Protocol

Version History / Amendment History

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Protocol	V1.0	20250204	Initial version

Investigator's Statement

I will conscientiously fulfill the investigator's responsibilities in accordance with China GCP requirements, and I will personally participate in or directly supervise this clinical study. We have read and confirmed this protocol, and agree to its scientific and ethical soundness. We will fulfill relevant responsibilities in accordance with Chinese laws and regulations, the Declaration of Helsinki, China GCP, and the provisions of this study protocol, and will implement the study only after approval by the academic committee and the ethics committee. Unless measures must be taken to protect the safety, rights, and interests of subjects, we will keep this study protocol confidential.

Study Site: Zhongshan Hospital, Fudan University
Principal Investigator: Zhou Jingmin
Principal Investigator (Signature):
Date of Signature:

Table of Contents

Protocol Summary

Protocol Title
China Heart Failure Center Accreditation Program: A Prospective Multicenter Cluster Randomized Controlled Trial

Study Objective
To evaluate the impact of HF-CAP versus usual care on heart failure management quality and 1-year outcomes in heart failure patients (a composite endpoint of HF rehospitalization or all-cause death).

Study Endpoints
Primary endpoints:
There are two primary endpoints: (1) HF rehospitalization and all-cause mortality within 12 months after discharge; (2) heart failure management quality score.

Secondary endpoints:

- First HF rehospitalization;
- Number of HF rehospitalizations;
- All-cause readmission;
- All-cause mortality.

Overall Design
A multicenter, open-label, cluster-randomized, controlled trial.

Sample Size
80 centers, 6,240 patients.

Grouping
Cluster randomization.

Inclusion / Exclusion Criteria
Center inclusion criteria:

1. Registered on the China Heart Failure Center website; applicants for Standard/Primary-level HF centers have already reported ≥300/100 HF cases, and continuously report ≥10/8 HF cases per month;
2. Capable of completing quality improvement measures.

Subject inclusion criteria:

1. Age ≥18 years;
2. Heart failure is the primary reason for hospitalization.

Whether hospitalization is due to heart failure will be determined by local investigators, but should meet the following criteria:

- Symptoms of HF (e.g., dyspnea, fatigue), signs (e.g., elevated jugular venous pressure, peripheral edema), or laboratory/imaging evidence (e.g., chest X-ray showing pulmonary congestion, elevated natriuretic peptides, echocardiographic evidence of structural or functional cardiac abnormality);
- Treatment directed at acute or chronic HF etiology (e.g., intravenous diuretics, vasodilators, inotropes, or revascularization).

Subject exclusion criteria:

1. Life-threatening conditions other than HF with expected survival <1 year, such as malignancy;
2. Unable to complete follow-up.

Intervention
China Heart Failure Center Accreditation Program (HF-CAP).

Withdrawal Criteria
If a participant stops participation before the planned end of the trial, it is considered withdrawal. This may be initiated by the participant or the investigator. Participants may voluntarily withdraw consent at any time for any reason. A participant is defined as withdrawn when all of the following are met:

1. Refuses to continue participation;
2. Refuses further visits or assessments;
3. Refuses further trial-related contact.

Statistical Analysis Plan

1. Descriptive analysis: Categorical variables will be described using frequency and proportion; continuous variables will be described using mean, standard deviation, median, 25th and 75th percentiles, maximum and minimum.
2. Baseline demographic analysis: Primarily descriptive. For subgroup comparisons as applicable: for categorical variables, use likelihood-ratio χ^2 test; when >25% of cells have expected counts <5, use Fisher's exact test. For normally distributed continuous variables, use independent-samples t test; for non-normally distributed continuous variables, use Wilcoxon rank-sum test.
3. Efficacy analysis:
    - **Primary endpoint analysis:**
      (1) The primary clinical endpoint will use the Kalbfleisch–Prentice nonparametric cumulative incidence function to estimate cumulative incidence over follow-up. A stratified Cox proportional hazards model will estimate hazard ratios (HRs) and 95% confidence intervals (CIs) to evaluate differences in event risk between groups, accounting for cluster effects.
      (2) The second primary endpoint, HF management quality score, will be analyzed using a mixed-effects model, treating hospital as a random effect to account for within-hospital clustering, and using a compound symmetry covariance structure to model correlations among repeated observations within the same participant.
    - **Secondary endpoints:** Fine–Gray competing-risk models will be used to avoid bias from competing events (e.g., death from other causes), accounting for cluster effects.
    - **Subgroup analysis:** Prespecified subgroups include age, sex, hypertension, diabetes, chronic kidney disease (defined as serum creatinine >1.5 mg/dL), other baseline treatments, and frailty/poor condition (defined by baseline NYHA and NT-proBNP). The impact on primary outcomes and interaction effects will be explored. No multiplicity adjustment will be performed.

- **Sensitivity analyses:**
  Excluding early events: exclude events occurring within 10 days after randomization and repeat the primary analysis to wash out pre-randomization effects.
  Tipping-point analysis: for subjects with potential underreporting risk, progressively add assumed events and fit Weibull models to assess robustness under different missing-event scenarios.

