Title: A Multicenter, Cluster-Randomized, Controlled Study Evaluating the Effectiveness and Safety of an Artificial Intelligence (AI)-Assisted Medical Treatment Decision Support System Compared to Conventional Care in Patients with Heart Failure with Reduced Ejection Fraction (HFrEF)

Sponsor: Zhongshan Hospital, Fudan University

- **Principal Investigator:** Zhou Jingmin
- **Protocol Version:** 1.3
- **Version Date:** September 8, 2025

2. Version History

Document	Version	Date	Summary of Changes
Protocol	V1.1	July 25, 2025	Revisions after initial review. Mainly modified background, AI system introduction, and remote intelligent platform content.
Protocol	V1.2	September 8, 2025	Revisions after secondary review. Modified background, AI-guided medication strategy. Submitted AI system test report.

3. Investigator's Statement

I will diligently fulfill the investigator's responsibilities in accordance with Chinese GCP regulations, personally participating in or directly supervising this clinical research. I have read and confirmed this protocol, agreeing with its scientific and ethical soundness. I will perform relevant duties according to Chinese laws and regulations, the Declaration of Helsinki, Chinese GCP, and this study protocol, and will only implement it after approval by the Academic Committee and Ethics Committee. I will keep this study protocol confidential unless disclosure is necessary to protect the safety, rights, and interests of the subjects.

- **Research Unit:** Zhongshan Hospital, Fudan University
- **Principal Investigator:** Zhou Jingmin

4. Protocol Synopsis

Item	Details
Protocol Title	A multicenter, cluster-randomized, controlled study evaluating the effectiveness and safety of Artificial Intelligence (AI)-assisted medical treatment decision support system compared to conventional care in HFrEF patients
Study Objective	To evaluate the effectiveness and safety of AI-assisted decision support system-guided pharmacotherapy compared to conventional care in HFrEF patients.
Primary Endpoint	Composite endpoint of first rehospitalization for heart failure or cardiovascular death.
Overall Design	A multicenter, open-label, cluster-randomized, controlled study.
Sample Size	40 centers, 1200 patients.
Study Groups	Cluster randomization.
Inclusion/Exclusion Criteria	**Center Inclusion:** Capable of randomly accepting the study interventions and completing the study. **Patient Inclusion:** Hospitalized patients diagnosed with HF and discharged as planned; LVEF ≤40% measured by echocardiography within 1 month prior to enrollment; Age ≥18 years; Signed informed consent. **Exclusion:** ① Patients unable or unsuitable for follow-up; ② Poor compliance, risk of switching groups.

Item	Details
Intervention	Pharmacotherapy guided by the AI-assisted decision support system.
Withdrawal Criteria	Subjects may withdraw if: ① Subject requests to withdraw consent for any reason; ② Investigator considers continuation contrary to the subject's best interests.
Statistical Analysis Plan	1) **Primary Endpoint:** Cumulative incidence will be estimated using Kalbfleisch-Prentice's method. A stratified Cox proportional hazards model will estimate Hazard Ratio (HR) and 95% Confidence Interval (CI), accounting for cluster effects. 2) **Secondary Endpoints:** Analyzed using Fine-Gray's competing risks model, accounting for cluster effects. 3) **Subgroup Analysis:** Predefined subgroups include hospital level, age, sex, BP<100mmHg, diabetes, chronic kidney disease (serum creatinine>1.5mg/dL), baseline treatments, frail patients (baseline NYHA, NT-proBNP). Interaction effects will be assessed. No adjustment for multiple comparisons. 4) **Sensitivity Analyses:** Excluding early events (within 10 days); using patient-reported GDMT as treatment variable; Per-Protocol analysis; Tipping-point analysis for potential underreporting.

