finding, symptom, or illness associated over time with a trial procedure, whether or not it is related to the trial procedure.

A serious adverse event (SAE) (ClinO, s. 63) is any untoward medical event that

- results in death or is life threatening,
- requires hospitalization or extension of an existing hospitalization,
- results in a persistent or significant disability or impairment, or
- causes a birth defect or congenital malformation.

The investigator and sponsor assess the causality of the event to the trial intervention (see table below based on terms given in the ICH E2A guidelines).

Any event assessed as possibly, probably, or definitely related is classified as related to the trial intervention (Table 3)

Table 3: Description of Adverse Drug Event Types

Relationship	Description

Some	Temporal relationship Improvement after stopping treatment*. Recurrence after resumption of treatment (or other evidence of the presence of the drug)
Probable	Temporal relationship Improvement after stopping treatment*. No other obvious cause
Possible	Temporal relationship No other obvious cause
Improbable	Any evaluable reaction that does not meet the above conditions.
Not related	A causal relationship can be excluded.
* Improvement after the "unchallenge" is only taken into account if it applies to the reaction	

The investigator and sponsor rate the severity of the event as mild, moderate or severe. Mild means the complication is tolerable, moderate means it interferes with daily activities, and severe means it makes daily activities impossible.

Reporting of SAEs (see ClinO, Art. 63)

All AEs are documented and reported immediately (within 24 hours) to the study sponsor.

If it cannot be excluded that the SAE in Switzerland is attributable to the intervention under study, the investigator reports it to the Ethics Committee via BASEC within 15 days.

Monitoring of serious adverse events

Any patient with an SAE who has agreed to participate in the study will be reassessed by the investigator to see if they still meet the inclusion criteria. If the patient no longer meets the criteria, they will be removed from the study.
The risk of an SAE being attributable to our intervention is very low because it does not directly impact patient care.
Each participant who presented an SAE attributable or not to the studied procedure will be analyzed by the investigator. The investigator will attempt to identify the reason for the SAE in each case by consulting the patient's physicians and will document it in the patient's CRF. If the SAE is caused by a drug, the investigator will declare a pharmacovigilance announcement.

6.3 (Periodic) Safety Report

An annual safety report will be submitted once a year to the local ethics committee by the investigator (ClinO, Art. 43 Abs) if applicable for this type of study.

6.4 Amendments

Substantial changes in study set-up and organization, protocol, and relevant study documents are subject to approval by the Ethics Committee prior to implementation. In emergency circumstances, deviations from the protocol to protect the rights, safety and welfare of human subjects may be made without prior approval of the Ethics Committee. Such deviations should be documented and reported to the Ethics Committee as soon as possible.
A list of all non-substantive changes will be submitted annually to the appropriate EC with the annual safety report

6.5 (Premature) study termination

The sponsor and the principal investigator may terminate the study prematurely under certain circumstances, such as

- Ethical issues,
- Insufficient recruitment of participants,
- When participant safety is in doubt or at risk (e.g., when the benefit-risk assessment is no longer positive),
- Changes in accepted clinical practice that make it unwise to continue the study, or
- Early evidence of harm or benefit from the experimental intervention.

In the event of the regular termination of the study, the ethics committee is informed via BASEC within 90 days (ClinO, art. 38).

In the event of premature termination or interruption of the study, the ethics committee is informed via BASEC within 15 days (ClinO, art. 38).

6.6 Insurance

In case of damage or injury related to the study, the University Hospitals of Geneva is liable for compensation, except for claims resulting from fault or gross negligence.