Abbreviations

ACEI: Angiotensin-Converting Enzyme Inhibitor, angiotensin-converting enzyme inhibitor
AI: Artificial Intelligence, artificial intelligence
ARB: Angiotensin II Receptor Blocker, angiotensin II receptor blocker
ARNI: Angiotensin Receptor–Neprilysin Inhibitor, angiotensin receptor–neprilysin inhibitor
BNP: B-type Natriuretic Peptide, B-type natriuretic peptide
eCRF: electronic Case Report Form, electronic case report form
EDC: Electronic Data Capture, electronic data capture system
GDMT: Guideline-Directed Medical Therapy, guideline-directed medical therapy
HF-CAP: Heart Failure Center Accreditation Program, China Heart Failure Center Accreditation Program
HFrEF: Heart Failure with reduced Ejection Fraction, heart failure with reduced ejection fraction
LVEDD: Left Ventricular End-Diastolic Diameter, left ventricular end-diastolic diameter
LVEF: Left Ventricular Ejection Fraction, left ventricular ejection fraction
MRA: Mineralocorticoid Receptor Antagonist, mineralocorticoid receptor antagonist
NT-proBNP: N-terminal pro–B-type Natriuretic Peptide, N-terminal pro–B-type natriuretic peptide
NYHA: New York Heart Association, New York Heart Association
SGLT-2i: Sodium-Glucose Cotransporter-2 Inhibitor, sodium-glucose cotransporter-2 inhibitor

I. Background

Heart failure (HF) affects more than 64 million people worldwide and has become a major clinical and public health problem, especially among those aged 65 years and older [1]. China is the world's second most populous country, accounting for approximately 17.7% of the world's population. There are approximately 12.10 million HF patients in China, accounting for more than 10% of HF patients

worldwide, and the annual healthcare costs related to HF exceed RMB 250 billion (USD 31 billion) [2].

HF treatment has made substantial progress over the past decades, particularly in heart failure with reduced ejection fraction (HFrEF), where multiple pharmacologic and device therapies have been proven to significantly improve prognosis and quality of life, driving updates of HF guidelines globally [3–5]. However, in real-world clinical practice, there remains a substantial gap between guideline recommendations and the use of guideline-directed medical therapy (GDMT). The CHAMP-HF registry reported that among outpatients with HFrEF, only 73%, 67%, and 33% received ACEI/ARB/ARNI, beta-blockers, and MRA, respectively [6]. Sumarsono et al. [7] recently reported that in newly diagnosed outpatients with HFrEF in the United States, GDMT utilization was similarly suboptimal: at 3 months after diagnosis, the use rates of ACEI/ARB/ARNI, beta-blockers, and MRA were 55.3%, 55.5%, and 18.4%, respectively; by 12 months after diagnosis, the rates increased only to 65.2%, 64.3%, and 24.7%, respectively.

There are many quality improvement programs in hospitals and healthcare systems aimed at optimizing GDMT in HFrEF patients, but the results have been mixed. In the United States, a nationwide guideline-based quality improvement initiative, Get With The Guidelines (GWTG), includes a HF program (GWTG-HF). Compared with non-participating hospitals during the same period, participating hospitals had a higher proportion of HF patients receiving standardized HF diagnosis and treatment, but did not reduce the risk of 30-day readmission and mortality [8]. More recently, two large randomized controlled trials showed that intensified quality improvement measures or patient-centered transitional care services did not significantly affect GDMT use or clinical outcomes. The CONNECT-HF trial showed that, compared with usual care, an intensified quality improvement intervention involving patient education and post-discharge follow-up did not reduce the composite endpoint of HF rehospitalization or all-cause death, nor did it improve the HF management quality score [9]. In the PACT-HF study, there was also no significant difference between the intensified management group and the usual care group in the composite outcome of all-cause readmission, emergency department visit, or death at 3 months after discharge (HR [CI]: 0.99 [0.83–1.19], P=0.93) [10].

The Heart Failure Center Accreditation Program (HF-CAP) in China is a nationwide HF quality improvement initiative launched in 2017 under the leadership of the Chinese Medical Doctor Association, aiming to improve HF management [11–12]. This prospective cohort study is the largest cohort study among HF patients in China and is also the first to comprehensively describe characteristics as well as short- and long-term outcomes of HF patients in China [13]. Registry data from HF center development show that the use of BNP/NT-proBNP and echocardiography for HF diagnosis increased year by year, the proportion of patients discharged on GDMT increased year by year, and 1-year mortality after discharge showed a downward trend. As a real-world prospective cohort study, although extensive adjustment for

potential confounders was performed, inherent limitations of observational studies mean that the risk of unknown confounding cannot be excluded; causal inference cannot be directly made, and effectiveness outcomes cannot be definitively attributed to the intervention itself. Therefore, the effectiveness of the accreditation program requires further validation.

This project plans to conduct a multicenter, prospective, cluster-randomized, controlled clinical trial in China to evaluate whether the HF-CAP program improves outcomes in HF patients.

II. Study Objectives

2.1 Primary Objectives

Two primary objectives:
(1) To evaluate the impact of HF-CAP versus usual care on 1-year outcomes in HF patients;
(2) To evaluate the effect of HF-CAP versus usual care on improving HF management quality.

2.2 Secondary Objectives

To evaluate:

- First HF rehospitalization;
- Number of HF rehospitalizations;
- All-cause readmission;
- All-cause mortality.

2.3 Exploratory Objective

To determine the effectiveness of HF-CAP in reducing healthcare system costs within 1 year after discharge for HF patients.

III. Study Overview

3.1 Overall Study Design and Plan

This study is a multicenter, open-label, cluster-randomized, controlled study designed to verify the effectiveness of the HF-CAP management strategy versus usual HF management in improving HF management quality scores and outcomes during the 12-month period after discharge.

3.2 Sample Size and Grouping Method

The total sample size is 6,240. The intervention group and the control group will each include 3,120 patients.

Grouping method: The study plans to include 80 tertiary hospitals and 80 secondary hospitals. Tertiary and secondary hospitals will be stratified, and within each hospital level, hospitals will be randomized 1:1 by cluster (hospital) allocation. Each hospital will enroll 40 patients.

Intervention group: Will receive HF-CAP management, including requiring hospitals to establish a multidisciplinary HF management team, set up dedicated HF beds and HF follow-up clinics, conduct regular staff training and patient/family education, establish a robust outpatient follow-up mechanism, and set quality control targets. An HF-CAP Expert Committee will form a trained and experienced team of HF management experts to conduct online document review, on-site review and guidance, and to assess and guide high-quality HF care during index hospitalization (including at discharge) and during 1-year post-discharge outpatient follow-up. For example, HF-CAP verification experts will meet the HF management team on site, review existing quality control indicators, standardize 制度建设 (system building), audit on-site operational cases, and provide regular guidance for training, typical case discussions, quality control meetings, and issue quality control data reports and feedback based on uploaded data.