5. Abbreviations

ACEI: Angiotensin-Converting Enzyme Inhibitor

AI: Artificial Intelligence

ARB: Angiotensin II Receptor Blocker

ARNI: Angiotensin Receptor-Neprilysin Inhibitor

eCRF: electronic Case Report Form

EDC: Electronic Data Capture

GDMT: Guideline-Directed Medical Therapy

HFrEF: Heart Failure with reduced Ejection Fraction

LVEDD: Left Ventricular End-Diastolic Diameter

LVEF: Left Ventricular Ejection Fraction

NT-proBNP: N-terminal pro-B-type Natriuretic Peptide

NYHA: New York Heart Association

SGLT-2i: Sodium-Glucose Cotransporter-2 Inhibitor

6. Study Details

6.1 Background

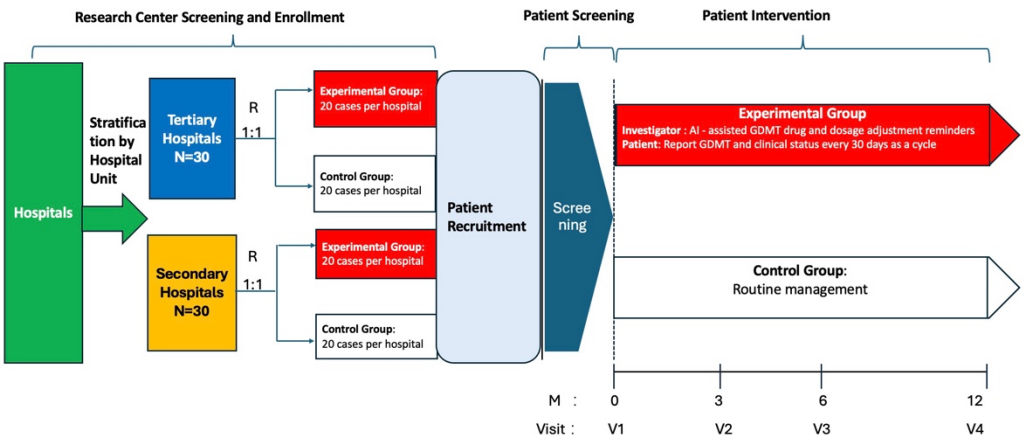
Heart Failure (HF) is a major global health burden. In China, the prevalence of HF in adults aged ≥25 is 1.1%, affecting approximately 12.1 million people, with high annual mortality (13.7%). HFrEF has the worst prognosis among HF types. While GDMT (including ACEI/ARB/ARNI, Beta-blockers, MRAs, SGLT2i) improves outcomes, real-world implementation faces challenges. This study aims to validate an AI-assisted decision support system designed to optimize GDMT use and dosing in HFrEF patients post-discharge, potentially improving outcomes and standardizing care across healthcare levels.

6.2 Objectives

- **Primary:** To validate if AI-guided pharmacotherapy reduces the composite endpoint of first HF rehospitalization or cardiovascular death compared to conventional care in HFrEF patients.
- **Secondary:** To evaluate the AI system's effect on dose adjustment, adherence, and guideline compliance; explore its applicability across subgroups; conduct an economic evaluation.

6.3 Study Design

- **Design:** Multicenter, Open-label, Cluster-Randomized, Controlled Trial.
- **Duration:** 6-month enrollment, 12-month follow-up. Planned end date: December 2026.
- **Randomization:** Centers (20 tertiary, 20 secondary) stratified by level and randomized 1:1 to Intervention or Control arm using a central system.
- **Blinding:** Subjects are blinded to group assignment.



6.4 Population

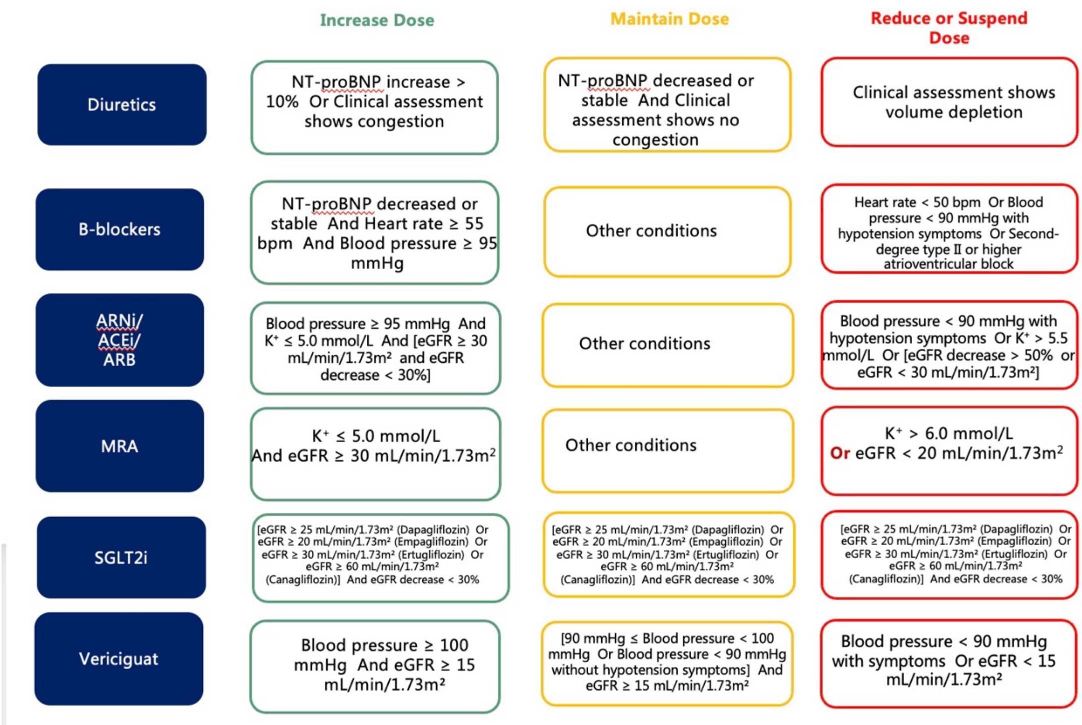
- **Sample Size:** 1200 patients (600 per arm), 30 patients per center.
- **Inclusion Criteria:** As per Synopsis.
- **Exclusion Criteria:** As per Synopsis.
- **Withdrawal Criteria:** As per Synopsis.