7 OTHER ASPECTS

7.1 Other ethical considerations

This trial will be able to generate results that will be important in the field of patient education. We want to evaluate whether the intervention of a hospital pharmacist with heart failure patients on their knowledge can have a positive impact on their health behavior. Offering patients the opportunity to access information on these high value-added drugs during their hospital stay seems to us to be essential in order to ensure the best possible long-term adherence to taking these drugs. If the results of this study show that the patient's knowledge, beliefs and adherence to treatment are improved, then these teaching interviews could be offered to all patients with heart failure in the hospital. This will allow the deployment of other interventions for other chronic conditions. If the results are negative, the reasons for this failure will be identified and evaluated in order to readjust the pharmacist's interventions to improve patients' knowledge and therapeutic adherence.

This study offers any hospitalized patient with heart failure who is being treated with medication a new tool to improve their health knowledge while receiving quality care from the hospital. This care will not be altered by this study.

7.2 Risk-benefit assessment

There is no risk of harm to patients by participating in this study.

The pharmaceutical intervention does not present any risk to the patient in the sense that it does not alter the patient's therapeutic management in any way. The project does not discourage any treatment or any change in the usual management of the patient by the medical and nursing staff.

This project even reinforces the care of the hospital medical and nursing team by educating the patient on his or her pathology and follow-up. It gives them the tools to take ownership of their disease and become autonomous in their follow-up. The participants will be able to benefit from the trial.

8 QUALITY CONTROL AND DATA PROTECTION

8.1 Quality measurement

For quality assurance, the sponsor, the ethics committee or an independent trial monitor may visit the research sites. Direct access to source data and all study-related files is granted on these occasions. All parties involved keep participant data strictly confidential.

8.2 Data recording and source data

All baseline data will be assessed with the medical record consultation, with the patient himself at the time of inclusion if not referenced in the computerized patient record or with the hospital physician in charge of the patient. These data as well as the results of the knowledge score, adherence beliefs and satisfaction surveys, the follow-up questionnaire, exploratory measures of CardioMeds usability® and self-care skills will be captured and physically stored in mySQL ver.7.x for REDCap™ . An electronic clinical data management system, a CDMS (Clinical Trial Data Management System). This software is validated by the HUG clinical research center for data management.
Ongoing data from the study will be stored, queried, viewed, cleaned and exported through this CDMS.

All research subject data will be coded to ensure confidentiality using a combined letter and number identifier. The data collected for each research subject will constitute a Case Report Form (CRF), which contains the following elements
- Inclusion criteria and consent
- Demographics
- Medical data (history, co-morbidities, laboratory tests, medications)
- Knowledge, adherence and belief questionnaires in pre-test and post-test as well as satisfaction questionnaires, follow-up questionnaire, exploratory measures of CardioMeds usability® and self-care skills measures
- Questionnaire Scores

- Adverse events

The collection of clinical data is done through the electronic case report form (eCRF) that will be created with REDcap™ .

The source documents are all the original documents related to the study, i.e. the research protocol, the ethics committee agreement, the original consent form signed by each participant and the CRF extraction. These will be stored in a study-specific file cabinet.

The identification data of the participants such as name, first name, date of birth, date of stay and any other data that can be used to identify a patient will be stored in an Excel file. This file will be stored in a computer file on the common and secured server of the HUG pharmacy. Access to this file will be strictly limited to the investigator and the file will be locked with a code accessible only by the investigator.

8.3 Privacy and Encryption

Trial and participant data will be treated with the utmost discretion and will be accessible only to authorized personnel who need the data to perform their duties in the study (investigator and

clinical research associate). On CRFs and other study-specific documents, participants are identified only by a unique participant number.

Storage:
The identification list of participants will be kept in a secure manner (see §8.2 data recording and source data)

For the duration of the study, the data will be stored in the CDMS, REDcap™, which can only be accessed by the investigator and a research assistant with a personal login and password.

All paper source data will be available in a dedicated study cabinet. This cabinet will be stored in the pharmacy's clinical trials office. All other source documents will be stored electronically, in the pharmacy's secure network, accessible only by the principal investigator and his/her research assistant.

Access to the database will be available to the study investigator and research assistant only during the inclusion process, but also during the data analysis phase and after the study is completed. Access will be password protected to prevent unauthorized access.