Control group: Will receive usual HF management, with requirements to regularly upload patient data and routinely monitor data quality to ensure normal data collection, but without other guidance or interventions.

All participants in the trial will agree to follow-up at the enrolling hospital after discharge (1 week, 1 month, 3 months, and 12 months). Clinical data, medication use, and outcomes will be uploaded to the China HF center registry platform.

3.3 Randomization and Blinding

This is a multicenter, cluster-randomized trial. The unit of randomization is the hospital. Trial assessments begin during index hospitalization and continue through 12 months of follow-up. Stratified randomization will be used: hospitals will be randomized 1:1 to the intervention group (HF-CAP program management) or the control group (usual care), stratified by hospital level (tertiary vs secondary) to ensure balance within strata. Randomization will be performed by an independent biostatistician using a central computer program. Randomization will be completed before collecting baseline HF management information at each center. Subjects will not be informed of the allocation between HF-CAP program management and usual care.

3.4 Study Flow Chart

Figure 1. Technical route and flow of the study.

IV. Study Population

Eligible patients are those hospitalized primarily for HF. Given the pragmatic design, inclusion and exclusion criteria are kept as simple as possible.

4.1 Inclusion Criteria

Center inclusion criteria:

1. Registered on the China HF Center website; applicants for Standard/Primary-level HF centers have already reported ≥300/100 HF cases and continuously report ≥10/8 HF cases per month;
2. Capable of completing quality improvement measures.

Subject inclusion criteria:

1. Age ≥18 years;
2. HF is the primary reason for hospitalization.

Whether hospitalization is due to HF will be determined by local investigators, but should meet the following criteria:

- HF symptoms (e.g., dyspnea, fatigue), signs (e.g., elevated jugular venous pressure, peripheral edema), or laboratory/imaging evidence (e.g., chest X-ray showing pulmonary congestion, elevated natriuretic peptide levels, echocardiographic evidence of structural or functional cardiac abnormality);
- Treatment directed at acute or chronic HF etiology (e.g., intravenous diuretics, vasodilators, inotropes, or revascularization).

4.2 Exclusion Criteria

1. Life-threatening conditions other than HF with expected survival <1 year, such as malignancy;
2. Unable to complete follow-up.

4.3 Withdrawal Criteria

If a participant stops participating before completion, it is considered withdrawal. This may be initiated by the participant or the investigator. Participants may

voluntarily withdraw consent at any time for any reason. A participant is defined as withdrawn when all of the following criteria are met:

1. Refuses to continue participation;
2. Refuses further visits or assessments;
3. Refuses further trial-related contact.

4.4 Exclusion After Enrollment (Protocol Violation)

- Subjects who violate the protocol inclusion criteria;
- Subjects who meet the protocol exclusion criteria.

V. Endpoints

5.1 Primary Endpoints

There are two primary endpoints: (1) HF rehospitalization and all-cause death within 12 months after discharge; (2) HF management quality score.

5.2 Secondary Endpoints

Within 12 months after discharge:

1. First HF rehospitalization;
2. Number of HF rehospitalizations;
3. All-cause readmission;
4. All-cause death.

HF rehospitalization is defined as hospitalization due to worsening HF, or an emergency visit requiring intravenous diuretic therapy.
All-cause readmission is defined as hospitalization due to worsening of any disease, or an emergency visit lasting more than 12 hours.

5.3 Safety Endpoints

At each visit, any adverse events will be recorded. Primary safety endpoints include hypotension, renal dysfunction, hyperkalemia, hypokalemia, arrhythmia, etc.

5.4 Exploratory Endpoints (if applicable)

- Compare direct medical costs, direct non-medical costs, and indirect costs within 12 months between intervention and control groups;
- Compare HF-CAP effects in specific subgroups, including different hospital levels, females vs males, older vs younger, diabetes vs non-diabetes, hypertension vs non-hypertension, CKD vs non-CKD, ischemic vs non-ischemic, sinus rhythm vs atrial fibrillation;
- Explore optimal GDMT dosing for the Chinese population;
- Explore onset time and duration of HF-CAP effectiveness.

VI. Study Procedures

6.1 Study Steps and Related Assessments

(1) **Hospital screening phase:** Hospitals registered on the China HF Center website that continuously upload data but have not applied for accreditation will be screened. Based on hospital level and annual HF admission volume, eligibility will be assessed against inclusion/exclusion criteria. Hospitals will be stratified by level, HF volume, and care capability into Standard and Primary-level categories. Hospitals meeting inclusion criteria, not meeting exclusion criteria, and willing to participate will be preliminarily screened. These hospitals will submit the study for ethics review; those obtaining ethics approval will become formally screened and enter the randomization phase.

(2) **Randomization phase:** The unit of randomization is the hospital. Stratified randomization will ensure balance within strata; both Standard and Primary-level centers will be randomized 1:1 into the HF-CAP intervention group and the usual care group.

(3) **Intervention and follow-up phase:** Intervention hospitals will implement a series of HF-CAP management measures under guidance of the HF-CAP Expert Committee. Usual care hospitals will not receive any intervention and will manage HF patients as usual.

After randomization, each participating unit should introduce the study to each HF patient who meets inclusion criteria and does not meet exclusion criteria. Patients who provide informed consent are successfully enrolled. Standard HF centers will consecutively enroll the first 10 non-selected patients each month in order of admission time; Primary-level HF centers will consecutively enroll the first 8 non-selected patients each month in order of admission time.