6.5 Endpoints

- **Primary Endpoint:** Time to first occurrence of HF rehospitalization or cardiovascular death.
- **Secondary Endpoints:** Time to first HF rehospitalization; all-cause rehospitalization; cardiovascular death; all-cause death; number of HF rehospitalizations; change from baseline in NT-proBNP, LVEF, LVEDD, EQ-5D score.
- **Safety Endpoints:** Adverse events including hypotension, renal dysfunction, hyperkalemia, hypokalemia, arrhythmia.
- **Exploratory Endpoints:** Compare effectiveness/safety of AI-guided vs. conventional dose adjustment for diuretics, beta-blockers, ACEI/ARB/ARNI, MRAs, SGLT2i; GDMT effects in specific subgroups.

6.6 Study Procedures

- **Baseline:** Informed consent, demographic/clinical/lab data collection, EQ-5D.
- **Follow-up:** Hybrid model (remote + site visits).
    - **Remote Visits (Monthly, V1, V2, V4, V5, V7, V8, V9, V10, V11):** Via WeChat mini-program/EDC system. Collects symptoms, signs, medications, lab data (e.g., electrolytes, NT-proBNP), endpoints, AEs.
    - **Site Visits (V3-3mo, V6-6mo, V12-12mo):** Physical exam, ECG, echocardiography, lab tests (including NT-proBNP), EQ-5D, endpoints, AEs.
- **Intervention Group:** AI system generates medication recommendations based on uploaded patient data, reviewed by investigator.
- **Control Group:** Investigator provides medication recommendations per conventional care based on uploaded data.



- **AI Medication Strategy (Based on GDMT guidelines):**
  - **Dose Increase Logic (if met):** Diuretics: double dose. Other GDMT: if <50% target -> increase to 50%; if ≥50% & <100% -> increase to 100%; if at 100% -> maintain.
  - **Dose Decrease/Pause Logic (if met):** Diuretics: halve dose. MRA: discontinue. Other GDMT: halve dose.
  - *Note: The AI system applies pre-set rules without self-learning/optimization.*

6.7 Data Management

Electronic Data Capture (EDC) system will be used. Database locking procedures will be followed.

6.8 Statistical Analysis

- **Sample Size Justification:** Based on estimated 15.3% event rate in control vs. 9.3% in intervention arm, ICC=0.005, alpha=0.05, power=80%, accounting for 5-10% dropout. Total 40 centers, 1200 patients.
- **Analysis Sets:** Full Analysis Set (FAS, Intent-to-Treat), Per-Protocol Set (PPS).
- **Analysis Methods:** As per Synopsis.

7. Ethics and Confidentiality

- **Ethics Approval:** The protocol and informed consent form must be approved by the Institutional Ethics Committee before study initiation. Amendments require prior approval unless for immediate subject safety.
- **Informed Consent:** Written informed consent must be obtained from each subject prior to any study procedures.
- **Confidentiality:** Subject confidentiality will be maintained in accordance with legal requirements. Results may be published without disclosing personal identifiers.

8. References

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