Once the data is collected and the REDCap™ database is complete, the data will first be extracted into an Excel spreadsheet. This will be stored in the pharmacy's secure network.

For the statistical analysis, the data of interest will be prepared for transfer to the statistician of the Methodological Support Unit, so that he can import them into the statistical software he will use. A do-file will be used to store all the statistics produced.

Where possible, we will store files in open archive formats, such as Word files converted to PDF-A or simple text files encoded as UTF-8 files and Excel files converted to CSV. If this is not possible, we will include information about the software used and its version number.

8.4 Retention and destruction of study data and biological materials

At the end of the project, the final research data collected will be extracted from Redcap™ and stored for archiving for 10 years. This means on the hospital's servers in a folder with limited access to the investigator and the sponsor for the electronic data and in a locked cabinet in the pharmacy for the paper documents related to the clinical study (study binder).
The data archives will also be deposited either in an appropriate database (data repository) managed by the University of Geneva (Yareta) or on a magnetic tape managed by the University of Geneva.

9 MONITORING AND RECORDING

The monitoring will be carried out in accordance with the ICH BPEC and coordinated by an internal auditor at the HUG pharmacy, Dr. Christel Bruggmann, trained in BPEC and in Clinical Research (CAS) and investigator of several clinical trials in the past.
As the monitor for this project, she will conduct this monitoring by following a risk-adapted monitoring plan and written standard operating procedures. She will verify that the clinical trial is conducted and that data is generated, documented, and reported in accordance with the protocol, good clinical practices, and applicable regulatory requirements. The site initiation visit, several interim monitoring visits, and the site closeout visit will be arranged by the clinical site monitor.

The investigator will provide direct access to all trial-related source data/documents and reports for monitoring purposes.
We will register the study in French in the Swiss National Clinical Trials Portal (SNCTP via BASEC) and in English in a WHO-recognized primary registry, such as the US ClinicalTrials.gov registry (as required by the WHO and the International Committee of Medical Journal Editors).

10. FUNDING / PUBLICATION / DECLARATION OF INTEREST

The investigator has no financial conflicts of interest. There is no financial compensation for participants for this study. This activity requires a full-time equivalent of 0.5. The source of funding is provided by the Pharmacy, as part of a doctoral thesis program. The clinical research associate, Mrs BOEHM-BOSMANI Cristina, will be paid by the HUG Pharmacy Service. A search for funding is underway with pharmaceutical companies to finance this position. They will have no influence on the content of the protocol and on the progress of the study.

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FORMULAIRE DE SIGNATURE DU PROTOCOLE

Titre de l'étude	Amélioration des connaissances sur la maladie et les médicaments: étude randomisée contrôlée mono-centrique chez les patients insuffisants cardiaques hospitalisés
Identification du protocole	2022-00731

Le Sponsor-Investigateur a approuvé cette version du protocole et confirme par la présente la réalisation de l'étude conformément au protocole, à la version actuelle de la Déclaration d'Helsinki de l'Association Médicale Mondiale, aux directives ICH-GCP ou à la norme ISO 14155 ainsi qu'aux exigences légales locales applicables.

Investigateur :

Nom: Mme Mégane Jermini

Date: 21/07/2022 Signature: Jermini

Chef de service (Promoteur) :

Pharmacie des HUG: Pr. Pascal Bonnabry

Date: 21.07.2022 Signature:

Médecins adjoints associés:

Service de médecine interne et générale: Dr. Jérôme Stirnemann

Dr Jérôme Stirnemann
Médecin adjoint
Service de médecine interne générale
Rue Gabrielle-Perret-Gentil 4
CH-1211 Genève 14

Date: 21.07.2022 Signature:

Service de cardiologie: Dr. Philippe Meyer

Date: 21.07.2022 Signature:

Dr Philippe Meyer
Médecin adjoint agrégé
Service de cardiologie - HUG
Tél. 022 372 95 97