All patients will have baseline data collected and uploaded to the HF Center EDC system, including:

- Sociodemographic characteristics: sex, age, height, weight, etc.;
- Socioeconomic characteristics: education level, employment status, insurance type;
- Medical history: HF symptoms, NYHA class, disease duration, etiology, triggers, comorbidities, personal history, family history, etc.;
- Physical examination: blood pressure, heart rate, oxygen saturation, jugular venous distention, lung rales, lower extremity edema, etc.;
- Tests: ECG, echocardiography, 6-minute walk distance;
- Laboratory tests: CBC, liver and renal function, electrolytes, BNP/NT-proBNP, glucose, lipids;
- Medications: HF medications, cardiovascular medications, other medications;
- In-hospital outcomes.

All patients are required to complete and upload follow-up data at 1 week, 1 month (±7 days), 3 months (±14 days), and 12 months (±28 days) after discharge in the HF Center EDC system.

The 1-week follow-up requires telephone follow-up only to collect HF rehospitalization and survival status.
The 1-month, 3-month, and 12-month follow-ups should be conducted on site whenever possible; telephone follow-up is allowed if an on-site visit cannot be completed. Follow-up includes symptom and sign assessment, NYHA class, vital signs (blood pressure, heart rate), weight, CBC, liver and renal function, electrolytes, BNP or NT-proBNP, ECG, medication record, and endpoint event collection. Echocardiography and 6-minute walk test will be performed at 3 and 12 months.

Table 1. Schedule of Assessments and Time Points

Stage	**Before discharge**	**Post-discharge follow-up**			
Visit	V0	V1	V2	V3	V4
Time		7 days	1 month ±7 days	3 months ±14 days	12 months ±28 days
Informed consent obtained	×				
Inclusion/exclusion criteria	×				
Sociodemographic characteristics	×				
Medical history	×				
Symptoms	×		×	×	×

Stage	Before discharge	Post-discharge follow-up			
Blood pressure	×		×	×	×
Heart rate	×		×	×	×
Oxygen saturation	×		×	×	×
Physical exam	×		×	×	×
12-lead ECG	×		×	×	×
Echocardiography	×			×	×
CBC	×		×	×	×
Fasting glucose	×		×	×	×
HbA1c	×		×	×	×
Lipids	×		×	×	×
Liver function	×		×	×	×
Renal function	×		×	×	×
Electrolytes	×		×	×	×
BNP or NT-proBNP	×		×	×	×
6-minute walk distance	×			×	×
Medication use	×		×	×	×
Endpoint events		×	×	×	×

HF-CAP Program

HF-CAP management measures include the following:

Heart failure center accreditation

HF center accreditation can leverage multiple resources of the program to improve HF management quality.

1. Accreditation is a measure of HF management quality. Only HF centers maintaining high standards for performance outcomes can obtain and maintain accreditation. Therefore, successful accreditation indicates that HF management at the center meets national standards.
2. Accreditation and national/regional HF network support: provide technical support and solutions to enable bidirectional referral.
3. Training and educational resources: access to various online educational resources provided by the program, including web-based training courses, learning materials, the latest national and international guidelines and expert interpretation, and case discussions; members may receive funding support to

attend regional program training courses and exchange seminars to understand program progress and work plans, share experiences in improving HF quality, and discuss best practices.
4. On-site exchange: as needed, conduct on-site visits to excellent centers with better HF management quality to promote dissemination of experience.

Education and training

HF-CAP staff training program:
Provide training for multidisciplinary teams at accredited HF centers:

1. Experts from the China HF Center Alliance and regional HF center alliances help centers identify major quality problems, propose improvement measures, and promote problem-oriented quality improvement.
2. Regional training courses: program progress summary, training, and experience exchange.
3. On-site communication: as needed, staff will visit higher-quality centers for on-site visits and exchange to promote experience dissemination.
4. Web-based courses (documents, slides, videos, etc.): participating centers can browse and download via the program website using dedicated usernames and passwords.
5. Other educational materials: academic conference presentations and exchanges, brochures, pocket guides with program logos, etc.

HF-CAP patient education program:

Intervention	Details
Exercise and rehabilitation guidance	Recommend different intensities of exercise according to cardiac function; reduce sedentary behavior; increase moderate-intensity exercise; proceed gradually; encourage participation in recommended exercise forms and community group activities; how to avoid or reduce exercise-related injuries.
Sodium restriction	In acute HF with volume overload, restrict sodium intake to <2 g/day; strict sodium restriction is not recommended for mild or stable HF.
Fluid restriction	1.5–2 L/day for severe HF; mild-to-moderate symptomatic HF does not benefit from routine fluid restriction.
Nutrition and diet	Low-fat diet; smoking cessation; abstain from alcohol; weight loss for obese patients; nutritional support for cardiac cachexia.
Weight monitoring	A sudden weight gain >2 kg within 3 days should be considered water and sodium retention.

Intervention	Details
Management of blood pressure, lipids, glucose	Control blood pressure, lipids, and glucose within appropriate ranges.
Psychological and mental guidance	Maintain a positive and optimistic attitude; comprehensive emotional intervention such as psychological down-regulation; consider anxiolytics or antidepressants when necessary and appropriate.
Medication guidance	Explain the medication list including name, dose, timing, frequency, purpose, adverse reactions, precautions; print the medication list to improve adherence.
Follow-up plan	Explain follow-up schedule and purpose in detail; individualized follow-up may be recommended (e.g., 2 weeks, 1 month, 3 months, 6 months, 1 year, 2 years post-discharge) with timely medical intervention based on results.
Self-assessment and management of symptoms	How to detect early worsening of HF symptoms and how to manage it.

Continuous improvement measures

Typical case discussion meetings
Select typical cases with rescue delay or decision errors for analysis; multidisciplinary team meets to discuss and analyze. Core departments should participate; held once every 2 months.

Quality improvement meetings
Conduct periodic data analysis of HF center operation to affirm achievements, identify problems, and formulate improvement measures. Core departments should participate; held once every 3 months.

6.2 Investigational Product (if applicable)

Not applicable.

6.3 Concomitant Medications and Treatments (if applicable)

Not applicable.

6.4 Dose Adjustment (if applicable)

Not applicable.

6.5 Study Completion

All patients complete the final visit.

6.6 Early Termination or Suspension

The study will be terminated or suspended early if unexpected, significant, or unacceptable risks to participants are identified, or if major protocol errors are found during study conduct.

6.7 Clinical Observation, Follow-up, and Measures to Ensure Compliance

Participant adherence will be regularly monitored and evaluated through data monitoring in the Zhongshan HF database.

VII. Adverse Event Collection and Reporting

7.1 Definitions of Adverse Events

Adverse event (AE): Any adverse medical event occurring during a medical device clinical trial, regardless of whether it is related to the investigational medical device or drug.
Serious adverse event (SAE): An event occurring during the clinical trial that results in death or severe deterioration of health, including life-threatening illness or injury, permanent defect in body structure or function, requiring hospitalization or prolongation of hospitalization, requiring medical or surgical intervention to prevent permanent defect in body structure or function; fetal distress, fetal death, congenital anomaly, or birth defect.

7.2 Recording and Reporting of Adverse Events

For any AE occurring in the trial, the investigator shall take appropriate treatment measures and manage actively; then, according to the participant's condition and AE control, the investigator will determine subsequent treatment and follow-up.

Any AE, including subjective discomfort and laboratory abnormalities, must be taken seriously, carefully analyzed, and managed to protect participant safety.

Study staff shall record all AEs in detail in the EDC, including: description of AE and related symptoms, time of occurrence, severity, duration, measures taken, final outcome, and relationship to the clinical trial, etc.

All AEs shall be followed until resolution, or until the investigator judges the condition is "chronic," "stable," or "relieved." If the trial ends, follow-up continues until the last follow-up visit. These AEs shall be recorded in the EDC.

Serious adverse event: As defined above, including death or severe deterioration, life-threatening illness or injury, permanent defect, hospitalization or prolonged hospitalization, intervention to avoid permanent defect, fetal distress/death, congenital anomaly/defect, etc.

Record clinically significant AEs from the time the subject signs informed consent until the end of follow-up (history/baseline conditions without clear worsening may be omitted). Planned hospitalization for existing disease or protocol-required follow-up without severe deterioration, or elective surgery, is not recorded as an SAE.

7.3 Risk Prevention and Management

This study does not involve implantable medical devices or drug trials, therefore it will not bring additional risks.

VIII. Data Management

This study will use the existing electronic data capture system (EDC) of the HF center to collect and manage trial data. Data management shall comply with the "Good Clinical Practice for Medical Device Trials," the "Technical Guideline for Clinical Trial Data Management," and the "Guidance on Electronic Data Capture in Clinical Trials," to ensure the authenticity, integrity, accuracy, and reliability of trial data.

Data entry and verification:
Investigators or clinical research coordinators shall complete and submit eCRFs within the specified time after each subject visit. Monitors, data managers, and medical personnel shall review data item by item. Queries identified during review will be sent to investigators in the EDC as data queries until closed. The data manager may close system-generated queries and data manager–generated queries; clinical monitors may close monitor-generated queries; medical personnel may close medical personnel–generated queries. After data cleaning, investigators sign to confirm reviewed eCRFs; audit trails of data modifications will be retained in the system.

External data management:
Based on an external data transfer protocol, including but not limited to data categories, data providers, data contents and formats, transfer methods, transfer frequency, etc.

Data review:
Before database lock, the principal investigator, sponsor, statistician, and data manager will jointly conduct final review of all data queries, dropouts and protocol deviations, concomitant medications, and AEs, and determine each case's analysis set (including FAS, PPS, SS), missing value determination, and outlier handling.

Database lock:
The data manager will develop a database lock checklist. After lock conditions are met, relevant personnel (sponsor, principal investigator, biostatistician, clinical project manager, data manager) will jointly approve database lock.

IX. Statistical Analysis

9.1 Sample Size Estimation

1. Total sample size

There are two primary endpoints: (1) first HF rehospitalization or death within 12 months after discharge; (2) improvement in HF management quality score.

Individual HF management quality score = (actual score − lowest possible score) / (highest possible score − lowest possible score).

Each participant may have a different total number of quality indicator opportunities (highest possible score). If a participant does not meet the eligibility criteria for certain quality indicators, those indicators will not be counted in the score. For example, if a participant does not have atrial fibrillation, they are not eligible for the anticoagulation indicator for AF. Similarly, if a participant has contraindications to beta-blockers, they are not eligible for that indicator. Eligibility for each quality indicator will be determined at baseline and carried forward during follow-up. The analysis will compare improvement from baseline to 1 year or the last recorded study visit.

The planned overall sample size is 120 hospitals, with an average cluster size of 52 patients (total ~6,240 patients), assuming: a 15% relative reduction in first HF rehospitalization or death in the intervention group, a 30% event rate in the control group, an intracluster correlation coefficient (ICC) of 0.01, a coefficient of variation of cluster size of 0.65, power (1−β) of 85%, and overall type I error of 0.05. For the clinical endpoint (HF rehospitalization or death), type I error is allocated 0.04; for the quality indicator endpoint, type I error is allocated 0.01. For the composite quality score, assume a 10% improvement rate in the control group within 12 months, and an absolute improvement rate of 20% in the intervention group; thus the planned sample size has >90% power to detect a 10% absolute improvement in the intervention group.

The study centers are distributed nationwide. To avoid patients seeking care and transferring across multiple centers, enrolling centers are within 50 km physical distance. During 12-month follow-up, the probability of cross-over care is small (~5%), and small cross-over is consistent with clinical practice. Therefore, cross-over is ignored in sample size estimation.

2. Sample size allocation and rationale

This trial will be conducted in multiple clinical trial institutions simultaneously. In principle, enrollment numbers will be distributed as evenly as possible across centers to ensure adequate representativeness. However, considering feasibility and enrollment progress, enrollment numbers may be adjusted according to actual conditions, striving to keep enrollment size relatively balanced across centers.

9.2 Definition and Selection of Analysis Sets

Analysis sets: Statistical analyses will be performed based on the following populations. The analysis populations will be clearly defined before statistical analysis begins. This study includes:

- **Full Analysis Set (FAS):** Defined according to the Intention-To-Treat (ITT) principle; a dataset consisting of all subjects who participated in the trial and received the study product treatment.
- **Per-Protocol Set (PPS):** A subgroup of treated subjects who completed the trial and excluded those with major protocol violations (e.g., violation of inclusion/exclusion criteria, dropout during the trial leading to inability to provide primary endpoint data, or circumstances severely affecting evaluation of primary endpoints).

Primary endpoint analyses will be conducted on both FAS and PPS. In addition, baseline demographics and secondary endpoint analyses will be conducted on FAS; safety evaluation is also planned on FAS (therefore SS is not defined separately).

9.3 Statistical Methods and Analyses

Baseline demographic analysis: Primarily descriptive. Data will be summarized and analyzed at both the cluster level and the participant level, with adjustment for cluster effects. For continuous variables, mean, standard deviation, median, 25th percentile, and 75th percentile will be used to compare baseline characteristics between groups; for categorical variables, counts and percentages will be used. For continuous variables, Wilcoxon rank-sum test will be used; for categorical variables, chi-square test or Fisher's exact test will be used. All trial objectives will be analyzed under the ITT principle.

Primary endpoint analysis: Two primary endpoints:

1. Composite endpoint of HF rehospitalization or all-cause death within 12 months after discharge: Kaplan–Meier cumulative risk method will be used to calculate event rates in each group. Due to potential clustering within centers, Cox models with shared frailties will be used. Demographic and baseline clinical characteristics will be included as covariates, and the treating hospital

will be included as a random effect, to estimate adjusted HRs and 95% CIs to evaluate differences in event risk between intervention and control groups.

2. Improvement in HF management quality score: Compare improvement from baseline to 1 year or last recorded visit. A mixed-effects linear model will compare score improvement between groups, including the treating hospital as a random effect. Correlation within hospital will be considered, and mean change and 95% CI will be reported.

Prespecified subgroup analyses: Center characteristics (tertiary vs secondary; geographic regions: western, eastern, central, and northeastern), age, sex, hypertension, diabetes, chronic kidney disease (serum creatinine >1.5 mg/dL), other baseline treatments, and frailty/poor condition (baseline NYHA, NT-proBNP). Effects on primary outcomes and interaction effects will be explored. No multiplicity adjustment will be performed.

Missing data strategy: Covariate missing data will not be handled. For outcome variables, loss to follow-up will be controlled within 10%. For patients who withdraw or are lost to follow-up before 12 months and have not experienced a primary endpoint event, the crude 12-month primary endpoint event risk will be analyzed; multiple imputation will not be performed. For quality improvement values, LOCF will be used.

Sensitivity analyses:
(1) Exclude early events: exclude events occurring within 10 days after randomization and repeat primary analysis to wash out pre-randomization effects.
(2) Tipping-point analysis: for subjects with potential underreporting risk, progressively add assumed events, fit Weibull models, and assess robustness under various missing-event scenarios.
(3) Analyses under different covariate missing-data strategies: (i) no handling; (ii) deletion; (iii) imputation. a) Mean/median/mode imputation: continuous quantitative data can be imputed with mean or median; discrete quantitative data can be imputed with mode. b) Build regression models to impute missing values.
(4) Analyses under different outcome event missing-data strategies: (i) deletion, no multiple imputation; (ii) worst-case strategy: patients who withdraw or are lost to follow-up before 12 months without primary endpoint events are all treated as having events; (iii) best-case strategy: all treated as having no events; (iv) multiple imputation of missing outcome data using chained equations (MICE).

For the primary clinical endpoint (HF rehospitalization or death), two-sided $P<0.04$ will be considered statistically significant; for the second primary endpoint (quality improvement), two-sided $P<0.01$ will be considered statistically significant. Other endpoints will be analyzed at a two-sided 0.05 significance level (unless otherwise specified). Statistical analyses will be performed using SAS 9.4 and R 4.3.2.

X. Ethics-Related Considerations

10.1 Ethics Committee Review

This protocol, written informed consent form, and materials directly related to subjects must be submitted to the ethics committee and approved in writing before formal study initiation. Investigators must submit at least annual reports to the ethics committee (if applicable). Investigators must notify the ethics committee in writing upon study termination and/or completion; investigators must promptly report any changes occurring during the study (e.g., revisions to the protocol and/or informed consent forms), and such changes must not be implemented before ethics approval unless required to eliminate an obvious and direct risk to subjects. In such cases, the ethics committee will be notified.

10.2 Informed Consent

In this study, subjects must not be enrolled before obtaining signed written informed consent. During participation, subjects will be provided with all updated versions of the informed consent form and written information. The informed consent form shall be retained as an essential clinical trial document for inspection.

XI. Confidentiality Measures

The results of this project may be published in medical journals, but we will keep patient information confidential in accordance with legal requirements. Unless required by relevant laws, patients' personal information will not be disclosed. When necessary, government authorities and hospital ethics committees and relevant personnel may review patient records as 规定 (as stipulated).

XII. Expected Study Timeline and Completion Date

Planned enrollment period: 12 months (January 2026 to December 2026). Follow-up period: 12 months. Planned study completion date: March 2028.

XIII. References

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Informed Consent Form

Participant Information Sheet

Protocol Title:
China Heart Failure Center Accreditation Program (HF-CAP): A Prospective Multicenter Cluster Randomized Controlled Trial

Principal Investigator at This Center:
Jingmin Zhou

Study Center:
Zhongshan Hospital, Fudan University

Sponsor:
Zhongshan Hospital, Fudan University

Dear Participant,

You are invited to participate in the research study entitled **"China Heart Failure Center Accreditation Program (HF-CAP): A Prospective Multicenter Cluster Randomized Controlled Trial."**
Please read this informed consent form carefully and make a prudent decision about whether to participate in this study.

Participation in this study is entirely voluntary. You may be considered for enrollment in this study only after you have signed this informed consent form. When your study physician or research staff discusses this informed consent form with you, you may ask him/her to explain any part that you do not understand. We encourage you to fully discuss your decision to participate in this study with your family members and friends before making a decision.

You have the right to refuse to participate in this study or to withdraw from the study at any time without penalty or loss of benefits to which you are otherwise entitled. If you are currently participating in another research study, please inform your study physician or research staff.

The background, purpose, procedures, and other important information of this study are described below.

I. Background of the Study

Heart failure (HF) represents the advanced and terminal stage of cardiovascular diseases and poses a serious threat to human health. It is a major public health burden in China and worldwide.

Over the past decades, significant progress has been made in the treatment of heart failure, particularly in heart failure with reduced ejection fraction (HFrEF), where multiple pharmacological and device-based therapies have been proven to significantly improve prognosis and quality of life, driving updates in international heart failure guidelines. However, in real-world clinical practice, there remains a substantial gap between guideline-recommended therapies and actual clinical implementation.

The China Heart Failure Center Accreditation Program (HF-CAP) is a nationwide heart failure quality improvement initiative launched in 2017 under the leadership of the Chinese Medical Association. Its aim is to improve the management of patients with heart failure. Registry data from heart failure centers indicate that during the development of heart failure centers, the utilization of standardized diagnostic techniques has increased annually, the use of guideline-recommended pharmacological therapies at discharge has progressively improved, and a downward trend in 1-year mortality after discharge has been observed.

This project intends to evaluate the impact of the HF-CAP program on patient outcomes through a multicenter, prospective, cluster-randomized, controlled clinical trial conducted across China.

II. Purpose of the Study

1. To evaluate the effect of HF-CAP compared with routine care on 1-year clinical outcomes in patients with heart failure;
2. To assess the effectiveness of HF-CAP compared with routine care in improving the quality of heart failure management.

III. Study Procedures

1. How many participants will take part in this study?

Approximately **6,240 participants** will be enrolled in this study, which will be conducted across **160 participating study centers/medical institutions**.

2. Study Procedures

If you agree to participate in this study, you will be asked to sign this informed consent form.

This study consists of three phases: the hospital screening phase, the randomization phase, and the intervention and follow-up period.

Hospital Screening Phase

Hospitals registered on the China Heart Failure Center platform that have continuously uploaded data but have not yet applied for accreditation will be screened. Based on hospital level and annual heart failure admission volume, eligibility will be assessed according to inclusion and exclusion criteria. Hospitals will be stratified according to hospital level, heart failure case volume, and medical care capacity into a **Standard Version** and a **Primary Version**.

Hospitals meeting the inclusion criteria, without exclusion criteria, and willing to participate in the study will be preliminarily selected. These hospitals will apply for ethics approval according to the study protocol. Hospitals that obtain ethics approval will be formally included and proceed to the randomization phase.

Randomization Phase

The unit of randomization in this study is the hospital. Stratified randomization will be performed to ensure balance of hospital characteristics within each stratum. Both the Standard Version and Primary Version hospitals will be randomly assigned in a 1:1 ratio to either the **HF-CAP intervention group** or the **routine care group**.

Intervention and Follow-up Period

Hospitals assigned to the HF-CAP intervention group will receive a series of HF-CAP management measures under the guidance of the HF-CAP Expert Committee. Hospitals assigned to the routine care group will not receive any additional intervention and will manage heart failure patients according to usual clinical practice.

After randomization, all participating hospitals will introduce the study to every heart failure patient who meets the inclusion criteria and does not meet the exclusion criteria. Patients who provide informed consent will be considered successfully enrolled.

Standard Version heart failure centers will enroll the **first 10 consecutively admitted eligible patients each month**, while Primary Version centers will enroll the **first 8 consecutively admitted eligible patients each month**, based on admission order without selection.

Baseline data will be collected for all enrolled patients and uploaded to the Heart Failure Center Electronic Data Capture (EDC) system, including:

1. **Sociodemographic characteristics:** sex, age, height, weight;
2. **Socioeconomic characteristics:** education level, employment status, type of medical insurance;
3. **Medical history:** heart failure symptoms, NYHA functional class, disease duration, etiology, precipitating factors, comorbidities, personal history, and family history;
4. **Physical examination:** blood pressure, heart rate, oxygen saturation, jugular venous distension, pulmonary rales, lower-limb edema;
5. **Diagnostic tests:** electrocardiogram, echocardiography, 6-minute walk distance;
6. **Laboratory tests:** complete blood count, liver and renal function, electrolytes, BNP or NT-proBNP, blood glucose, blood lipids;
7. **Medication use:** heart failure medications, cardiovascular medications, and other medications;
8. **In-hospital outcomes.**

Follow-up visits are required at **1 week**, **1 month (±7 days)**, **3 months (±14 days)**, and **12 months (±28 days)** after discharge, with data uploaded to the Heart Failure Center EDC system.

The 1-week follow-up will be conducted by telephone only, collecting information on heart failure rehospitalization and survival status.

Follow-up visits at 1 month, 3 months, and 12 months should preferably be conducted as on-site visits. Telephone follow-up is acceptable if an on-site visit cannot be completed. Follow-up assessments include symptom evaluation, physical signs, NYHA functional class, vital signs (blood pressure, heart rate), body weight, laboratory tests (complete blood count, liver and renal function, electrolytes, BNP or NT-proBNP), electrocardiogram, medication records, and endpoint events. Echocardiography and 6-minute walk tests will be performed at the 3-month and 12-month follow-up visits.

All examinations conducted during the study period are recommended routine assessments according to current heart failure guidelines. No additional examinations are required specifically for this study.

3. How long will this study last?

The overall study is planned to last **27 months**. Your individual participation in this study will last approximately **12 months**.

You may choose to withdraw from the study at any time without losing any benefits to which you are otherwise entitled. If you decide to withdraw during the study, we encourage you to discuss your decision with your physician. If you experience a serious adverse event or if your study physician believes that continued participation is not in your best interest, he/she may decide to withdraw you from the study. The sponsor or regulatory authorities may also terminate the study during the study period. Your withdrawal will not affect your standard medical care or rights.

4. Biological Specimens

No biological specimens will be collected in this study.

IV. Risks and Benefits

1. What are the risks of participating in this study?

The interventions involved in this study are based on current domestic and international heart failure guideline recommendations, and their risks are comparable to those of routine clinical treatment. There may also be risks related to information security. We will make every effort to protect your information from unauthorized disclosure and to safeguard your personal privacy within the limits permitted by law.

If you experience any discomfort, changes in your condition, or unexpected events during the study, whether or not related to the study, you should promptly inform your study physician.

You will be required to attend follow-up visits and undergo certain examinations during the study, which may take up some of your time and may cause inconvenience.

2. What are the benefits of participating in this study?

Direct benefits: By participating in this study, you may potentially receive optimized treatment strategies through the Heart Failure Center Accreditation Program and experience improvement in your heart failure condition; however, such benefits cannot be guaranteed.

Potential benefits: The information obtained from your participation may benefit you or other patients with similar conditions in the future.

V. Alternative Treatment Options

In addition to participating in this study, you may receive routine medical care provided by your physician, including regular follow-up visits and adjustment of heart failure medications according to standard clinical practice.

Please discuss these and other possible options with your physician.

VI. Confidentiality of Personal Information

During the study, the research team may need access to your medical history and necessary past medical records and test results for research purposes. By signing this informed consent form, you authorize the research team to contact other healthcare providers involved in your care to obtain necessary medical information.

Only members of the research team will have access to your identifiable medical information. Without violating confidentiality principles and relevant regulations, authorized investigators, ethics committees, and regulatory authorities may review your original medical records to verify clinical trial data.

Your personal identifying information (such as name and contact details) will be coded to prevent identification. If study results are published in medical journals or presented at scientific conferences, no information that could identify you will be disclosed.

You may withdraw your authorization for the use and sharing of your personal information at any time by contacting your study physician. If you do so, you will no longer be able to participate in the study. No new identifiable health data will be collected thereafter; however, previously collected data may continue to be used and shared as described in this consent form.

To ensure scientific integrity, you may not be able to access certain study-related records before the study is completed. After study completion, you may request access to your health data collected during the study and request correction of any errors.

All personal information and study data collected during this study will be coded and stored at Zhongshan Hospital, Fudan University, and destroyed after three years. Your information will not be used for future research beyond this study.

VII. Disclosure of Study Results

Overall study results (excluding personal identifiable information) will be described after study completion at . You may search for the study using relevant keywords.

VIII. Study Costs and Compensation

1. Study-related medications/devices and examinations

Electrocardiograms, echocardiography, laboratory tests, and medications during the study are part of routine clinical care. The study does not incur additional costs and does not provide free medications or examinations. Treatment and examinations for other concurrent conditions are not covered.

2. Compensation for participation

As there are no additional examinations or medical expenses associated with participation, follow-up management support will be provided, and no additional compensation will be offered.

3. Compensation for injury

This study does not involve investigational drugs or devices. All medical care follows guideline recommendations, and no additional risk of injury is anticipated.

IX. Participant Rights and Responsibilities

1. Your Rights

Your participation is voluntary. Refusal to participate will not affect your access to standard medical care. You may withdraw from the study at any time without discrimination or unfair treatment, and your medical care and rights will not be affected. If new information arises that may affect your rights or safety, an updated informed consent form will be provided for re-consent.

2. Participant Responsibilities

As a participant, you are required to provide truthful information regarding your medical history and current health status; report any discomfort experienced during the study; refrain from restricted medications or foods as instructed; and inform the study physician if you are participating or have recently participated in other studies.

X. Contact Information

If important new information arises during the study that may affect your willingness to continue participation, your physician will inform you promptly. If you have questions about your study data or wish to learn about the study findings after completion, you may contact **Xu Yamei** at **139-1713-3371** at any time.

This study has been reviewed and approved by the Ethics Committee. If you have any concerns regarding your rights or wish to provide comments or complaints related to the study, please contact the **Medical Ethics Committee of Zhongshan Hospital, Fudan University**:
Tel: 021-3158-7871
Email: ec@zs-hospital.sh.cn

Participant Signature Page

Informed Consent Statement

I have been informed of the purpose, background, procedures, risks, and benefits of this study. I have had sufficient time and opportunity to ask questions, and all my questions have been answered satisfactorily. I agree to participate in this study.

I have been informed of whom to contact if I have questions, concerns, suggestions, or wish to obtain further information or assist with the study.

I understand that I may choose not to participate or may withdraw from the study at any time without providing a reason.

I understand that if my condition worsens, if I experience a serious adverse event, or if my study physician determines that continued participation is not in my best interest, I may be withdrawn from the study. The sponsor or regulatory authorities may also terminate the study during the study period without my consent. In such cases, I will be informed promptly and alternative options will be discussed.

I will receive a copy of this informed consent form signed by myself and the investigator.

I understand that participation in this study requires the use of my personal information, and I consent to the use and processing of my personal information for the purposes described in this informed consent form.

☐ **Agree** ☐ **Disagree (not eligible to participate in this study)**

Participant Signature: _____ **Date:** _____

Legal Representative Signature: _____
Relationship to Participant ( ) **Date: _____**
(Applicable when the participant lacks or has limited capacity for civil conduct)

Impartial Witness Signature: _____ **Date: _____**
(Applicable when the participant is unable to read this informed consent form)

Investigator Signature: _____ **Date: _____**